

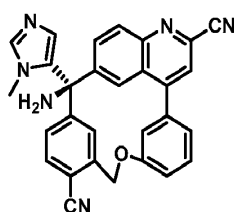
METHODS OF TREATING SQUAMOUS CELL CARCINOMA WITH A FARNESYLTRANSFERASE INHIBITOR AND A PI3K INHIBITOR

1. FIELD

[0001] This application claims the benefit of priority from U.S. Provisional Application No. 63/501,119, filed May 9, 2023, which is incorporated by reference in its entirety.

2. FIELD

[0002] Provided herein are methods of using Compound (I):



Compound (I)

or a pharmaceutically acceptable form thereof, optionally in combination with a phosphatidylinositol-3-kinase (PI3K) inhibitor, to treat squamous cell carcinoma (SCC). Pharmaceutical compositions, kits, and related products are also embodied within this disclosure.

3. BACKGROUND

[0003] Squamous cell carcinoma (SCC) is a class of cancer that includes a number of different cancer types that begin in squamous cells. Common types of SCC include esophageal, lung, thyroid, cervical, urothelial, bladder, vaginal, prostate, and head and neck squamous cell carcinomas. Head and neck squamous cell carcinoma (HNSCC) is the sixth most common invasive carcinoma, accounting for more than 900,000 new diagnoses annually worldwide (Johnson et al., Nat. Rev. Dis. Primers 6:92 (2020)). Exposure to carcinogens (e.g., tobacco, alcohol) and infection with the human papillomavirus (HPV) are described as the two major etiological causes of HNSCC, with the incidence of HPV-positive tumors rapidly on the rise (Chaturvedi et al., J. Clin. Oncol., 26:612-9 (2008)).

[0004] HNSCC is a complex group of malignancies with tumors arising from epithelial linings of the oral cavity, pharynx, tonsil, and larynx, posing several challenges to treating physicians. Most patients are diagnosed with locally advanced disease and treated with strategies integrating surgery, chemotherapy, and radiotherapy. About 50% of these treated

patients will experience a recurrence of disease. About 55% of patients with localized disease survive at least five years (American Cancer Society, Survival rates for oral cavity and oropharyngeal cancer (2020)). Regardless of etiology, once the disease has become advanced, or recurrent and/or metastatic (R/M), rates of survival decrease dramatically. Patients having R/M HNSCC have poor prognosis with a median survival of about 12 months despite treatments, with only an estimated 40% of patients surviving at least 5 years (American Cancer Society (2020)). While high cure rates have been achieved for localized and loco-regional disease using surgery, radiation, chemoradiation, and induction chemotherapy, survival rates for recurrent/metastatic diseases remain very poor, and better treatment options are necessary.

4. SUMMARY

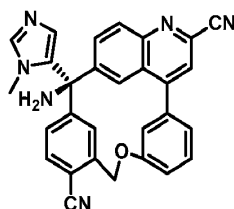
[0005] Numerous genetic mutations and dysregulations are commonly seen in HNSCC. According to the Cancer Genome Atlas (TCGA) Network, some of the most common mutations include TP53 (84%), CDKN2A (58%), CCND1 (31%), and PIK3CA (34%) (Cancer Genome Atlas Network, *Nature*, 517:576-82 (2015)). The Cancer Genome Atlas (TCGA) shows the overexpression of HRAS (wild-type, mutant, or both) in 25% to 30% of HNSCC patients, indicating a potential dependence on HRAS that may be analogous to HRAS as a driver oncogene to a broader population of HNSCCs ('cBioPortal for Cancer Genomics' (2020), <https://www.cbioportal.org/>). Furthermore, mutant HRAS requires PI3K for activity, and is insufficient to be tumorigenic in isolation (Gupta et al., *Cell*, 129:957-68 (2007)). Similarly, mutant PI3K requires Ras protein in order to drive tumor biology (Zhao and Vogt, *Oncogene*, 27:5486-96 (2008)). PI3K α (the catalytic subunit of PI3K), another prominent driver in HNSCC, is activated by PIK3CA mutations or PIK3CA gene amplification in about 30% of HNSCC patients. Overexpression of mutant or wild-type ("WT") HRAS can drive resistance to PI3K inhibition in PIK3CA-mutant HNSCC cells. Feedback reactivation of PI3K or compensatory parallel pathways limits the single agent efficacy of PI3K inhibitors, necessitating development of rational combination strategies. Cooperation and crosstalk of the HRas protein and PI3K pathways can drive tumor progression and resistance to targeted therapies in SCCs.

[0006] Alpelisib is a potent and selective inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3K α . PIQRAY® (also referred to as alpelisib or BYL719; *see* PIQRAY®'s July 20, 2021 label, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212526Orig1s004lbl.pdf. Also

posted on Novartis' website at <https://www.novartis.us/sites/www.novartis.us/files/piqray.pdf>) was approved by the United States Food and Drug Administration ("US FDA") in 2019 for treating, in combination with fulvestrant, postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer. While alpelisib has shown some promise in HNSCC in a phase I setting (Juric et al., J. Clin. Oncol. 36:1291-1299 (2018)), its single agent efficacy will likely be limited by feedback re-activation of PI3K or compensatory parallel pathways, necessitating the development of rational combination strategies to address issues with drug resistance.

[0007] There remains a need for the treatment of SCCs, in particular, treatment of HNSCC. There is also a need for therapeutic options with enhanced efficacy, increased durability of response, and/or faster onset of antitumor response, compared to existing therapies, or compared to a PI3K inhibitor, such as alpelisib, alone. There is also a need for effective therapies in relapsed or refractory settings, such as second or third line treatments, including those that mitigate emergence or progression of EGFR resistance or PI3K inhibitor resistance.

[0008] Provided herein are methods of treating squamous cell carcinoma (SCC) in a subject comprising administering to the subject (a) Compound (I):



Compound (I)

or a pharmaceutically acceptable form thereof, and (b) a PI3K inhibitor, such as alpelisib. Also provided herein are methods of treating PI3K-dysregulated SCC in a subject comprising administering to the subject Compound (I), or a pharmaceutically acceptable form thereof. Compound (I) is a farnesyltransferase inhibitor, and such inhibitors have been shown to block hyperactivated growth factor signaling at multiple nodes, including farnesylation-dependent proteins, such as HRas protein and Rheb protein, which depend on farnesylation for their activation and/or cellular localization (and as Rheb is a non-redundant TORC1 activator, indirectly blocks mTOR activity as well). Use of the combination of Compound (I) and a PI3K

inhibitor, such as alpelisib, according to the methods disclosed herein, can provide increased efficacy, durable resistance pathway inhibition, and/or enhanced tumor cell death, or a combination thereof, in PI3K- and/or HRAS-dysregulated cancers, compared to either agent alone or to standard of care treatments, such as chemotherapy.

[0009] In another aspect is a method of mitigating PI3K inhibitor (such as alpelisib) resistance in a SCC in a subject, comprising administering to the subject (a) Compound (I), or a pharmaceutically acceptable form thereof, and (b) a PI3K inhibitor, such as alpelisib.

[0010] In another aspect is a method of mitigating EGFR inhibitor (e.g., anti-EGFR antibody such as cetuximab) resistance in a SCC in a subject, comprising administering to the subject (a) Compound (I), or a pharmaceutically acceptable form thereof, (b) a PI3K inhibitor, such as alpelisib, and optionally (c) an EGFR inhibitor, such as cetuximab.

[0011] Without being limited by any theory, the use of the farnesyltransferase inhibitor and the PI3K inhibitor in SCC patients provides a more effective therapy compared to either single agent alone or compared to standard of care, such as chemotherapy. In some embodiments, the combined use of the two agents is synergistic. In some embodiments, the combination of the two agents, according to the methods disclosed herein, provides increased efficacy, provides increased durability of response, provides a more rapid onset of antitumor response, or prevents or delays relapse or disease progression, or combinations thereof, as compared to use of either agent alone, or as compared to standard of care, such as chemotherapy. In some embodiments, the combination has these improved effects while also mitigating therapeutic resistance to an EGFR inhibitor or PI3K inhibitor, thereby reducing the impact of the development of resistance to those therapies.

[0012] The present disclosure also provides a pharmaceutical composition comprising Compound (I), or a pharmaceutically acceptable form thereof, and a pharmaceutically acceptable carrier, diluent, or excipient. In some aspects, the pharmaceutical composition also comprises a PI3K inhibitor, such as alpelisib.

[0013] The present disclosure also provides a pharmaceutical kit or packaging comprising (a) a pharmaceutical composition comprising Compound (I), or a pharmaceutically acceptable form thereof, and a pharmaceutically acceptable carrier, diluent, or excipient. In some aspects, the pharmaceutical kit or packaging also comprises a pharmaceutical composition comprising a PI3K inhibitor, such as alpelisib, and a pharmaceutically acceptable carrier, diluent, or excipient.

5. BRIEF DESCRIPTION OF THE FIGURES

[0014] **FIGS. 1A-1D:** Heat maps indicating relative cytotoxicity of Compound (I), alpelisib, or the combination, in panel of head and neck squamous carcinoma (HNSCC) cell lines, including CAL33 (**FIG. 1A**), BICR22 (**FIG. 1B**), SCC9 (**FIG. 1C**), and HSC3 (**FIG. 1D**).

[0015] **FIG. 2:** Plot of tumor volume over time for vehicle, Compound (I), alpelisib, and Compound (I) with alpelisib in an HN2594 (HRAS^{WT-high}) patient-derived xenograft model.

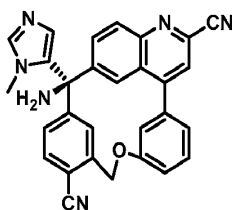
6. DETAILED DESCRIPTION

[0016] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0017] As used herein, and in the specification and the accompanying claims, the indefinite articles “a” and “an” and the definite article “the” include plural as well as single referents, unless the context clearly indicates otherwise.

[0018] As used herein, and unless otherwise specified, the terms “about” and “approximately,” when used in connection with doses, amounts, or weight percentages of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent within 30%, within 20%, within 15%, within 10%, or within 5%, of the specified dose, amount, or weight percent.

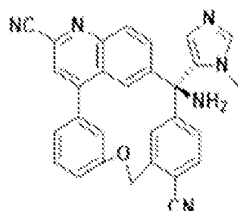
[0019] As used herein, Compound (I) has the structure shown below, which can be named “(S)-3-amino-3-(1-methyl-1H-imidazol-5-yl)-6-oxa-2(4,6)-quinolina-1,4(1,3)-dibenzenacyclohexaphane-2²,4⁴-dicarbonitrile.”



Compound (I)

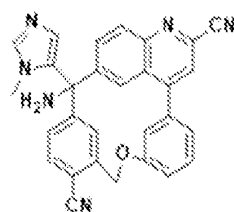
Compound (I) may be prepared as described in PCT Intl. Pat. Appl. No. PCT/US2022/80565, filed November 29, 2022.

[0020] As used herein, Compound (II) has the structure shown below, which can be named “(*R*)-3-amino-3-(1-methyl-1*H*-imidazol-5-yl)-6-oxa-2(4,6)-quinolina-1,4(1,3)-dibenzenacyclohexaphane-2²,4⁴-dicarbonitrile.”



Compound (II)

[0021] As used herein, Compound (III) has the structure shown below, which can be named “3-amino-3-(1-methyl-1*H*-imidazol-5-yl)-6-oxa-2(4,6)-quinolina-1,4(1,3)-dibenzenacyclohexaphane-2²,4⁴-dicarbonitrile.”



Compound (III)

[0022] As used herein, the term “first-line therapy” refers to therapies for treating SCC or HNSCC that include the use of a platinum-based doublet chemotherapy (e.g., cisplatin or carboplatin, such as cisplatin/5-FU or carboplatin/paclitaxel), optionally in combination with anti-EGFR antibody therapy (e.g., cetuximab, panitumumab, afatinib). In some embodiments, the first-line therapy includes pembrolizumab monotherapy or pembrolizumab in combination with platinum-based doublet chemotherapy. In some embodiments, the first-line therapy is in the context of a patient having R/M HNSCC or an HNSCC patient only having received a localized or loco-regional disease therapy. First-line therapy of a R/M SCC or HNSCC patient is the first time a patient is treated after recurrence or diagnosis of metastatic disease. (See Haddad, J. Natl. Compr. Canc. Netw., 18(7.5):982–984 (2020); <https://doi.org/10.6004/jnccn.2020.5009> (“Haddad (2020)”); and Borcoman et al., Cancers 13, 2573 (2021), <https://doi.org/10.3390/cancers13112573> (“Borcoman (2021)”).

[0023] As used herein, the term “second-line therapy” refers to therapies for treating SCC or HNSCC in a patient having R/M SCC or HNSCC, or for treating SCC or HNSCC wherein at

least one prior treatment has failed to mitigate or reduce the severity of at least one symptom associated with the SCC or HNSCC in the patient. For example, a second-line therapy can include the use of a taxane, methotrexate, and/or cetuximab. Second-line therapy of a R/M SCC or HNSCC patient is treatment of the patient after they have progressed on or after their first-line treatment. (*See* Haddad (2020) and Borcoman (2021).)

[0024] As used herein, the term “anti-EGFR antibody therapy” refers to therapies for treating HNSCC that include cetuximab (a chimeric IgG1) or panitumumab used as a single agent, used with chemotherapy (e.g. platinum/5-FU, cisplatin; see EXTREME study NCT00122460), or used with radiation therapy. (*See* Haddad (2020) and Borcoman (2021).)

[0025] As used herein, the term “immunotherapy” refers to therapies for treating SCC or HNSCC that include the use of anti-PD1 or anti-PDL1 antibodies. (*See* Haddad (2020) and Borcoman (2021).)

[0026] As used herein, the terms “localized regional disease therapy,” “loco-regional disease therapy,” “localized regional disease therapies” or “loco-regional disease therapies” refer to therapies for treating HNSCC that include the use of surgery, radiation, chemoradiation, or induction chemotherapy, or combinations thereof. (*See* Haddad (2020) and Borcoman (2021).)

[0027] The term “isomer” as used herein comprises a stereoisomer or tautomer as defined herein. As used herein, the term “stereoisomers” is understood to mean isomers that differ only in the way the atoms are arranged in space. As used herein, the term “isomer” includes any and all geometric isomers and stereoisomers. For example, “isomers” include geometric double bond *cis*- and *trans*-isomers, also termed *E*- and *Z*- isomers; *R*- and *S*-enantiomers; diastereomers, (*d*)-isomers and (*l*)-isomers, racemic mixtures thereof, and other mixtures thereof, as falling within the scope of this disclosure.

[0028] The term “isotopologue” refers to isotopically-enriched compounds that are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. Examples of isotopes that can be incorporated into compounds described herein include isotopes of hydrogen or carbon, such as ²H (deuterium) or ¹⁴C, respectively, each of which is also within the scope of this description. When the compounds are enriched with deuterium, the deuterium-to-hydrogen

ratio on the deuterated atoms of the molecule substantially exceeds the naturally occurring deuterium-to-hydrogen ratio.

[0029] An embodiment described herein may include an isotopologue form of Compound (I), (II), or (III), or a pharmaceutically acceptable form thereof, wherein the isotopologue is substituted on one or more atom members of said compound, or a pharmaceutically acceptable form thereof, with one or more deuterium atoms in place of one or more hydrogen atoms. An embodiment described herein may include Compound (I), (II), or (III), or a pharmaceutically acceptable form thereof, wherein a carbon atom may have from 1 to 3 hydrogen atoms optionally replaced with deuterium.

[0030] As used herein, a “pharmaceutically acceptable form” of compounds disclosed herein includes, but is not limited to, a pharmaceutically acceptable salt, solvate, isomer, and isotopologue (*i.e.*, isotopically labeled derivative) of compounds disclosed herein. In some embodiments, a “pharmaceutically acceptable form” includes, but is not limited to, a pharmaceutically acceptable salt, solvate, isomer (*e.g.*, tautomer or stereoisomer), and isotopologue (*i.e.*, isotopically labeled derivative) of Compound (I), (II), or (III), as disclosed herein.

[0031] In certain embodiments, the pharmaceutically acceptable form is a pharmaceutically acceptable salt. As used herein, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of subjects without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, *Remington's Pharmaceutical Sciences*, 18th eds., Mack Publishing, Easton PA (1990) or *Remington: The Science and Practice of Pharmacy*, 19th eds., Mack Publishing, Easton PA (1995). Pharmaceutically acceptable salts of the compounds provided herein include those derived from suitable inorganic and organic acids and bases, such as suitable inorganic and organic addition acids and bases.

[0032] In certain embodiments, the pharmaceutically acceptable form of the compounds disclosed herein is exclusive of a salt form (*i.e.*, is not a salt), sometimes referred to as a free base form, of the compounds disclosed herein. For example, in one embodiment, the pharmaceutically acceptable form of Compound (I), (II), or (III), as disclosed herein, is exclusive of a salt form and includes a pharmaceutically acceptable solvate, isomer, or isotopologue (*i.e.*,

isotopically labeled derivative) of Compound (I), (II), or (III), as disclosed herein. In some embodiments, the pharmaceutically acceptable form is a salt form and a solvate Compound (I), (II), or (III), as disclosed herein.

[0033] As used herein, the term “pharmaceutically acceptable carrier, diluent, or excipient” means a carrier, diluent, or excipient approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term “carrier” refers to a diluent, adjuvant (*e.g.*, Freund’s adjuvant (complete and incomplete)), excipient, or vehicle with which a therapeutic agent is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water is a specific carrier for intravenously administered pharmaceutical compositions. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. For example, the term pharmaceutically acceptable carrier, diluent, or excipient includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions as disclosed herein is contemplated. Supplementary active ingredients can also be incorporated into the pharmaceutical compositions. Examples of excipients that can be used in oral dosage forms provided herein include, but are not limited to, binders, fillers, disintegrants, and lubricants.

[0034] In certain embodiments, the pharmaceutically acceptable form is a solvate (*e.g.*, a hydrate). As used herein, the term “solvate” refers to compounds that further include a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. The solvate can be of a disclosed compound or a pharmaceutically acceptable salt thereof. Where the solvent is water, the solvate is a “hydrate”. In some embodiments, the solvate is a hydrate. Pharmaceutically acceptable solvates and hydrates are complexes that, for example, can include 0.1, 0.25, 0.50, 0.75, or 1 solvent or water molecules, or can include 1 to about 100, or 1 to about 10, or one to about 2, about 3 or about 4, solvent or water molecules. It will be understood that the term “compound” as used herein encompasses the compound and

solvates of the compound, as well as mixtures thereof.

[0035] As used herein and unless otherwise indicated, the term “stereoisomer” or “stereoisomerically pure” means one stereoisomer of a compound that is substantially free of other stereoisomers of that compound. For example, a stereoisomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the compound. For example, stereoisomerically pure Compound (I) (*i.e.*, (*S*)-3-amino-3-(1-methyl-1*H*-imidazol-5-yl)-6-oxa-2(4,6)-quinolina-1,4(1,3)-dibenzenacyclohexaphane-2²,4⁴-dicarbonitrile, or Compound (*S*-1)), substantially free of Compound (II) (*i.e.*, (*R*)-3-amino-3-(1-methyl-1*H*-imidazol-5-yl)-6-oxa-2(4,6)-quinolina-1,4(1,3)-dibenzenacyclohexaphane-2²,4⁴-dicarbonitrile, or Compound (*R*-2)). A stereoisomerically pure compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereoisomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. The compounds can have chiral centers and can occur as racemates, individual enantiomers or diastereomers, and mixtures thereof. All such isomeric forms are included within the embodiments provided herein, including mixtures thereof.

[0036] The use of stereoisomerically pure forms of such compounds, as well as the use of mixtures of those forms, are encompassed by the embodiments provided herein. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular compound may be used in methods and compositions provided herein. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. *See, e.g.*, Jacques, J., *et al.*, (Wiley-Interscience, New York, 1981); Wilen, S. H., *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972); Todd, M., *Separation Of Enantiomers : Synthetic Methods* (Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2014); Toda, F., *Enantiomer Separation: Fundamentals and Practical Methods* (Springer Science & Business

Media, 2007); Subramanian, G. *Chiral Separation Techniques: A Practical Approach* (John Wiley & Sons, 2008); Ahuja, S., *Chiral Separation Methods for Pharmaceutical and Biotechnological Products* (John Wiley & Sons, 2011).

[0037] In certain embodiments, the pharmaceutically acceptable form is a tautomer. As used herein, the term “tautomer” is a type of isomer that includes two or more interconvertible compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency. “Tautomerization” includes prototropic or proton-shift tautomerization, which is considered a subset of acid base chemistry. “Prototropic tautomerization” or “proton-shift tautomerization” involves the migration of a proton accompanied by changes in bond order. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Where tautomerization is possible (e.g., in solution), a chemical equilibrium of tautomers can be reached. Tautomerizations (i.e., the reaction providing a tautomeric pair) can be catalyzed by acid or base, or can occur without the action or presence of an external agent. The concentrations of the isomeric forms will depend on the environment the compound is found in and may be different depending upon, for example, whether the compound is a solid or is in an organic or aqueous solution. Exemplary tautomerizations include, but are not limited to, keto-enol; amide-imide; lactam-lactim; enamine-imine; and enamine-(a different) enamine tautomerizations.

[0038] It should be noted that if there is a discrepancy between a depicted structure and a name for that structure, the depicted structure is to be accorded more weight.

[0039] As used herein and unless otherwise indicated, the term “therapeutically effective amount” or “effective amount” in connection with a compound means an amount capable of treating a disorder, disease, or condition, or symptoms thereof, or otherwise achieving the desired therapeutic or mechanistic effect, such as mitigating, preventing emergence of, or delaying emergence of drug resistance.

[0040] As used herein and unless otherwise indicated, the term “subject” to which administration is contemplated, can be an animal, including, but not limited to, a human (e.g., a male or female of any age group, such as an adult subject or an adolescent subject); primates (e.g., cynomolgus monkeys, rhesus monkeys), and/or other mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, dogs, rabbits, rodents, and/or birds. In some embodiments, the subject is a mammal. In some embodiments, the subject is a

human. In some embodiments, the subject is an adolescent human. In some embodiments, the subject is an adult human. In some embodiments wherein the subject is a human, the subject is a smoker. In some embodiments, the subject is a non-smoker. In some embodiments, the subject is a non-smoker who had previously been a smoker.

[0041] In some embodiments, the subject is a human patient having SCC or HNSCC that has been previously treated with first-line therapy, such as platinum-based doublet therapy (e.g., cisplatin/5-FU or carboplatin/paclitaxel), optionally in combination with anti-EGFR antibody therapy (e.g., cetuximab, panitumumab, afatinib). In some embodiments, the subject is a human patient having SCC or HNSCC that has been previously treated with second-line therapy, such as a taxane, methotrexate, and/or cetuximab. In some embodiments, the subject is a human patient having SCC or HNSCC that has been previously treated with anti-EGFR antibody therapy, such as cetuximab or panitumumab used as a single agent, used with chemotherapy (e.g., platinum/5-FU, cisplatin), or used with radiation therapy. In some embodiments, the subject is a human patient having SCC or HNSCC that has been previously treated with immunotherapy, such as anti-PD1 or anti-PDL1 antibodies. In some embodiments, the subject is a human patient having SCC or HNSCC that has been previously treated with localized or loco-regional disease therapies, such as surgery, radiation, chemoradiation, or induction chemotherapy, or combinations thereof. In some embodiments, the subject is a human SCC or HNSCC patient that has R/M SCC or HNSCC. In some embodiments, the subject is a human SCC or HNSCC patient that has received at least one prior treatment. In some embodiments, the subject is a human SCC or HNSCC patient that has received at least one prior treatment, and the at least one prior treatment has failed to treat the SCC or HNSCC, has failed to delay, halt, or prevent progression of the SCC or HNSCC, or has failed to mitigate or reduce the severity of at least one symptom associated with the SCC or HNSCC. In some embodiments, the subject is a human patient having SCC or HNSCC that has received at least one prior treatment. In some embodiments, the at least one prior treatment is a first-line therapy. In some embodiments, the at least one prior treatment is a second-line therapy. In some embodiments, the at least one prior treatment is an anti-EGFR antibody therapy. In some embodiments, the at least one prior treatment is an immunotherapy. In some embodiments, the at least one prior treatment is a localized or loco-regional disease therapy.

[0042] In some embodiments, the SCC is HNSCC. In some embodiments, the HNSCC is

oral cavity, pharynx, larynx, tonsil, sinonasal, or nasopharyngeal HNSCC. In some embodiments, the SCC is esophageal, lung, thyroid, cervical, urothelial, bladder, vaginal, prostate, or head and neck SCC. In some embodiments, the SCC is cutaneous squamous cell carcinoma.

[0043] As used herein and unless otherwise indicated, the terms “treat,” “treating,” and “treatment,” are used interchangeably herein, and means an alleviation or amelioration, in whole or in part, of a disorder, disease or condition, such as SCC or HNSCC, or one or more of the symptoms associated with a disorder, disease, or condition, such as SCC or HNSCC, or slowing or halting of further progression or worsening of those symptoms, or alleviating or eradicating the cause(s) of the disorder, disease, or condition itself, such as SCC or HNSCC. In some embodiments, these terms refer to an approach for obtaining beneficial or desired results including, but not limited to, a therapeutic benefit or a prophylactic benefit. A therapeutic benefit resulting from the methods of treatment provided herein includes the eradication or amelioration of the underlying disorder, such as SCC or HNSCC, being treated, the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder (*e.g.*, HNSCC) such that an improvement is observed in the patient, notwithstanding that the patient can still be afflicted with the underlying disease or disorder (*e.g.*, HNSCC). For example, when used in reference to a patient having SCC or HNSCC, refers to an action that reduces the severity of the SCC or HNSCC, or retards or slows the progression of the SCC or HNSCC, including (a) inhibiting the SCC or HNSCC growth, or arresting development of the SCC or HNSCC, and (b) causing regression of the SCC or HNSCC, or delaying or minimizing one or more symptoms associated with the presence of the SCC or HNSCC.

[0044] As used herein, the terms “prevention” and “preventing” refer to an approach for obtaining beneficial or desired results including, but not limited, to prophylactic benefit. For prophylactic benefit, the compounds and pharmaceutical compositions disclosed herein can be administered to a patient at risk of developing SCC or HNSCC, to a patient reporting one or more of the physiological symptoms of SCC or HNSCC, even though a diagnosis of the SCC or HNSCC, may not have been made, or to a patient in remission from SCC or HNSCC. A prophylactic benefit resulting from the methods of treatment provided herein includes delaying or eliminating the appearance of a disease or disorder (*e.g.*, HNSCC), delaying or eliminating the onset of symptoms of a disease or disorder (*e.g.*, HNSCC), slowing, halting, or reversing the

progression of a disease or disorder (*e.g.*, HNSCC), or any combination thereof.

[0045] As used herein, the terms “mitigate” and “mitigating” with respect to resistance to a therapy includes slowing or delaying the time to drug resistance, preventing drug resistance from occurring, or reducing or overcoming drug resistance.

[0046] As used herein and unless otherwise indicated, the term “relapsed” refers to a disorder, disease, or condition that responded to treatment (*e.g.*, achieved a complete response) then had progression. The treatment can include one or more lines of therapy. For example, “relapsed” SCC or HNSCC may refer to SCC or HNSCC that has been previously treated with one or more lines of therapy. In one embodiment, the relapsed SCC or HNSCC is SCC or HNSCC that has been previously treated with one, two, three or four lines of therapy. In one embodiment, the relapsed SCC or HNSCC is SCC or HNSCC that has been previously treated with two or more lines of treatment.

[0047] As used herein and unless otherwise indicated, the term “refractory” refers to a disorder, disease, or condition that has not responded to prior treatment that can include one or more lines of therapy. In some embodiments, the disorder, disease, or condition has been previously treated one, two, three or four lines of therapy. In some embodiments, the disorder, disease, or condition has been previously treated with two or more lines of treatment, and has less than a complete response (CR) to most recent systemic therapy containing regimen. For example, the disorder, disease, or condition is SCC or HNSCC .

[0048] As used herein, the term “overexpression” refers to tumors that produce an elevated number of copies of a protein relative to a reference level. In some embodiments, the overexpressed protein is a wild-type protein. In some embodiments, the overexpressed protein is a mutant protein.

[0049] As used herein, the term “amplification” refers to tumors with an increase in the number of copies of a gene relative to a reference level. In some embodiments, the amplified gene is a wild-type gene. In some embodiments, the amplified gene is a mutant gene.

[0050] As used herein and unless otherwise indicated, the term “copy gain” refers to amplification of a gene between diploid ($n=2$) and the designated cutoff for “amplification” of the particular gene (for example, $n = 4, 5, \text{ or } 6$). For example, the designated cutoff for amplified HRAS gene may be $n = 4 \text{ or } 5 \text{ or } 6$, and thus copy gain of the HRAS gene would cover $n = 2$ up to $n = 4 \text{ or } 5 \text{ or } 6$, respectively.

[0051] As used herein and unless otherwise indicated, the terms “dysregulated PI3K” or “PI3K dysregulation” refer to an oncogenic alteration in the PI3K pathway in a tumor that renders the tumor dependent on PI3K. Such alterations include, but are not limited to, oncogenic PIK3CA mutations, oncogenic amplification of the PIK3CA gene, oncogenic copy gain of the PIK3CA gene, and loss of PTEN function, or combinations thereof. In some embodiments, PI3K-dysregulated SCC or HNSCC is PI3K-mutant and/or PI3K-amplified, or a combination thereof.

[0052] As used herein and unless otherwise indicated, the terms “dysregulated HRAS” or “HRAS dysregulation” refer to an oncogenic alteration in HRAS in a tumor that renders the tumor dependent on HRAS. Such alterations include, but are not limited to, an HRAS mutation, amplification, or overexpression, or any combination thereof. In some embodiments, HRAS-dysregulated SCC or HNSCC is HRAS-mutant, HRAS-amplified, or HRAS-overexpressed, or a combination thereof.

[0053] As used herein and unless otherwise indicated, the term “PIK3CA alteration” refers to a PI3K dysregulation comprising a modified PIK3CA gene, such as a mutated PIK3CA gene or an amplified PIK3CA gene, in a tumor.

[0054] As used herein and unless otherwise indicated, the term “HRAS alteration” refers to an HRAS dysregulation comprising a modified HRAS gene, such as an HRAS gene mutation, amplification, or overexpression.

[0055] As used herein and unless otherwise indicated, the term “copy gain” refers to amplification of a gene between diploid ($n = 2$) and the designated cutoff for “amplification” of the particular gene (for example, $n = 4$ or 5 or 6). For example, the designated cutoff for amplified PIK3CA gene may be $n = 4$ or 5 or 6 , and thus copy gain of the PIK3CA gene would cover $n = 2$ up to $n = 4$ or 5 or 6 , respectively. The designated cutoff for amplified HRAS gene may be determined in an analogous manner.

[0056] As used herein and unless otherwise indicated, the term “Duration of Response” or “DoR” is the time from achieving a response until relapse or disease progression. In some embodiments, DoR is the time from achieving a response $\geq$ partial response (PR) until relapse or disease progression. In some embodiments, DoR is the time from the first documentation of a response until the first documentation of progressive disease or death. In some embodiments, DoR is the time from the first documentation of a response $\geq$ partial response (PR) until to the

first documentation of progressive disease or death.

[0057] As used herein and unless otherwise indicated, the term “Event-Free Survival” or “EFS” means the time from treatment onset until any treatment failure, including disease progression, treatment discontinuation for any reason, or death.

[0058] As used herein and unless otherwise indicated, the term “Overall Response Rate” or “ORR” means the percentage of patients who achieve a response. In some embodiments, ORR means the sum of the percentage of patients who achieve complete and partial responses. In some embodiments, ORR means the percentage of patients whose best response $\geq$ partial response (PR).

[0059] As used herein and unless otherwise indicated, the term “Overall Survival” or “OS” means the time from treatment onset until death from any cause.

[0060] As used herein and unless otherwise indicated, the term “Progression Free Survival” or “PFS” means the time from treatment onset until tumor progression or death. In some embodiments, PFS means the time from the first dose of compound to the first occurrence of disease progression or death from any cause. In some embodiments, PFS rates are computed using the Kaplan-Meier estimates.

[0061] As used herein and unless otherwise indicated, the term “Time to Progression” or “TTP” means the time from treatment onset until tumor progression; TTP does not include deaths.

[0062] As used herein and unless otherwise indicated, the term “Time to Response” or “TTR” means the time from the first dose of compound to the first documentation of a response. In some embodiments, TTR means the time from the first dose of compound to the first documentation of a response $\geq$ partial response (PR).

[0063] As used herein, the terms “HRAS immunohistochemistry assay,” “HRAS immunohistochemistry (IHC) assay,” or “HRAS IHC assay,” refer to a method of determining HRas protein expression level intensity and cellular location in a tumor tissue using IHC and an HRAS antibody. In certain embodiments, the HRAS IHC assay uses an antibody, such as a monoclonal antibody, to detect HRAS expression in a tumor tissue sample collected from a subject having or suspected of having SCC or HNSCC. In certain embodiments, the HRAS IHC assay can detect HRAS expression, such as HRAS overexpression, at a plasma membrane of a cell within a tumor tissue sample. In certain embodiments, the HRAS IHC assay can detect

HRAS expression, such as HRAS overexpression, in the cytoplasm of a cell within a tumor tissue sample. In certain embodiments, the HRas protein detected is wild-type HRas protein. In certain embodiments, the tumor tissue sample is an SCC or HNSCC tissue sample, such as from a subject having or suspected of having SCC or HNSCC. An exemplary IHC assay is described in U.S. Provisional Application No. 63/479,683.

[0064] In certain embodiments, the HRAS IHC assay can be performed to screen SCC or HNSCC tumors for HRAS expression levels, and in particular, to determine if a patient has an HRAS-overexpressing SCC or HNSCC. In some examples, the HRAS IHC assay is performed on a paraffin-embedded tumor tissue sample collected from a subject having or suspected of having SCC or HNSCC. Tumor tissue samples are subjected to an immunohistochemistry method using an antibody, such as a monoclonal antibody, that has binding affinity for human HRAS in the tissue sample. Any method known in the art can be used to detect the monoclonal antibody bound to HRAS in the tumor tissue sample. In some examples, a dual link system can be used that detects the monoclonal antibody and generates a chemical reaction which can be visualized after incubation of the tissue in a chromogen solution containing 3,3'-diaminobenzidine (DAB). Optionally, the tumor tissue can be stained with hemotoxin and eosin (H&E) after performing the HRAS IHC assay. Staining the tumor tissue sample with H&E may be useful in assisting the viewer (e.g., a pathologist) in assessing HRas protein expression.

[0065] In certain embodiments, the HRAS IHC assay can include scoring for HRAS expression. Scoring for HRAS expression includes assessing the number of tumor cells having HRAS staining (i.e., HRas protein expression). HRAS staining is recorded at a corresponding differential intensity on a four-point semi-quantitative scale (0, 1+, 2+, 3+). On this scale: 0= null, negative or non-specific staining, 1+= low or weak staining, 2+= medium or moderate staining, and 3+= high or strong staining. Percentages of cells having the differential intensities of HRAS expression can be used to determine Percent Scores and H-Scores. H-Scores are calculated by summing the percentage of cells with intensity of expression (positive staining) multiplied by their corresponding differential intensity on a four-point semi-quantitative scale (0, 1+, 2+, 3+). Thus, H-scores range from 0 to 300. Percent Scores are calculated by summing the percentages of intensities at either $\geq 1+$, $\geq 2+$ or $\geq 3+$. Thus, percent scores range from 0 to 100. In some aspects, Plasma Membrane Percent Scores can be determined by summing the percentages of tumor cells having plasma membrane HRAS staining intensities at either $\geq 1+$,

$\geq 2+$ or $\geq 3+$. In other aspects, Cytoplasmic Percent Scores can be determined by summing the percentages of tumor cells having cytoplasm HRAS staining intensities at either $\geq 1+$, $\geq 2+$ or $\geq 3+$.

[0066] In some embodiments, the HRAS IHC assays can be used to determine if an SCC or HNSCC is an HRAS-overexpressing SCC or HNSCC. In some embodiments, an SCC or HNSCC is determined to be an HRAS-overexpressing SCC or HNSCC when 50% or more of the stained cells in a tissue sample from the SCC have a Plasma Membrane Percent Score of $\geq 3+$. In some embodiments, an SCC or HNSCC is determined to be an HRAS-overexpressing SCC or HNSCC when 50% or more of the stained cells in a tissue sample have a Cytoplasmic Percent Score of $\geq 3+$, according to the HRAS IHC assay.

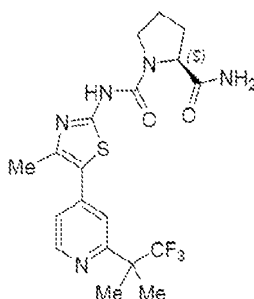
6.1 COMPOUNDS

[0067] In some embodiments, the methods provided herein include administering (a) Compound (I), or an enantiomer, mixture of enantiomers, or racemate thereof (e.g., Compound (II) or Compound (III)), or a pharmaceutically acceptable form thereof, and optionally (b) a phosphatidylinositol-3-kinase (PI3K) inhibitor (such as alpelisib) to a subject. In some embodiments, the methods provided herein comprise administering Compound (I), or pharmaceutically acceptable salt or solvate thereof. In some embodiments, the methods comprise administering a mixture of from 1000:1 to 51:49 of Compound (I) and Compound (II), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the methods comprise administering Compound (III) or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the PI3K inhibitor is a PI3K α inhibitor. In some embodiments, the PI3K inhibitor is alpelisib.

[0068] The preparations of Compound (I), (II), or (III), as provided herein, are described in PCT International Application No. PCT/US2022/80565.

[0069] In some embodiments, the PI3K inhibitor is selected from the group comprising, but is not limited to, alpelisib (PIQRAY®; BYL719), AMG319, AZD8168, AZD8835, buparlisib, B591, CH5132799, copanlisib (aliqopa), delalisib (zydelig), duvelisib (copiktra), eganelisib, GSK2636771, leniolisib, linperlisib, parsaclisib, pictilisib, pilaralisib, RIDR-PI-103, serabelisib, sonolisib, taselisib, tenalisib, TG-100-115, umbralisib, zandelisib, ZSTK474, STX-478, RLY-2608, LOXO-783, or inavolisib, or a pharmaceutically acceptable form thereof. In some embodiments, the PI3K inhibitor, for example, a PI3K α inhibitor, used in the methods provided

herein has the structure shown below, which can be named as (2*S*)-*N*¹-[4-Methyl-5-[2-(2,2,2-trifluoro-1,1-dimethylethyl)-4-pyridinyl]-2-thiazolyl]-1,2-pyrrolidinedicarboxamide (or alternatively, as alpelisib, PIQRAY®, or BYL719).



Alpelisib

6.2 PHARMACEUTICAL COMPOSITIONS, KITS, AND PACKAGING

[0070] In some embodiments, provided herein is a pharmaceutical composition comprising Compound (I), or a pharmaceutically acceptable form thereof, and a pharmaceutically acceptable carrier, diluent, or excipient. In some embodiments, the pharmaceutical composition comprises Compound (I) or a pharmaceutically acceptable salt or solvate thereof.

[0071] In some embodiments, provided herein is a pharmaceutical composition comprising a PIK3 inhibitor, such as alpelisib, and a pharmaceutically acceptable carrier, diluent, or excipient.

[0072] In some embodiments, provided herein is a pharmaceutical composition comprising Compound (I), or a pharmaceutically acceptable form thereof, and a PI3K inhibitor, such as alpelisib, and a pharmaceutically acceptable carrier, diluent, or excipient.

[0073] In some embodiments, the pharmaceutical composition comprises 0.5-1000 mg of Compound (I), or a pharmaceutically acceptable form thereof, such as an amount selected from 0.5-2.5 mg, 0.5-5 mg, 0.5-10 mg, 0.5-25 mg, 0.5-50 mg, 0.5-75 mg, 0.5-100 mg, 0.5-200 mg, 0.5-250 mg, 0.5-300 mg, 0.5-600 mg, 0.5-900 mg, 1-5 mg, 1-10 mg, 1-25 mg, 1-50 mg, 1-75 mg, 1-100 mg, 1-300 mg, 1-600 mg, 1-900 mg, 20-100 mg, 20-200 mg, 20-250 mg, 20-300 mg, 40-75 mg, 50-75 mg, 50-100 mg, 50-150 mg, 50-200 mg, 50-250 mg, 50-300 mg, 75-100 mg, 100-200 mg, 125-200 mg, 150-300 mg, 200-250 mg, 200-400 mg, 300-600 mg, 250-500 mg, 400-600 mg, 500-750 mg, 600-900 mg, 700-100 mg, 650-1000 mg, and 800-1000 mg of Compound (I), or a pharmaceutically acceptable form thereof. In some embodiments, the pharmaceutical composition comprises an amount selected from about 0.5 mg, about 1 mg, about 1.5 mg, about 1.6 mg, about 1.7 mg, about 1.8 mg, about 1.9 mg, about 2 mg, about 2.5 mg, about 3 mg, about

4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, and about 1000 mg of Compound (I), or pharmaceutically acceptable form thereof. In some embodiments, the pharmaceutical composition comprising Compound (I), or a pharmaceutically acceptable form thereof, is formulated in a tablet, such as a film-coated tablet. In some embodiments, the pharmaceutical composition comprising Compound (I), or a pharmaceutically acceptable form thereof, is formulated in a capsule.

[0074] In some embodiments, the pharmaceutical composition comprises 10-400 mg of alpelisib, such as an amount selected from 10-300 mg, 10-200 mg, 10-150 mg, 10-100 mg, 10-50 mg, 25-400 mg, 25-300 mg, 25-200 mg, 25-150 mg, 25-100 mg, 25-50 mg, 50-400 mg, 50-300 mg, 50-200 mg, 50-150 mg, 50-100 mg, 100-400 mg, 100-300 mg, 100-200 mg, 150-250 mg, 175-225 mg, 200-400 mg, and 200-300 mg of alpelisib. In some embodiments, the pharmaceutical composition comprises about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 260 mg, about 270 mg, about 275 mg, about 280 mg, about 290 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, or about 400 mg of alpelisib.

[0075] In some embodiments, the pharmaceutical composition comprises about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, or about 300 mg of alpelisib. In some embodiments, the pharmaceutical composition comprises about 50 mg, about 150 mg, or

about 200 mg of alpelisib. In some embodiments, the pharmaceutical composition comprises about 50 mg of alpelisib. In some embodiments, the pharmaceutical composition comprises about 150 mg of alpelisib. In some embodiments, the pharmaceutical composition comprises about 200 mg of alpelisib.

[0076] In some embodiments, the pharmaceutical composition comprising the alpelisib is formulated in a tablet, such as a film-coated tablet. In some embodiments, the pharmaceutical composition comprising the alpelisib is formulated in a capsule. In some embodiments, the pharmaceutical composition comprising the alpelisib further comprises an excipient. In some embodiments, the excipient is selected from the group consisting of hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, and sodium starch glycolate. In some embodiments, the pharmaceutical composition comprising the alpelisib is formulated in a tablet. In some embodiments, the tablet comprises a coating. In some embodiments, the coating comprises hypromellose, iron oxide black, iron oxide red, macrogol/polyethylene glycol (PEG) 4000, talc, and titanium dioxide.

[0077] In some embodiments, the pharmaceutical compositions are provided for administration to a subject in unit dosage forms, such as tablets, capsules, microcapsules, pills, powders, granules, troches, suppositories, injections, syrups, patches, creams, lotions, ointments, gels, sprays, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable salts thereof. In some embodiments, the pharmaceutical compositions provided herein are in the form of a tablet. In some embodiments, the pharmaceutical compositions provided herein are in the form of a capsule. In some embodiments, the capsules contain a compound provided herein without an additional carrier, excipient or vehicle. Typically the compound disclosed herein is formulated into pharmaceutical compositions using techniques and procedures well known in the art (see, *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Twelfth Edition 2021). In some embodiments, the pharmaceutical compositions are formulated and administered in unit dosage forms or multiple dosage forms. Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. Unit dose forms as used herein refer to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit dose contains a predetermined quantity of the therapeutically active compound

sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit dose forms include ampules and syringes and individually packaged tablets or capsules. Unit dose forms may be administered in fractions or multiples thereof. A multiple dose form is a plurality of identical unit dosage forms packaged in a single container to be administered in segregated unit dose form. Examples of multiple dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit doses which are not segregated in packaging.

[0078] The pharmaceutical compositions provided herein may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens may be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the pharmaceutical compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed pharmaceutical compositions.

[0079] The pharmaceutical compositions are intended to be administered by a suitable route, including but not limited to orally, parenterally, rectally, topically and locally. For oral administration, capsules and tablets can be formulated. The pharmaceutical compositions are in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration. In one embodiment, when administered orally, a compound provided herein is administered with a meal and water. In another embodiment, the compound provided herein is dispersed in water or juice (*e.g.*, apple juice or orange juice) and administered orally as a solution or a suspension. In one embodiment, a compound provided herein is administered when the subject is fed. In one embodiment, a compound provided herein is administered when the subject is fed with high-fat and/or high-calorie food. In one embodiment, a compound provided herein is administered when the subject is fed with FDA-standard high-fat high-calorie breakfast. In one embodiment, a compound provided herein is administered when the subject is fasted. In one embodiment, a compound provided herein is administered after the subject has an at least 8-

hour overnight fast. In one embodiment, a compound provided herein is administered with or without food.

[0080] The pharmaceutical compositions provided herein can also be administered intradermally, intramuscularly, intraperitoneally, percutaneously, intravenously, subcutaneously, intranasally, epidurally, sublingually, intracerebrally, intravaginally, transdermally, rectally, mucosally, by inhalation, or topically to the ears, nose, eyes, or skin. In some embodiments, the pharmaceutical compositions provided herein are administered orally.

[0081] In some embodiments, the pharmaceutical compositions provided herein can be delayed or prolonged by proper formulation. For example, a slowly soluble pellet of the compound provided herein can be prepared and incorporated in a tablet or capsule, or as a slow-release implantable device. The technique also includes making pellets of several different dissolution rates and filling capsules with a mixture of the pellets. Tablets or capsules can be coated with a film that resists dissolution for a predictable period of time. Parenteral preparations can be made long-acting, by dissolving or suspending the compound provided herein in oily or emulsified vehicles that allow it to disperse slowly in the serum.

[0082] In some embodiments, provided herein is a pharmaceutical kit comprising (a) Compound (I), or a pharmaceutically acceptable form thereof, and (b) a PI3K inhibitor, such as alpelisib. In some embodiments, provided herein is a pharmaceutical kit comprising (a) a pharmaceutical composition comprising Compound (I), or a pharmaceutically acceptable form thereof, and a pharmaceutically acceptable carrier, diluent, or excipient, and (b) a pharmaceutical composition comprising a PI3K inhibitor, such as alpelisib, and a pharmaceutically acceptable carrier, diluent, or excipient. In some embodiments, the pharmaceutical kit further comprises instructions that detail a dosing regimen for administering Compound (I), or a pharmaceutically acceptable form thereof, and for administering the PI3K inhibitor, such as alpelisib, for one or more cycles. In some embodiments, the pharmaceutical kit comprises a color-coded system that details a dosing regimen for administering Compound (I), or a pharmaceutically acceptable form thereof, and administering the PI3K inhibitor, such as alpelisib, for one or more cycles. In some embodiments, the pharmaceutical kit is a pharmaceutical packaging.

[0083] In some embodiments, the pharmaceutical kit or the pharmaceutical packaging comprises instructions for administering the contents of the kit to a subject having SCC, such as HNSCC. For example, in some embodiments, the instructions may be color-coded with one

color indicating the dosing regimen for administering Compound (I), or a pharmaceutically acceptable form thereof, during a treatment cycle, such as a 28-day treating cycle, such as administering once or twice per day on days 1-7, on days 1-7 and 15-21, on days 1-21, or on each day of a 28-day treatment cycle, while indicating with a different color the dosing regimen for administering the PI3K inhibitor, such as alpelisib, during a treatment cycle, such as a 28-day treating cycle, for example, administering the alpelisib once or twice per day on each day of a 28-day treatment cycle, such as administering the alpelisib once per day on each day of a 28-day treatment cycle. For example, in some embodiments, the instructions may be color-coded detailing an escalation dosing period, a reduction dosing period, or a loading dosing cycle, for administering Compound (I), or pharmaceutically acceptable form thereof. For example, in some embodiments, the instructions may be color-coded detailing an escalation dosing period or reduction dosing period for administering the PI3K inhibitor, such as alpelisib.

6.3 METHODS, DOSING REGIMENS AND SCHEDULES

6.3.1 THERAPEUTIC USES AND METHODS

[0084] In some embodiments, provided herein is a method of treating SCC, such as HNSCC, in a subject, comprising administering to the subject (a) Compound (I), or a pharmaceutically acceptable form thereof, and (b) a PI3K inhibitor, such as alpelisib. In some embodiments, the method of treating comprises administering to the subject (a) a therapeutically effective amount of Compound (I), or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of a PI3K inhibitor, such as alpelisib. In some embodiments, the method of treating provided herein comprises administering to the subject (a) a pharmaceutical composition comprising a therapeutically effective amount of Compound (I), or a pharmaceutically acceptable form thereof, and a pharmaceutically acceptable carrier, diluent, or excipient, and (b) a therapeutically effective amount of a PI3K inhibitor, such as alpelisib, and a pharmaceutically acceptable carrier, diluent, or excipient. In some embodiments, the PI3K inhibitor is an PI3K α inhibitor. In some embodiments, the PI3K α inhibitor is alpelisib. In some embodiments, Compound (I), or pharmaceutically acceptable form thereof, is administered before, after, or simultaneously with the PI3K inhibitor, such as alpelisib, optionally during one or more treatment cycles, such as one or more 28-day cycles.

[0085] In some embodiments, the method of treating mitigates PI3K inhibitor (e.g., alpelisib) resistance. In some embodiments, the subject was previously treated with the PI3K inhibitor or

alpelisib, and may be relapsed or refractory to such treatment. In some embodiments, the subject was not previously treated with a PI3K inhibitor- or alpelisib (e.g., alpelisib-naïve).

[0086] In some embodiments, the method of treating mitigates EGFR inhibitor (e.g., cetuximab) resistance. In some embodiments, the method of treating further comprises administering to the subject an EGFR inhibitor or cetuximab. In some embodiments, the subject was previously treated with the EGFR inhibitor or cetuximab, and may be relapsed or refractory to such treatment. In some embodiments, the subject was not previously treated with the EGFR inhibitor or cetuximab (e.g., cetuximab-naïve).

[0087] In another aspect is a method of mitigating PI3K inhibitor (such as alpelisib) resistance in an SCC or HNSCC in a subject, comprising administering to the subject (a) Compound (I), or a pharmaceutically acceptable form thereof (or a pharmaceutical composition comprising the same), and (b) a PI3K inhibitor, such as alpelisib (or a pharmaceutical composition comprising the same). In some embodiments, a therapeutically effective amount of each agent or pharmaceutical composition is administered. In some embodiments, the subject was previously treated with the PI3K inhibitor or alpelisib, and may be relapsed or refractory to such treatment. In some embodiments, the subject was not previously treated with a PI3K inhibitor- or alpelisib (e.g., alpelisib-naïve). In some embodiments, the method comprises administering the two agents during one or more cycles, such as one or more 28-day cycles.

[0088] In some embodiments is a method of mitigating EGFR inhibitor (e.g., cetuximab) resistance in an SCC or HNSCC in a subject, comprising administering to the subject (a) Compound (I), or a pharmaceutically acceptable form thereof (or a pharmaceutical composition comprising the same), and (b) a PI3K inhibitor, for example, a PI3K α inhibitor, such as alpelisib (or a pharmaceutical composition comprising the same). In some embodiments, the method also comprises administering to the subject an EGFR inhibitor, e.g., cetuximab. In some embodiments, the subject was previously treated with the EGFR inhibitor or cetuximab, and may be relapsed or refractory to such treatment. In some embodiments, the subject was not previously treated with the EGFR inhibitor or cetuximab (e.g., cetuximab-naïve). In some embodiments, the method comprises administering the agents during one or more cycles, such as one or more 28-day cycles.

[0089] In some embodiments, provided herein is a method of treating PI3K-dysregulated SCC or HNSCC in a subject comprising administering to the subject Compound (I), or a

pharmaceutically acceptable form thereof. In some embodiments, provided herein is a method of treating PI3K-dysregulated SCC or HNSCC in a subject comprising administering to the subject (a) Compound (I), or a pharmaceutically acceptable form thereof, and (b) a PI3K inhibitor, such as alpelisib. In some embodiments, the method of treating comprises administering to the subject (a) a therapeutically effective amount of Compound (I), or a pharmaceutically acceptable form thereof, and (b) a therapeutically effective amount of a PI3K inhibitor, such as alpelisib. In some embodiments, the PI3K-dysregulated SCC or HNSCC is PIK3CA-mutant, PIK3CA-amplified, or PIK3CA-overexpressed, or a combination thereof. In some embodiments, the PI3K-dysregulated SCC or HNSCC is PI3KCA-mutant. In some embodiments, the PI3K-dysregulated SCC or HNSCC is HRAS-dependent (HRAS-mutant, HRAS-amplified, or HRAS-overexpressed, or a combination thereof; particularly, HRAS-mutant or HRAS-overexpressed). In some embodiments, the PI3K-dysregulated SCC or HNSCC is HRAS wild-type (not HRAS-mutant, HRAS-amplified, or HRAS-overexpressed).

[0090] In some embodiments, the subject has symptoms associated with SCC or HNSCC. In some embodiments, the subject is diagnosed as having SCC or HNSCC. In some embodiments, the subject may be diagnosed by one skilled in the art, for example, by analysis of plasma or a tissue biopsy, such as a tumor tissue biopsy, from the subject. In some embodiments, the SCC or HNSCC is in remission. In some embodiments, the SCC or HNSCC is early stage, metastatic, advanced, relapsed, refractory, or recurrent. In some embodiments, the SCC or HNSCC is early stage. In some embodiments, the SCC or HNSCC is metastatic or advanced. In some embodiments, the SCC or HNSCC is relapsed or refractory. In some embodiments, the SCC or HNSCC is recurrent and/or metastatic (R/M). In some embodiments, the SCC or HNSCC is human papillomavirus (HPV)-negative. In some embodiments, the SCC or HNSCC is a solid tumor. In some embodiments, the HNSCC is oral cavity, pharynx, larynx, tonsil, sinonasal, or nasopharyngeal HSNCC, or HNSCC of unknown primary origin. In some embodiments, the SCC is esophageal, lung, thyroid, cervical, urothelial, bladder, vaginal, prostate, or head and neck SCC. In some embodiments, the subject is a mammal, for example, a human, such as a human patient having HNSCC.

[0091] In some embodiments, the subject has an SCC or HNSCC that is associated with a farnesylation-dependent protein. For example, in some embodiments, the farnesylation-dependent protein associated with the SCC or HNSCC is an HRas protein, such as wild-type

HRas protein or an HRas protein having a mutation. For example, in some embodiments, the farnesylation-dependent protein associated with the SCC or HNSCC is a Rheb protein.

[0092] In some embodiments, the SCC or HNSCC is an HRAS-dependent SCC or an HRAS-dependent HNSCC, respectively. In some embodiments, the HRAS-dependent SCC or HNSCC overexpresses wild-type HRas protein and/or mutant HRas protein (i.e., HRAS-overexpressing). In some embodiments, the HRAS-dependent SCC or HNSCC comprises an HRAS gene amplification (i.e., HRAS-amplified). In some embodiments, the HRAS-dependent SCC or HNSCC comprises an HRAS mutation (i.e., HRAS-mutant). For example, in some embodiments, the HRAS-mutant SCC or HNSCC comprises a modification in a codon that encodes an amino acid substitution at a specific position selected from G12, G13, Q61, Q22, K117, A146, and any combination thereof, in the corresponding mutant HRas protein. For example, in some embodiments, the HRAS-mutant SCC or HNSCC comprises two or more, or three or more, modifications in a codon that encodes an amino acid substitution at a specific position selected from G12, G13, Q61, Q22, K117, A146, and any combination thereof, in the corresponding mutant HRas protein. In some embodiments, the *HRAS* gene mutation is a mutation at a codon that encodes an amino acid substitution at a position of G12 in the mutant H-Ras protein, optionally a G12C, G12D, G12A, G12V, G12S, G12F, G12R, or G12N substitution in the mutant H-Ras protein. In some embodiments, the *HRAS* gene mutation is a mutation at a codon that encodes an amino acid substitution at a position of G13 in the mutant H-Ras protein, optionally a G13A, G13C, G13V, G13D, G13R, G13S, G13N, or G13V substitution in the mutant H-Ras protein. In some embodiments, the *HRAS* gene mutation is a mutation at a codon that encodes an amino acid substitution at a position of Q61 in the mutant H-Ras protein, optionally a Q61E, Q61K, Q61H, Q61L, Q61P, or Q61R substitution in the mutant H-Ras protein. In some embodiments, the *HRAS* gene mutation is a mutation at a codon that encodes an amino acid substitution at a position of Q22 in the mutant H-Ras protein, optionally a Q22K or Q22T substitution in the mutant H-Ras protein. In some embodiments, the *HRAS* gene mutation is a mutation at a codon that encodes an amino acid substitution at a position of K117 in the mutant H-Ras protein, optionally a K117N or K117L substitution in the mutant H-Ras protein. In some embodiments, the *HRAS* gene mutation is a mutation at a codon that encodes an amino acid substitution at a position of A146 in the mutant H-Ras protein, optionally an A146V, A146T, or A146P substitution in the mutant H-Ras protein. In some embodiments, the mutation

can be a mutation at another codon that results in activation of H-Ras protein.

[0093] In some embodiments, the SCC or HNSCC is HRAS-mutant and HRAS-overexpressed. Without being bound by any one theory, in some embodiments, Compound (I), or a pharmaceutically acceptable form thereof, inhibits the farnesylation of a farnesylation-dependent protein, for example, a Rheb protein or a HRas protein, such as an HRas protein having a mutation, in a cell, such as in a cell of a subject. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell a human cell. In some embodiments, the inhibition of the farnesyltransferase present in the cell takes place in a subject suffering from SCC or HNSCC .

[0094] In some embodiments, the HNSCC is a PIK3CA-dependent SCC or HNSCC. In some embodiments, the PIK3CA-dependent SCC or HNSCC comprises a PIK3CA alteration or dysregulation, which is or comprises a PIK3CA mutation (PIK3CA-mutant), a PIK3CA gene amplification (PIK3CA-amplified), or a PIK3CA copy gain, or a PIK3CA overexpression (PIK3CA-overexpressed), or combinations thereof. In some embodiments, the SCC or HNSCC is PIK3CA-mutant. In some embodiments, the SCC or HNSCC is PIK3CA-amplified. In some embodiments, the SCC or HNSCC comprises a PIK3CA copy gain. In some embodiments, the PIK3CA-mutant SCC or HNSCC comprises a modification in a codon that encodes an amino acid substitution at a specific position selected from R38, E39, E78, R88, R93, E103, P104, V105, G106, R108, E109, E110, K111, G118, P124, E218, V344, N345, D350, G364, E365, P366, C378, C420, P447, P449, H450, G451, E453, P471, P539, E542, E545, Q546, D549, E579, E600, C604, S629, V638, C901, G914, D939, E970, M1004, G1007, Y1021, T1025, D1029, E1037, M1043, N1044, H1047, G1049, A1066, and N1068, and any combination thereof, in the corresponding mutant PI3K protein. In some embodiments, the PIK3CA-mutant SCC or HNSCC comprises a modification in a codon that encodes an amino acid substitution at a specific position selected from G118, C420, E542, E545, Q546, H1047, and any combination thereof, in the corresponding mutant PI3K protein. In some embodiments, the PIK3CA-mutant SCC or HNSCC has two or more, or three or more, PIK3CA mutations, wherein the PIK3CA mutations are or comprise a modification in a codon that encodes an amino acid substitution at a specific position selected from G118, C420, E542, E545, Q546, H1047, and any combination thereof, in the corresponding mutant PI3K protein. In some embodiments, the SCC or HNSCC comprises a mutant PI3K protein having an activating mutation, such as an activating mutation

in the helicase domain or the kinase domain. In some embodiments, SCC or HNSCC comprises a mutant PI3K protein having an activating mutation in the helicase domain, for example, in Exon 7 (e.g., C420R), or in Exon 9 (e.g., E542K, E545A, E545D, E545G, E545K, Q546E, or Q546R). In some embodiments, the SCC or HNSCC comprises a mutant PI3K protein having an activating mutation in the kinase domain, for example, in Exon 20 (e.g., H1047L, H1047R, or H1047Y).

[0095] Without being bound by any one theory, it is thought that the HRAS and PIK3CA cellular pathways are interdependent, such as they show codependency in SCC or HNSCC. There exists evidence that HRAS preferentially activates PI3K five-fold more efficiently than KRAS, while KRAS is a more efficient activator of Raf protein (Yan et al., J. Biol. Chem., 273: 24052-6 (1998)). Furthermore, mutant HRAS requires PI3K for activity, and is insufficient to be tumorigenic in isolation (Gupta et al., Cell, 129:957-68 (2007)). Similarly, mutant PI3K requires RAS in order to drive tumor biology (Zhao and Vogt, Oncogene, 27: 5486-96 (2008)).

[0096] In some embodiments, the PIK3CA-dependent SCC or HNSCC is further dependent or associated with a farnesylation-dependent protein. In some embodiments, the PIK3CA-dependent SCC or HNSCC is further dependent on HRAS or mutated HRAS. In some embodiments, the HRAS-dependent SCC or HNSCC is further dependent on PIK3CA. In some embodiments, the subject has an SCC or HNSCC that is dependent on HRAS and PIK3CA. In some embodiments, the HRAS-dependent and PIK3CA-dependent SCC or HNSCC overexpresses wild-type HRas protein. In some embodiments, the SCC or HNSCC is HRAS-mutant and PIK3CA-dependent. In some embodiments, the HRAS-dependent and PIK3CA-dependent SCC or HNSCC has a PIK3CA alteration or dysregulation. In some embodiments, the SCC or HNSCC is PIK3CA-mutant. In some embodiments, the SCC or HNSCC is PIK3CA-mutant and HRAS-overexpressing, and is optionally HRAS-mutant. In some embodiments, the SCC or HNSCC is HRAS-overexpressing and PIK3CA-amplified.

[0097] In some embodiments, the subject may be diagnosed as having an SCC or HNSCC that is associated with a farnesylation-dependent protein, an HRAS-dependent SCC or HNSCC, such as an HRAS-mutant, an HRAS-amplified, and/or an HRAS-overexpressed SCC or HNSCC, or a PIK3CA-dependent SCC or HNSCC, or combinations thereof, by detection methods known in the art. For example, in some embodiments, the subject may be diagnosed by common testing practices known in the art, such as by detection and/or analysis of plasma or a tissue biopsy with

detection and/or analysis of plasma or a tissue biopsy with Next Gene Sequence (NGS) testing of tumor tissue, real time quantitative reverse transcription polymerase chain reaction (qRT-PCR) or immunohistochemistry (IHC). In some embodiments, HRAS overexpression may be tested by IHC assay or RNA assay.

[0098] In some embodiments, the SCC or HNSCC has wild-type HRAS, for example, having high levels of HRAS (“HRAS^{WT-high}”), such as having overexpression of wild-type HRas protein (high wild-type HRas protein expression levels; “HRas^{WT-high}”) and having wild-type PIK3CA (PIK3CA^{WT}) expression levels, for example, as in a PDX model, such as in HN2594, HN3411, and/or HN2576 model.

[0099] In some embodiments, the SCC or HNSCC has wild-type HRAS (e.g., HRAS^{WT-high}), such as having overexpression of wild-type HRas protein (HRas^{WT-high}) and having amplified PIK3CA (PIK3CA^{AMP}), for examples, having amplified expression levels of the corresponding PI3K protein, such as amplified expression levels of wild-type PI3K protein, for example, as in a PDX model, such as in HN3067 model (HRAS^{WT-high} and PIK3CA^{AMP}).

[00100] In some embodiments, the SCC or HNSCC has wild-type HRAS (e.g., HRAS^{WT-high}), such as having overexpression of wild-type HRas protein (HRas^{WT-high}) and having mutated PIK3CA (PIK3CA^{mutant}), such as having expression of mutated PI3K protein, for example, as in a PDX model, such as in HN2593 (HRAS^{WT-high} and PIK3CA^{E545K}) and HN3690 (HRAS^{WT-high} and PIK3CA^{G118D}) models. For example, in some embodiments, the PIK3CA mutation is or comprises a modification in a codon of the mutant PIK3CA gene encoding an amino acid at the specified position selected from a group consisting of G118, C420, E542, E545, Q546, H1047, and any combination thereof, to provide the resulting mutated PI3K protein, such as a mutated PI3K- α protein. In some embodiments, the PIK3CA gene mutation is or comprises PIK3CA^{G118D}, PIK3CA^{E545K}, or a combination thereof. In some embodiments, the PIK3CA mutated protein is or comprises PI3K- α G118D, PI3K- α E545K, or a combination thereof.

[00101] In some embodiments, the methods disclosed herein of administering Compound (I), or pharmaceutically acceptable form thereof, and alpelisib, are effective in treating SCC or HNSCC having mutated HRAS and/or mutated HRas protein, for example, as in a PDX model, such as in HN1420 (HRAS A146 (mutated HRas protein A146T), PIK3CA WT), HN2581 (HRAS G13 (mutated HRas protein G13C), PIK3CA WT), HN2579 (HRAS G12 (mutated HRas protein G12S), PIK3CA WT), and HN3504 models (HRAS K117 (mutated HRas protein

K117L), PIK3CA H1047R (mutated PI3K protein H1047R).

[00102] In some embodiments, the methods disclosed herein of administering Compound (I), or pharmaceutically acceptable form thereof, and alpelisib, are effective in treating SCC or HNSCC having mutated HRas protein and having mutated PIK3CA expression levels as seen in PDX models, for example, in HN3504 model. In some embodiments, the HRas protein mutation is or comprises a modification in a codon of the mutant HRAS gene encoding an amino acid at the specified position to provide the resulting mutated HRas protein comprising or consisting of HRAS G12S, HRAS G13C, HRAS K117L, HRAS A146T, or a combination thereof. In some embodiments, the PI3KCA mutation is or comprises PIK3CA H1047R protein mutation.

[00103] In some embodiments, the methods disclosed herein provide a synergistic or therapeutic benefit to the subject, for example, such as by improving efficacy, suppressing tumor growth, or inducing tumor regression, better than either compound therapy alone. In some embodiments, the methods provided herein improve efficacy, suppress tumor growth, or induce tumor regression, better than the sum of the results for each single compound therapy. In some embodiments, the methods provided herein delay, halt, or prevent progression of SCC or HNSCC or SCC or HNSCC tumor growth. In some embodiments, the methods provided herein reduce HNSCC tumors, such as reduce a primary HNSCC tumor, delay the appearance of primary or secondary tumors, slow the development of primary or secondary tumors, decrease the occurrence of primary or secondary tumors, or arrest tumor growth. In some embodiments, the methods provided herein relieve tumor-related symptoms. In some embodiments, the methods provided herein inhibit tumor secreted factors. In some embodiments, the methods provided herein slow or decrease the severity of secondary effects associated with SCC or HNSCC. In some embodiments, the methods provided herein increase Time to Progression (TTP), Progression Free Survival (PFS), Event-free survival (EFS), Overall Survival (OS), overall response rate (ORR), duration of response (DoR), disease control rate (DCR; complete response (CR) plus partial response (PR) plus stable disease (SD)), rate of CR, or rate of SD, better than no therapy or either compound therapy alone. In some embodiments, the methods provided herein increase TTP, PFS, EFS, OS, ORR, DoR, DCR, rate of CR, or rate of SD, better than first-line therapy. In some embodiments, the methods provided herein increase TTP, PFS, EFS, OS, ORR, DoR, DCR, rate of CR, or rate of SD, better than second-line therapy. In some embodiments, the methods provided herein increase TTP, PFS, EFS, OS, ORR, DoR, DCR, rate

of CR, or rate of SD, better than anti-EGFR antibody therapy. In some embodiments, the methods provided herein increase TTP, PFS, EFS, OS, ORR, DoR, DCR, rate of CR, or rate of SD, better than immunotherapy. In some embodiments, the methods provided herein increase TTP, PFS, EFS, OS, ORR, DoR, DCR, rate of CR, or rate of SD, better than localized or loco-regional disease therapies. In some embodiments, the methods provided herein decrease time to response (TTR) better than no therapy or either compound therapy alone. In some embodiments, the methods provided herein decrease TTR better than first-line therapy. In some embodiments, the methods provided herein decrease TTR better than second-line therapy. In some embodiments, the methods provided herein decrease TTR better than anti-EGFR antibody therapy. In some embodiments, the methods provided herein decrease TTR better than immunotherapy. In some embodiments, the methods provided herein decrease TTR better than localized or loco-regional disease therapies.

[00104] In some embodiments, the increased TTP, PFS, OS, EFS, ORR, DoR, DCR, rate of CR, or rate of SD, provided by the methods described herein is independently 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 5 to 10%, 10 to 20%, 20 to 30%, 30 to 40%, 40 to 50%, 2 fold, 3 fold, or 4 fold, or more than 4 fold, better than either compound therapy alone, better than first-line therapy, better than second-line therapy, better than anti-EGFR antibody therapy, better than immunotherapy, or better than localized or loco-regional disease therapies. In some embodiments, the methods provided herein increase TTP better than either compound therapy alone, better than first-line therapy, better than second-line therapy, better than anti-EGFR antibody therapy, better than immunotherapy, or better than localized or loco-regional disease therapies. For example, in some embodiments, the methods provided herein increase TTP 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 5 to 10%, 10 to 20%, 20 to 30%, 30 to 40%, 40 to 50%, 2 fold, 3 fold, or 4 fold, or more than 4 fold. For example, in some embodiments, the methods provided herein increase PFS better than either compound therapy alone, better than first-line therapy, better than second-line therapy, better than anti-EGFR antibody therapy, better than immunotherapy, or better than localized or loco-regional disease therapies. For example, in some embodiments, the methods provided herein increase PFS 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 5 to 10%, 10 to 20%, 20 to 30%, 30 to 40%, 40 to 50%, 2 fold, 3 fold, or 4 fold, or more than 4 fold. In some embodiments, the methods provided herein increase OS better than either compound therapy alone, better than first-line therapy, better than second-line

therapy, better than anti-EGFR antibody therapy, better than immunotherapy, or better than localized or loco-regional disease therapies. For example, in some embodiments, the methods provided herein increase OS 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 5 to 10%, 10 to 20%, 20 to 30%, 30 to 40%, 40 to 50%, 2 fold, 3 fold, or 4 fold, or more than 4 fold. In some embodiments, the methods provided herein increase PFS and/or OS better than either compound therapy alone, better than first-line therapy, better than second-line therapy, better than anti-EGFR antibody therapy, better than immunotherapy, or better than localized or loco-regional disease therapies. In some embodiments, the methods provided herein increase EFS better than either compound therapy alone, better than first-line therapy, better than second-line therapy, better than anti-EGFR antibody therapy, better than immunotherapy, or better than localized or loco-regional disease therapies. For example, in some embodiments, the methods provided herein increase EFS 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 5 to 10%, 10 to 20%, 20 to 30%, 30 to 40%, 40 to 50%, 2 fold, 3 fold, or 4 fold, or more than 4 fold. In some embodiments, the methods provided herein increase ORR better than either compound therapy alone, better than first-line therapy, better than second-line therapy, better than anti-EGFR antibody therapy, better than immunotherapy, or better than localized or loco-regional disease therapies. For example, in some embodiments, the methods provided herein increase ORR 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 5 to 10%, 10 to 20%, 20 to 30%, 30 to 40%, 40 to 50%, 2 fold, 3 fold, or 4 fold, or more than 4 fold. In some embodiments, the methods provided herein increase DoR better than either compound therapy alone, better than first-line therapy, better than second-line therapy, better than anti-EGFR antibody therapy, better than immunotherapy, or better than localized or loco-regional disease therapies. For example, in some embodiments, the methods provided herein increase DoR 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 5 to 10%, 10 to 20%, 20 to 30%, 30 to 40%, 40 to 50%, 2 fold, 3 fold, or 4 fold, or more than 4 fold. In some embodiments, the methods provided herein increase DCR, or an individual component thereof, better than either compound therapy alone, better than first-line therapy, better than second-line therapy, better than anti-EGFR antibody therapy, better than immunotherapy, or better than localized or loco-regional disease therapies. For example, in some embodiments, the methods provided herein increase DCR, or an individual component thereof, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 5 to 10%, 10 to 20%, 20 to 30%, 30 to 40%, 40 to 50%, 2 fold, 3 fold, or 4 fold, or more than 4 fold. In some embodiments,

the methods provided herein increase rate of complete response (CR), or an individual component thereof, better than either compound therapy alone, better than first-line therapy, better than second-line therapy, better than anti-EGFR antibody therapy, better than immunotherapy, or better than localized or loco-regional disease therapies. For example, in some embodiments, the methods provided herein increase rate of CR, or an individual component thereof, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 5 to 10%, 10 to 20%, 20 to 30%, 30 to 40%, 40 to 50%, 2 fold, 3 fold, or 4 fold, or more than 4 fold. In some embodiments, the methods provided herein increase rate of stable disease (SD), or an individual component thereof, better than either compound therapy alone, better than first-line therapy, better than second-line therapy, better than anti-EGFR antibody therapy, better than immunotherapy, or better than localized or loco-regional disease therapies. For example, in some embodiments, the methods provided herein increase rate of SD, or an individual component thereof, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 5 to 10%, 10 to 20%, 20 to 30%, 30 to 40%, 40 to 50%, 2 fold, 3 fold, or 4 fold, or more than 4 fold. In some embodiments, the methods provided herein decrease TTR better than either compound therapy alone, better than first-line therapy, better than second-line therapy, better than anti-EGFR antibody therapy, better than immunotherapy, or better than localized or loco-regional disease therapies. For example, in some embodiments, the methods provided herein decrease TTR 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 5 to 10%, 10 to 20%, 20 to 30%, 30 to 40%, 40 to 50%, 2 fold, 3 fold, or 4 fold, or more than 4 fold.

[00105] In some embodiments, the methods provided herein delays the progression or the time to emergence of drug resistance (such as resistance to an EGFR inhibitor, such as cetuximab, or to a PI3K inhibitor, such as alpelisib). In some embodiments, the methods provided herein overcomes cetuximab resistance. In some embodiments, the methods provided herein reduce the therapeutically effective amount of the alpelisib compared to alpelisib monotherapy. In some embodiments, the methods provided herein reduce alpelisib-associated toxicity, such as reduces a toxicity selected from the group consisting of reduced glucose increase, creatinine increase, diarrhea, rash, lymphocyte count decrease, GGT increase, nausea, ALT increase, fatigue, hemoglobin decrease, lipase increase, decrease appetite, stomatitis, vomiting, weight decrease, calcium decrease, glucose decrease, a PTT prolonged, and alopecia, or a combination thereof. In some embodiments, the methods provided herein reduce the

therapeutically effective amount of the cetuximab. In some embodiments, the methods provided herein reduce cetuximab-associated toxicity, such as reduces a toxicity selected from the group consisting of skin toxicity, including skin rash, dry skin, hair growth disorders, pruritus, nail changes, headache, and diarrhea. In some embodiments, the methods disclosed herein provide a combination of one or more of the above mentioned benefits.

[00106] In some embodiments, the methods provided herein mitigate one or more symptoms of SCC or HNSCC. In some embodiments, the methods provided herein retard the progression, delays the time to emergence of, or overcomes drug resistance, such as cetuximab resistance, or PI3K inhibitor or alpelisib resistance, in the SCC or HNSCC. In some embodiments, the methods provided herein reduce the risk of the SCC or HNSCC relapse, e.g., delay relapse.

[00107] In some embodiments, the therapeutically effective amount of Compound (I), or pharmaceutically acceptable form thereof, and/or the PI3K inhibitor such as alpelisib, in the pharmaceutical composition, or the pharmaceutical kit or pharmaceutical packaging comprising the same, can depend on absorption, tissue distribution, metabolism, and excretion rates of the active compound, the dosage schedule, the amount administered, and the particular formulation, as well as other factors known to those of skill in the art. The therapeutically effective amount may be determined empirically by testing the compounds in *in vitro* and *in vivo* systems described herein and then extrapolated therefrom for dosages for humans.

[00108] In some embodiments, the methods provided herein reduce the therapeutically effective amount of the alpelisib administered per day or administered per dose. For example, in some embodiments, the therapeutically effective amount of the alpelisib is reduced relative to the therapeutically effective amount required for alpelisib monotherapy, for example is reduced from 300 mg to 250 mg, 200 mg, 150 mg, or 75 mg, once per day, such as from 300 mg to 200 mg, from 250 mg to 200 mg, from 200 mg to 150 mg, or from 150 mg to 100 mg, once per day. In some embodiments, a reduction in the therapeutically effective amount of the alpelisib administered per day or administered per dose reduces the incidence or severity of, or the risk of, one or more alpelisib-associated toxicities. In some embodiments, the methods provided herein reduces alpelisib-associated toxicity or the risk thereof, such as reduces a toxicity selected from glucose increase, creatinine increase, diarrhea, rash, lymphocyte count decrease, GGT increase, nausea, ALT increase, fatigue, hemoglobin decrease, lipase increase, decrease appetite, stomatitis, vomiting, weight decrease, calcium decrease, glucose decrease (hypoglycemia), aPTT

prolonged, and alopecia, or a combination thereof. In some embodiments, the methods provided herein delays emergence of alpelisib-resistance. In some embodiments, the methods provided herein unexpectedly delays emergence of alpelisib-resistance. In some embodiments, the delay in emergence of alpelisib-resistance comprises weeks, months, or years.

[00109] In some embodiments, the methods provided herein reduce the therapeutically effective amount of the cetuximab administered per day or administered per dose. In some embodiments, the methods provided herein reduce cetuximab-associated toxicity, such as reduces a toxicity selected from skin toxicity, including skin rash, dry skin, hair growth disorders, pruritus, nail changes, headache, and diarrhea or combinations thereof. In some embodiments, the methods provided herein delay emergence of cetuximab resistance. In some embodiments, the methods provided herein unexpectedly delay emergence of cetuximab resistance. In some embodiments, the delay in emergence of cetuximab resistance comprises weeks, months, or years.

[00110] In some embodiments, the methods provided herein comprise administering an additional active agent to the subject. In some embodiments, the additional active agent is a chemotherapy, a taxane, a platinum anti-cancer agent, cetuximab, an mTOR inhibitor, or an immunotherapeutic agent. In some embodiments, additional active agent is selected from a PD1 inhibitor or anti-PD1 antibody (e.g., pembrolizumab, nivolumab, cemiplimab, dostarlimab, retifanlimab, toripalimab, or tislelizumab), a PDL1 inhibitor or anti-PDL1 antibody (e.g., atezolizumab, avelumab, or durvalumab), a CLTA4 inhibitor or an anti-CTLA4 antibody (e.g., ipilimumab or tremelimumab), a LAG3 inhibitor or an anti-LAG3 antibody (e.g., relatlimab), or a TIGIT inhibitor or an anti-TIGIT antibody (e.g., tiragolumab). In some embodiments, the methods comprise administering to the subject Compound (I) or a pharmaceutically acceptable form thereof, a PI3K inhibitor, and an immunotherapeutic agent. In some embodiments, the method comprise administering to the subject Compound (I) or a pharmaceutically acceptable form thereof, a PIK3CA inhibitor, and an immunotherapeutic agent. In some embodiments, the immunotherapeutic agent is an anti-PD1 antibody, for example, pembrolizumab.

6.3.2 DOSES AND REGIMENS

[00111] In some embodiments, the methods provided herein comprise administering to the subject (a) Compound (I), or a pharmaceutically acceptable form thereof (or a pharmaceutical composition comprising the same), and, for combinations methods, (b) a PI3K inhibitor such as

alpelisib (or a pharmaceutical composition comprising the same). In some embodiments, the methods provided herein comprise administering to the subject (a) a dose amount of Compound (I), or a pharmaceutically acceptable form thereof (or a pharmaceutical composition comprising the same), and for combination methods, (b) a dose amount of a PI3K inhibitor such as alpelisib (or a pharmaceutical composition comprising the same). In some embodiments, the administration of the two agents is concurrent, sequential, continuous, intermittent, or in cycles. In some embodiments, PI3K inhibitor is a PI3K α inhibitor, such as alpelisib. In some embodiments, a dose amount is a dose amount per day.

[00112] In some embodiments, Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject according to the methods provided herein at a dose of 0.5-2400 mg per day. In some embodiments, the dose of Compound (I), or pharmaceutically acceptable form thereof, is selected from the group consisting of 0.5-2.5 mg, 0.5-5 mg, 0.5-10 mg, 0.5-25 mg, 0.5-50 mg, 0.5-75 mg, 0.5-100 mg, 0.5-300 mg, 0.5-600 mg, 0.5-1200 mg, 1-5 mg, 1-10 mg, 1-25 mg, 1-50 mg, 1-75 mg, 1-100 mg, 1-300 mg, 1-600 mg, 1-1200 mg, 1-2400 mg, 20-100 mg, 40-75 mg, 50-75 mg, 50-100 mg, 50-150 mg, 75-100 mg, 100-200 mg, 125-200 mg, 150-300 mg, 200-250 mg, 200-400 mg, 300-600 mg, 250-500 mg, 400-600 mg, 500-750 mg, 600-900 mg, 700-100 mg, 650-1000 mg, 800-1200 mg, 900-1500 mg, 1000-1600 mg, 1000-2000 mg, 1200-1600 mg, 1500-2000 mg, 1500-2400 mg, 1800-2400 mg and 2000-2400 mg per day. In some embodiments, the dose of Compound (I), or pharmaceutically acceptable form thereof, is selected from the group consisting of about 0.5 mg, about 1.5 mg, about 1.6 mg, about 1.7 mg, about 1.8 mg, about 1.9 mg, about 1 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1650 mg,

about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1900 mg, about 1950 mg, about 2000 mg, about 2050 mg, about 2100 mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, and about 2400 mg per day. In some embodiments, the dose above is administered 1, 2, 3, or 4 times per day, for example, is administered once or twice per day, such as once per day. In some embodiments, the dose above is split into two doses that are administered to the subject according to the methods provided herein.

[00113] In some embodiments, Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject according to the methods provided herein at a dose of 0.01-50 mg/kg body weight per day. In some embodiments, the dose of Compound (I), or pharmaceutically acceptable form thereof, is selected from the group consisting of 0.01-1 mg/kg, 0.01-2.5 mg/kg, 0.01-5 mg/kg, 0.1-5 mg/kg, 0.1-10 mg/kg, 0.1-20 mg/kg, 1-30 mg/kg, 1-40 mg/kg, 5-50 mg/kg, 10-50 mg/kg, 15-50 mg/kg, 20-50 mg/kg, 25-50 mg/kg, 30-50 mg/kg, 40-50 mg/kg, 20-40 mg/kg, and 20-25 mg/kg body weight per day. In some embodiments, the dose of Compound (I), or pharmaceutically acceptable form thereof, is selected from the group consisting of about 0.01 mg/kg, about 0.02 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.09 mg/kg, about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, and about 50 mg/kg body weight per day. In some embodiments, the dose above is split into two doses that are administered to the subject according to the methods provided herein. In some embodiments, the dose above is administered 1, 2, 3, or 4 times per day, for example, is administered once or twice per day, such as once per day.

[00114] In some embodiments, the dose of Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject monthly, weekly, or daily, according to the methods provided herein. In some embodiments, the dose of Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject for one or more cycles, for example, once or twice per day for one or more cycles, such as once per day for one or more cycles. In some embodiments, the dose of Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject 1, 2, 3 or 4 times per day continuously for unlimited days or until remission achieved in said subject, or until relapse occurs. In some embodiments, Compound (I), or pharmaceutically acceptable salt thereof, is administered to the subject once per day

(sometimes referred to as QD) for one or more cycles, such as QD for two or more cycles, QD for three or more cycles, or QD for four or more cycles. In some embodiments, Compound (I), or pharmaceutically acceptable salt thereof, is administered to the subject twice per day (sometimes referred to as BID) for one or more cycles, such as BID for two or more cycles, BID for three or more cycles, or BID for four or more cycles. In some embodiments, the cycle (sometimes referred to herein as a treating cycle or maintenance cycle) is 1 day, 7 days, 14 days, 21 days, or 28 days. In some embodiments, the treating cycle is a 28-day cycle. In some embodiments, Compound (I), or pharmaceutically acceptable salt thereof, is administered to the subject once per day (QD) for one or more 28-day cycles. In some embodiments, Compound (I), or pharmaceutically acceptable salt thereof, is administered to the subject twice per day (BID) for one or more 28-day cycles. In some embodiments, Compound (I), or pharmaceutically acceptable salt thereof, is administered to the subject once or twice per day every other week during a 28-day cycle, with alternating weeks of rest.

[00115] In some embodiments, Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject 1, 2, 3 or 4 times per day on days 1-7, days 1-7 and 15-21, days 1-21, or each day (*i.e.*, days 1-28) of a 28-day cycle, for one of more cycles, according to the methods provided herein. For example, in some embodiments, Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject QD on days 1-7, days 1-7 and 15-21, days 1-21, or each day (*i.e.*, days 1-28) of a 28-day cycle, for one of more cycles. For example, in some embodiments, Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject BID on days 1-7, days 1-7 and 15-21, days 1-21, or each day (*i.e.*, days 1-28) of a 28-day cycle, for one of more cycles. In some embodiments, Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject on QD on days 1-7 of a 28-day cycle, for one of more cycles. In some embodiments, Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject BID on days 1-7 of a 28-day cycle, for one of more cycles. In some embodiments, Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject QD on days 1-7 and 15-21 of a 28-day cycle, for one of more cycles. In some embodiments, Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject BID on days 1-7 and 15-21 of a 28-day cycle, for one of more cycles. In some embodiments, Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject QD on days 1-21 of a 28-day cycle, for one of more cycles. In some

embodiments, Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject BID on days 1-21 of a 28-day cycle, for one of more cycles. In some embodiments, Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject QD on each day (*i.e.*, days 1-28) of a 28-day cycle, for one of more cycles. In some embodiments, Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject BID on each day (*i.e.*, days 1-28) of a 28-day cycle, for one of more cycles.

[00116] In some embodiments, the PI3K inhibitor administered to the subject according to the methods provided herein is alpelisib. In some embodiments, the alpelisib is administered to the subject at a dose of 10-400 mg per day. In some embodiments, the dose of the alpelisib administered to the subject is selected from the group consisting of 10-300 mg, 10-200 mg, 10-150 mg, 10-100 mg, 10-50 mg, 25-300 mg, 25-200 mg, 25-150 mg, 25-100 mg, 25-50 mg, 50-400 mg, 50-300 mg, 50-200 mg, 50-150 mg, 50-100 mg, 100-400 mg, 100-300 mg, 100-200 mg, 150-250 mg, 175-225 mg, 200-400 mg, or 200-300 mg per day. In some embodiments, the alpelisib is administered to the subject at a dose selected from the group consisting of about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 260 mg, about 270 mg, about 275 mg, about 280 mg, about 290 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg or about 400 mg per day. In some embodiments, the dose of the alpelisib administered to the subject is about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, or about 300 mg per day. In some embodiments, the dose of the alpelisib administered to the subject is about 50 mg, about 150 mg, or about 200 mg per day. In some embodiments, the dose of the alpelisib administered to the subject is about 100 mg, about 150 mg, about 200 mg, about 250 mg, or about 300 mg per day. In some embodiments, the alpelisib is administered to the subject at a dose of about 50 mg per day. In some embodiments, the alpelisib is administered to the subject at a dose of about 100 mg per day. In some embodiments, the alpelisib is administered to the

subject at a dose of about 150 mg per day. In some embodiments, the alpelisib is administered to the subject at a dose of about 200 mg per day. In some embodiments, the alpelisib is administered to the subject at a dose of about 250 mg per day. In some embodiments, the alpelisib is administered to the subject at a dose of about 300 mg per day. In some embodiments, the dose above of the alpelisib is split into two doses that are administered to the subject according to the methods provided herein. In some embodiments, the alpelisib is administered to the subject 1, 2, 3 or 4 times per day, for example, is administered once or twice per day, such as once per day.

[00117] In some embodiments, the dose of the alpelisib is administered to the subject daily for one or more cycles according to the methods provided herein. In some embodiments, the dose of the alpelisib is split into two doses that are administered to the subject according to the methods provided herein. In some embodiments, the dose of the alpelisib is administered 1, 2, 3 or 4 times per day for one or more cycles, for example, is administered once or twice per day for one or more cycles, such as once per day for one or more cycles. In some embodiments, the dose of the alpelisib is administered to the subject 1, 2, 3 or 4 times per day continuously for unlimited days or until remission achieved in said subject. In some embodiments, the dose of the alpelisib is administered to the subject once per day (QD) for one or more cycles, such as QD for two or more cycles, QD for three or more cycles, or QD for four or more cycles. In some embodiments, the dose of the alpelisib is split into two doses that are administered to the subject according to the methods provided herein. For example, in some embodiments, the dose of the alpelisib is administered to the subject twice per day (BID) for one or more cycles, such as BID for two or more cycles, BID for three or more cycles, or BID for four or more cycles. In some embodiments, the cycle (*e.g.*, a treating cycle or maintenance cycle) is 1 day, 7 days, 14 days, 21 days, or 28 days. In some embodiments, the treating cycle is a 28-day cycle. In some embodiments, the dose of the alpelisib is administered to the subject once per day for one or more 28-day cycles. In some embodiments, the dose of the alpelisib is administered to the subject twice per day for one or more 28-day cycles. In some embodiments, the dose of the alpelisib is administered to the subject once or twice per day every other week during a 28-day cycle.

[00118] In some embodiments, the methods provided herein comprise (1) an escalating dosing cycle, followed by (2) one or more treating cycles (sometimes referred to as maintenance cycles).

In some embodiments, the methods provided herein comprise (1) an escalating dosing cycle, comprising administering (a) escalating daily doses of Compound (I), or a pharmaceutically acceptable form thereof, and for combinations, (b) a dose of alpelisib, followed by (2) one or more treating cycles (sometimes referred to as maintenance cycles), comprising administering (a) a dose of Compound (I), or pharmaceutically acceptable form thereof, and for combination methods (b) a dose of the alpelisib. In some embodiments, Compound (I), or pharmaceutically acceptable form thereof, is administered 1, 2, 3, or 4 times per day during the escalating dosing cycle, for example, once or twice per day. In some embodiments, the escalating dosing cycle is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 14 days, 21 days, or 28 days. In some embodiments, inclusion of an escalating dosing cycle provides a synergistic or therapeutic benefit to the subject, including but not limited to, identifying a therapeutically effective dose of Compound (I), or pharmaceutically acceptable form thereof, for the subject; identifying a therapeutically effective dose of the alpelisib for the subject; improving the efficacy of the alpelisib; improving the efficacy of cetuximab; mitigating or avoiding toxicities, adverse events or adverse symptoms, or combinations thereof, associated with Compound (I), or pharmaceutically acceptable form thereof; mitigating or avoiding toxicities, adverse events or adverse symptoms, or combinations thereof, associated with alpelisib; or mitigating or avoiding toxicities, adverse events or adverse symptoms, or combinations thereof, associated with cetuximab; or combinations thereof.

[00119] In some embodiments, the methods provided herein comprises escalating the therapeutically effective amount of the alpelisib administered per day or administered per dose. For example, in some embodiments, the therapeutically effective amount of the alpelisib is escalated from 150 mg to 200 mg, from 150 to 250 mg, from 150 to 300 mg, from 200 mg to 250 mg, from 200 mg to 300 mg, or from 250 mg to 300 mg, once per day. In some embodiments, the therapeutically effective amount of the alpelisib administered per day or administered per dose is escalated while maintaining the therapeutically effective amount of the tipifarnib administered per day or administered per dose.

[00120] In some embodiments, the methods provided herein comprises escalating the therapeutically effective amount of Compound (I), or pharmaceutically acceptable form thereof, administered per day or administered per dose. In some embodiments, the therapeutically effective amount of Compound (I), or pharmaceutically acceptable form thereof, administered

per day or administered per dose is escalated while maintaining the therapeutically effective amount of the alpelisib administered per day or administered per dose.

[00121] In some embodiments, the methods provided herein comprises (1) a loading dosing cycle, followed by (2) one or more treating cycles (sometimes referred to as maintenance cycles).

In some embodiments, the methods provided herein comprises (1) a loading dosing cycle, comprising administering (a) a loading dose of Compound (I), or a pharmaceutically acceptable form thereof, and for combination methods (b) a dose of alpelisib, followed by (2) one or more treating cycles (sometimes referred to as maintenance cycles), comprising administering (a) a dose of Compound (I), or pharmaceutically acceptable form thereof, and for combination methods (b) a dose of the alpelisib. In some embodiments, the loading dose (sometimes referred to as an elevated dose or a bolus dose) of Compound (I), or pharmaceutically acceptable form thereof, is 1.1-10 times the dose administered during the one or more treating cycles. For example, in some embodiments, the loading dose of Compound (I), or pharmaceutically acceptable form thereof, is 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times the dose administered during the one or more treating cycles. In some embodiments, administration of Compound (I), or pharmaceutically acceptable form thereof, during the loading dosing cycle is 1, 2, 3, or 4 times per day. In some embodiments, administration of Compound (I), or pharmaceutically acceptable form thereof, during the loading dosing cycle is once per day. In some embodiments, administration of Compound (I), or pharmaceutically acceptable form thereof, during the loading dosing cycle is twice per day. In some embodiments, the loading dosing cycle is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 14 days, 21 days, or 28 days. In some embodiments, inclusion of a loading dosing cycle prior to treating the subject with one or more treating or maintenance cycles, provides a synergistic or therapeutic benefit to the subject, including but not limited to, mitigating or avoiding toxicities, adverse events or adverse symptoms, or combinations thereof, associated with Compound (I), or pharmaceutically acceptable form thereof; mitigating or avoiding toxicities, adverse events or adverse symptoms, or combinations thereof, associated with alpelisib; or mitigating or avoiding toxicities, adverse events or adverse symptoms, or combinations thereof, associated with cetuximab; or combinations thereof.

[00122] In some embodiments, the dose of Compound (I), or pharmaceutically acceptable form thereof, and the dose of the alpelisib, are administered to the subject concurrently or

sequentially. In some embodiments, the dose of Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject before the administration of the dose of the alpelisib. In some embodiments, the dose of Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject after the administration of the dose of the alpelisib. In some embodiments, the dose of Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject QD or BID on days 1-7, days 1-7 and 15-21, days 1-21, or each day, of a 28-day treatment cycle, and the dose of the alpelisib is administered QD or BID each day of the 28-day treatment cycle. For example, in some embodiments, the dose of Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject QD on days 1-7, days 1-7 and 15-21, days 1-21, or each day, of a 28-day treatment cycle, and the dose of the alpelisib is administered QD each day of the 28-day treatment cycle. In some embodiments, the dose of Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject BID on days 1-7, days 1-7 and 15-21, days 1-21, or each day, of a 28-day treatment cycle, and the dose of the alpelisib is administered QD each day of the 28-day treatment cycle. In some embodiments, the dose of Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject QD on days 1-7, days 1-7 and 15-21, days 1-21, or each day, of a 28-day treatment cycle, and the dose of the alpelisib is administered BID each day of the 28-day treatment cycle. In some embodiments, the dose of Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject BID on days 1-7, days 1-7 and 15-21, days 1-21, or each day, of a 28-day treatment cycle, and the dose of the alpelisib is administered BID each day of the 28-day treatment cycle.

7. EXAMPLES

[00123] EXAMPLE 1: Tumor Spheroid Growth Assay

[00124] Head and neck squamous carcinoma (HNSCC) cell lines were obtained from ATCC (SCC9: PIK3CA^{wt}, high HRAS activity), Sigma (BICR22: PIK3CA-amplified, HRAS^{wt}; and HSC3: PIK3CA^{wt}, low HRAS activity), or DSMZ (CAL33: PIK3CA-mutant (H1047R)) and maintained in a humidified atmosphere with 5% CO₂ at 37 °C, cultured in DMEM (BICR22, CAL33, HSC3) or DMEM/F12 (SCC9) supplemented with 10% FBS and penicillin/streptomycin. All lines tested negative for mycoplasma. Matrigel matrix was purchased from Corning and diluted in respective media prior to plating. Active GTPase Pulldown kit was purchased from ThermoFisher. Alpelisib was purchased from

MedChemExpress and dissolved in DMSO.

[00125] Cells were resuspended in 4% Matrigel and seeded in 96-well ultralow attachment plates at a density of 1000-2000 cells/well. The following day, spheroids were treated with alpelisib and/or Compound (I) and baseline growth measured using 3D Cell Titer Glo reagent (Promega). Spheroids were incubated with drug for 7 days and a final CTG reading taken. Percentage growth was calculated by $[(T_i - T_z)/(C - T_z)] \times 100$ for concentrations for which $T_i \geq T_z$ and $[(T_i - T_z)/T_z] \times 100$ for concentrations for which $T_i < T_z$, where T_z = time zero, C = control growth, and T_i = test growth at each drug concentration.

[00126] The sensitivity of a panel of head and neck squamous carcinoma (HNSCC) cell lines harboring PIK3CA mutation (CAL33), PIK3CA copy gain (BICR22), or PIK3CA wild types (SCC9 and HSC3) to Compound (I), alpelisib, or a combination was assessed. Lines with PIK3CA^{wt} were further characterized based on activity levels of HRAS as assayed by GTP pull-down kit using an HRAS specific antibody (ab32417, Abcam), identifying SCC9 as HRAS high and HSC3 as HRAS low. The cell lines were cultured as 3D tumor spheroids and treated for 7 days in a checkerboard dose-response fashion. Results are shown in **FIGS. 1A-1D**. Compound (I) exhibited cytotoxicity in cell lines with a PIK3CA mutation and PIK3CA amplification, or high HRAS activity, and the combination of Compound (I) and alpelisib exhibited increased cytotoxicity in these cell lines compared to the single agents, as indicated by the red gradient in the heat maps. In contrast, the control cell line with neither PIK3CA activation nor high HRAS activity (HSC3) did not respond to either single agent or to the combination.

[00127] EXAMPLE 2: Compound (I) may potentiate the antitumor effects of PI3K α blockade in HNSCC via convergent inhibition of mTOR activity

[00128] The PI3K-AKT-mTOR signaling cascade is the most frequently activated pathway in HNSCC. PIK3CA (encoding the α isoform of PI3K's catalytic subunit) is activated by gain-of-function mutation or amplification in approximately 30% of HNSCCs.

[00129] Because a farnesyltransferase inhibitor can block hyperactivated growth factor signaling at multiple nodes, including HRas protein and Rheb protein, the impact of Compound (I) on growth of PIK3CA-altered HNSCC models *in vitro* and *in vivo* will be examined. In cell lines harboring PIK3CA mutation or amplification, Compound (I) may reduce proliferation of both monolayer and spheroid cultures, and when combined with alpelisib, may induce

cytotoxicity. In PIK3CA mutant/amplified PDX models, the Compound (I)/alpelisib doublet may lead to deeper antitumor responses compared to alpelisib monotherapy.

[00130] To interrogate the mechanistic underpinnings of synergy, HNSCC cell lines will be exposed to Compound (I), alpelisib, or the combination, and the effects on RAS/PI3K pathway activity assessed. In PIK3CA altered lines, single agent Compound (I) or alpelisib may reduce phosphorylation of p90 RSK and mTOR substrates, particularly S6 kinase and ribosomal protein S6. In cells exposed to alpelisib alone, marked rebound of RSK and mTOR substrate phosphorylation may occur after 24 hours, correlating with restored AKT activity. In contrast, though AKT activity may rebound in cells treated with the combination, RSK phosphorylation and markers of mTOR activity (including 4EBP1) may remain suppressed. Thus, Compound (I) may blunt both MAPK and mTOR reactivation following PI3K inhibition. Combination treatment effects may provide robust and induced rapid apoptosis.

[00131] Immunoblots of MAPK/PI3K pathway components and apoptotic markers in PIK3CA-mutant CAL33 cells are to be treated with alpelisib for 0, 1, 2, 6, and 24 hours in the absence or presence of Compound (I) (48-hour treatment). A shift in Rheb protein mobility may be indicative of defarnesylation. Combination treatment may result in stronger inhibition of mTOR activity/target phosphorylation (p70 S6K, S6, 4EBP1), cell cycle arrest (RB phosphorylation), and cell death (PARP and caspase cleavage).

[00132] Such a dual effect may indicate that the activity of Compound (I) in this context stems from inhibition of multiple targets, such as HRas protein and Rheb protein, which converge upon mTOR and synergize with alpelisib to durably block tumor growth.

[00133] EXAMPLE 3: Compound (I) and alpelisib activity in PIK3CA-altered cell lines

[00134] The activity of the combination of Compound (I) and alpelisib in cell lines harboring PIK3CA mutation or copy gain may be assessed by Loewe synergy score, which is plotted against combination sensitivity score. Calculations are made using SynergyFinder® package (Zheng, et al., Genomics Proteomics Bioinformatics, 2022).

[00135] EXAMPLE 4: Compound (I) and alpelisib activity in HRAS-altered patient-derived xenograft model

[00136] Female NOD/SCID mice were inoculated subcutaneously in the right upper flank

with primary human tumor xenograft model tumor fragments (human head and neck, HN2594 (HRAS^{WT-high}, Crown Bioscience, Beijing; 2-3 mm in diameter) harvested from stock mice for tumor development. All animals were randomly allocated to 4 study groups, 5 mice in each group. Randomization started when the mean tumor size reached approximately 220 mm³. Randomization was performed based on “Matched distribution” method (StudyDirectorTM software, version 3.1.399.19). Dosing was initiated on the date of randomization (Day 0). Mice were dosed orally for 35 days with: control vehicle, QD; Compound (I), 20 mg/kg, BID; alpelisib, 40 mg/kg, QD; or combination of Compound (I), 20 mg/kg, BID, and alpelisib, 40mg/kg, QD. After tumor inoculation, the animals were checked daily for morbidity and mortality. During routine monitoring, the animals were checked for any effects of tumor growth and treatments on behavior such as mobility, food and water consumption, body weight gain/loss (body weights were measured three times/daily per week after randomization), eye/hair matting and any other abnormalities. Mortality and observed clinical signs were recorded for individual animals in detail. Tumor volumes were measured three times per week after randomization in two dimensions using a caliper, and the volume was expressed in mm³ using the formula: $V = (L \times W \times W)/2$, where V is tumor volume, L is tumor length (the longest tumor dimension), and W is tumor width (the longest tumor dimension perpendicular to L). Dosing and tumor and body weight measurements were conducted in a Laminar Flow Cabinet. The body weights and tumor volumes were measured by using Study DirectorTM software (version 3.1.399.19). As shown in **FIG. 2**, the combination of Compound (I) and alpelisib produced tumor regression in this model.

[00137] EXAMPLE 5: Rheb protein localization to lysosome

[00138] Active Rheb protein is thought to localize to lysosomes to regulate mTOR activity. Density gradient ultracentrifugation is utilized to extract lysosomes from CAL33 cells treated with DMSO or Compound (I). Lysosomes are lysed and subjected to immunoblot analysis alongside whole-cell lysate (WCL). LAMP1 is a lysosome-specific marker and is used in this assay.

[00139] EXAMPLE 6: Compound (I) and Alpelisib Combination Clinical Trial

[00140] This study is designed to evaluate the safety, tolerability and preliminary antitumor activity of Compound (I), or a pharmaceutically acceptable form thereof, in combination with

alpelisib in patients having HNSCC that is HRAS- and/or PIK3CA-dependent, such as (a) HRAS-mutant, HRAS-amplified, and/or HRAS overexpressing; and/or (b) PIK3CA-mutated and/or -amplified. PIK3CA activating mutations may include: Exon 7: C420R; Exon 9: E542K, E545A, E545D, E545G, E545K, Q546E, or Q546R; and kinase domain: (Exon 20: H1047L, H1047R, H1047Y).

[00141] PIK3CA (activating) and HRAS mutations and/or amplifications may be determined by next generation sequencing (NGS) on a tumor tissue biopsy. Increased HRAS dependency based on HRAS overexpression may be determined by an immunohistochemistry assay or an RNA assay.

[00142] Dose levels for the combination are defined in Table 1 below.

Table 1: Dosing of Compound (I), or a pharmaceutically acceptable form thereof, and alpelisib

Combinations	Compound (I) *	Alpelisib (QD)**
1	0.5-1200 mg BID	300 mg
2	1-2400 mg QD	300 mg
3	1-100 mg QD	300 mg
4	5-50 mg QD	300 mg
5	100-200 mg QD	300 mg
6	0.5-1200 mg BID	250 mg
7	1-2400 mg QD	250 mg
8	1-100 mg QD	250 mg
9	5-50 mg QD	250 mg
10	100-200 mg QD	250 mg
11	0.5-1200 mg BID	200 mg
12	1-2400 mg QD	200 mg
13	1-100 mg QD	200 mg
14	5-50 mg QD	200 mg
15	100-200 mg QD	200 mg
16	0.5-1200 mg BID	150 mg
17	1-2400 mg QD	150 mg
18	1-100 mg QD	150 mg
19	5-50 mg QD	150 mg
20	100-200 mg QD	150 mg
21	0.5-1200 mg BID	100 mg
22	1-2400 mg QD	100 mg
23	1-100 mg QD	100 mg
24	5-50 mg QD	100 mg
25	100-200 mg QD	100 mg

Combinations	Compound (I) *	Alpelisib (QD)**
26	0.5-1200 mg BID	50 mg
27	1-2400 mg QD	50 mg
28	1-100 mg QD	50 mg
29	5-50 mg QD	50 mg
30	100-200 mg QD	50 mg

BID, twice daily; mg, milligram; QD, once daily. *Days 1-7 and 15-21 of 28-day cycle. **Each day of 28-day cycle.

[00143] Pharmacokinetics analyses will be performed on blood samples collected from patients at various timepoints throughout the study, including at multiple timepoints during Cycle 1, Day 1, and on Day 1 of subsequent cycles. Plasma concentrations of Compound (I) and alpelisib will be evaluated.

[00144] Dose limiting toxicity (DLT) will be evaluated according to NCI CTCAE v5.0 and will be assessed in cycle 1 (28 days) for all patients.

[00145] Inclusion Criteria

1. At least 18 years of age.
2. Histologically confirmed head and neck cancer (oral cavity, pharynx, larynx, sinonasal, nasopharyngeal, or unknown primary) of squamous histology not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).
3. Documented treatment failure from at least 1 prior therapy (e.g., tumor progression, clinical deterioration, or recurrence) in the R/M setting, or not appropriate for treatment with standard of care in this setting, with documented rationale.
4. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 that meets the criteria for selection as a target lesion according to RECIST v1.1. The presence of at least one measurable target lesion per RECIST v1.1 must be confirmed by local radiology prior to participant entry.
5. Has a tumor that per criteria outlined in the protocol, is dependent upon HRAS and/or PIK3CA.

[00146] Exclusion Criteria

[00147] Participants are excluded from the trial if any of the following criteria apply.

1. Prior treatment (at least 1 full treatment cycle) with a farnesyltransferase inhibitor.

2. Prior treatment (at least 1 full treatment cycle) with a PI3K, mTOR, or AKT inhibitor.

[00148] Efficacy Assessments

[00149] Objective response (CR and PR) as determined by the participant's best tumor response, DOR, and time to progression will be assessed using RECIST v1.1 (Appendix 3) by investigator assessment. Tumor response assessments will continue until disease progression, initiation of new anticancer therapy, or trial withdrawal. Radiological assessments will be made at least once approximately every 8 weeks ($\pm$ 5 days) for the first 12 months of study intervention (through and including Cycle 13), and once approximately every 12 weeks ($\pm$ 5 days) for year 2 and beyond of study intervention.

[00150] Lesions to be included in the tumor assessments should follow RECIST v1.1.

Computed tomography scan with a contrast agent is the preferred imaging method and the same technique should be used at screening and post-treatment assessments. CT scan coverage at screening should encompass scans of the neck (including the skull base), chest and abdomen (including the liver and adrenals). Any other areas of disease involvement should be scanned based on the participant's signs and symptoms. Participants with contrast allergy or renal insufficiency may use non-contrast CT or magnetic resonance imaging (MRI), whichever is required to adequately assess all disease. For participants who develop a contraindication to contrast after screening scans are performed with a contrast agent, the decision to use non-contrast CT or MRI (enhanced or non-enhanced) should be based on tumor type, anatomic location of disease and should be optimized to allow for comparison to the prior scans if possible. The one exception where MRI would not be recommended is for the evaluation of parenchymal lung metastases. In this instance, CT would be preferred. If imaging of the brain is indicated, MRI of the brain with and without gadolinium should be performed for optimal evaluation of the brain. If MRI is medically contraindicated, CT of the brain with and without contrast would be suggested.

[00151] Participants will be monitored by follow-up contact following the end of treatment visit until death or the end of the trial to evaluate survival and DOR.

[00152] EXAMPLE 7: IHC Assay for HRAS Overexpression in Head and Neck Cancers

[00153] Overexpression of HRAS in HNSCC patients indicates that HRAS may be a viable target for biomarker-driven clinical studies for patients with recurrent/metastatic HNSCC. As

such, a Clinical Laboratory Improvement Amendments (CLIA)-validated immunohistochemistry (IHC) assay was developed to assess HRAS expression in tumor biopsies. Development and validation of an IHC assay is described in U.S. Provisional Application No. 63/479,683.

[00154] The IHC staining procedure used was as follows:

[00155] STEP 1) *Slide Preparation*: Formalin-fixed, paraffin-embedded (FFPE) human cancer tissues blocks were cut at 4-5 μm thickness and sections were mounted onto positively-charged glass slides. Slides were baked (60°C, dry heat) for 1 hour prior to Step 2. The appropriate Autostainer Link 48 program was loaded by selecting the appropriate protocol.

[00156] STEP 2) *Dewaxing/Automated Antigen Retrieval*: Tissue sections were de-waxed and pre-treated using the PT Link. Antigen/epitope retrieval (antigen unmasking) was performed using a Heat Induced Epitope Recovery (HIER) solution. Slides were loaded in racks and placed in pre-heated (65°C) 1x High pH Target Retrieval Solution in the PT Link. The PT Link was heated to 97°C for 20 minutes and automatically cooled to 65°C. After cooling, racks were placed in a container with 1x FLEX wash buffer for 1-5 minutes.

[00157] STEP 3) *Automated Immunohistochemistry*: All procedures were automated at room temperature using the Dako/Agilent Autostainer Link 48 platform. Slides were treated with Proteinase K (diluted in FLEX wash buffer), to further expose the epitopes for binding, on the Autostainer Link 48 platform. The Dako/Agilent Autostainer Link 48 platform protocol was ran as follows with intervening rinses of 1x FLEX wash buffer between each step: a) 10 minutes in Proteinase K, 300 μL per slide; b) 5 minutes in FLEX HP Block, 300 μL per slide; c) 60 minutes HRAS primary antibody (H-Ras recombinant rabbit monoclonal antibody, rabbit IgG (clone ARC0098), Invitrogen (Catalog No. MA5-35323)) diluted in Dako Antibody Diluent, 300 μL per slide; d) 20 minutes in FLEX HRP, 300 μL per slide; e) 5 minutes in FLEX wash buffer, 300 μL per slide; f) 10 minutes in FLEX DAB + Substrate-Chromogen, 300 μL per slide; g) 5 minutes in FLEX Hematoxylin, 300 μL per slide; h) Rinse in Deionized (DI) Water; i) 5 minutes in FLEX wash buffer, 300 μL per slide.

[00158] STEP 4) *Dehydration/Coverslipping*: Slides were immersed in room temperature deionized water and transferred to the coverslip area. Slides were rinsed in distilled water and dehydrated with washes in an alcohol series (95%, 100% ethanol) and organic solvent (xylene, 100%, four changes). After dehydration, slides were coverslipped using non-aqueous semi-permanent mounting media.

[00159] A species-matched positive control (standard antibody) with established signal strength in control tissues was used in each IHC run (run control) to confirm proper detection reagent performance. The IHC run control used was CD3 (derived in rabbit) tested on formalin-fixed, paraffin-embedded (FFPE) control tonsil tissues. Rabbit IgG isotype-matched negative controls for the corresponding HRAS biomarker assay conditions were used to determine any non-specific staining inherent in the detection reagents or tissues and to define any potential background reactivity from these sources. Previously tested cancer tissues served as a control for HRAS reactivity during each IHC run. A multi-tissue block included different samples of head and neck (H&N) cancer and normal tonsil with various levels of HRAS expression as determined during previous testing.

[00160] A cut-off for HRAS (ARC0098) positivity was selected that considers plasma membrane or cytoplasmic tumor staining as follows: Plasma Membrane Percent Score $\geq 3+$ (consisting of 3+ intensities) of ≥ 50 or Cytoplasmic Percent Score $\geq 3+$ (consisting of 3+ intensities) of ≥ 50 = Positive. Using this cut-off to assess the 46 evaluable H&N cancer samples in the tumor screen, 35% (16/46) were positive (i.e., with 50% or more cells having a Percent Score $\geq 3+$ Plasma Membrane or Cytoplasmic) and 65% (30/46) were negative. In the tumor screen, no samples showed cytoplasmic tumor staining with Percent Score $\geq 3+$ above 25. As such, only plasma membrane tumor staining contributed to the positivity determinations for this data set.

[00161] Pathology Concordance Testing

[00162] HRAS (ARC0098) staining was observed in a subset of tumor cells where it localized to the plasma membrane and the cytoplasm. Pathology analyses and HRAS (ARC0098) plasma membrane and cytoplasmic tumor staining were evaluated by board-certified pathologists using H-Scores and/or Percent Scores according to the scoring methods described as follows:

- For tumor cell evaluation, HRAS staining is scored separately for plasma membrane and cytoplasmic staining. Staining in tumor cells is evaluated semi-quantitatively for each localization.
- The pathologist only provides semi-quantitative scores for HRAS expression in tumor cells. That is, numeric scoring excludes any signal in surrounding stroma and areas of non-tumor.
- Areas of ischemic changes, thermal artifact, and necrosis are also not scored.

- Each tissue is stained with H&E to assist the pathologist in sample evaluation during scoring.
- The main components for scoring HRAS expression in tumor cells include percentages at differential intensities to determine Percent Scores and H-Scores (described below).
- The percentage of tumor cells with HRAS staining are recorded at a corresponding differential intensity on a four-point semi-quantitative scale (0, 1+, 2+, 3+). On this scale: 0= null, negative or non-specific staining, 1+= low or weak staining, 2+= medium or moderate staining, and 3+= high or strong staining.
- The percentage of tumor cells staining at each intensity is estimated directly and typically reported as one of the following; though other increments can also be used at the pathologist's discretion: 0, 1, 2, 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 97, 98, 99, or 100%.

[00163] Analysis and scoring for HRAS expression included determination of Percent scores and H-scores. For the percent score method, tumor percent scores were calculated by summing the percentages of intensities at either $\geq 1+$, $\geq 2+$ or $\geq 3+$. Thus, scores range from 0 to 100.

$$\text{Percent Score } \geq 1+ = (\% \text{ at } 1+) + (\% \text{ at } 2+) + (\% \text{ at } 3+)$$

$$\text{Percent Score } \geq 2+ = (\% \text{ at } 2+) + (\% \text{ at } 3+)$$

$$\text{Percent Score } \geq 3+ = (\% \text{ at } 3+)$$

[00164] For the H-Score method, the tumor H-score was calculated by summing the percentage of cells with intensity of expression (brown staining) multiplied by their corresponding differential intensity on a four-point semi-quantitative scale (0, 1+, 2+, 3+). Thus, scores ranged from 0 to 300.

$$\begin{aligned} \text{H-Score} = & [(\% \text{ at } <1) \times 0] + [(\% \text{ at } 1+) \times 1] + [(\% \text{ at } 2+) \times 2] \\ & + [(\% \text{ at } 3+) \times 3] \end{aligned}$$

[00165] A positivity cut-off for HRAS positivity was applied to confidence interval (CI) assessments to demonstrate positive/negative agreement for acceptable concordance in the validation studies herein. The positivity cut-off is also intended for use in clinical sample testing. The cut-off is described below:

Positivity Cut-Off: Plasma Membrane Percent Score $\geq 3+$

(consisting of 3+ intensities) of ≥ 50 OR Cytoplasmic Percent Score
 $\geq 3+$ (consisting of 3+ intensities) of ≥ 50 = Positive.

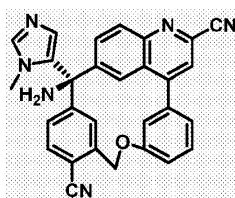
[00166] The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or are able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the invention and are encompassed by the appended claims.

INCORPORATION BY REFERENCE

[00167] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference in their entireties to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference in its entirety. In case of conflict, the present application, including any definitions herein, will control.

What is claimed is:

1. A method of treating squamous cell carcinoma (SCC) in a subject comprising administering to the subject (a) Compound (I):



Compound (I)

- or a pharmaceutically acceptable form thereof, and (b) a PI3K inhibitor.
2. The method of claim 1, wherein the method mitigates PI3K inhibitor resistance.
3. A method of mitigating PI3K inhibitor resistance in an SCC in a subject comprising administering to the subject (a) Compound (I), or a pharmaceutically acceptable form thereof, and (b) a PI3K inhibitor.
4. The method of claim 2 or claim 3, wherein the subject is PI3K inhibitor-naïve, PI3K inhibitor relapsed, or PI3K inhibitor refractory.
5. The method of claim 1, wherein the method mitigates EGFR inhibitor resistance.
6. A method of mitigating EGFR inhibitor resistance in an SCC in a subject comprising administering to the subject (a) Compound (I), or a pharmaceutically acceptable form thereof, and (b) a PI3K inhibitor.
7. The method of claim 5 or claim 6, comprising administering the EGFR inhibitor to the subject, optionally wherein the subject is EGFR inhibitor-naïve, EGFR inhibitor relapsed, or EGFR inhibitor refractory.
8. The method of any one of claims 5 to 7, wherein the EGFR inhibitor is cetuximab, panitumumab, or afatinib.
9. The method of any one of claims 1 to 8, wherein the SCC is a PIK3CA-dependent SCC.

10. A method of treating PI3K-dependent SCC in a subject comprising administering to the subject Compound (I) or a pharmaceutically acceptable form thereof.
11. The method of claim 9 or claim 10, wherein the PIK3CA-dependent SCC comprises a PIK3CA mutation.
12. The method of claim 11, wherein the PIK3CA mutation is or comprises a modification in a codon that encodes an amino acid substitution at a specific position selected from a group consisting of R38, E39, E78, R88, R93, E103, P104, V105, G106, R108, E109, E110, K111, G118, P124, E218, V344, N345, D350, G364, E365, P366, C378, C420, P447, P449, H450, G451, E453, P471, P539, E542, E545, Q546, D549, E579, E600, C604, S629, V638, C901, G914, D939, E970, M1004, G1007, Y1021, T1025, D1029, E1037, M1043, N1044, H1047, G1049, A1066, and N1068, and any combination thereof, in the corresponding mutant PI3K protein, optionally wherein the PIK3CA mutation is or comprises a modification in a codon that encodes an amino acid substitution at a specific position selected from a group consisting of G118, C420, E542, E545, Q546, H1047, and any combination thereof, in the corresponding mutant PI3K protein.
13. The method of any one of claims 10 to 12, wherein the PI3K-dependent SCC comprises a PIK3CA gene amplification or a PIK3CA copy gain.
14. The method of any one of claims 1 to 13, wherein the SCC is an HRAS-dependent SCC.
15. The method of claim 14, wherein the SCC comprises an HRAS mutation.
16. The method of claim 15, wherein the HRAS mutation is or comprises a modification in a codon that encodes an amino acid substitution at a specific position selected from a group consisting of G12, G13, Q61, Q22, K117, A146, and any combination thereof, in the corresponding mutant HRas protein.
17. The method of any one of claims 14 to 16, wherein the SCC overexpresses wild-type HRas protein.

18. The method of any one of claims 1 to 17, wherein Compound (I), or a pharmaceutically acceptable form thereof, is administered orally.

19. The method of any one of claims 1 to 18, wherein Compound (I), or a pharmaceutically acceptable form thereof, is administered at a dose of 0.01-50 mg/kg body weight per day, or at a dose of 0.5-2400 mg per day, or at a dose selected from about 0.5 mg, about 1 mg, about 1.5 mg, about 1.6 mg, about 1.7 mg, about 1.8 mg, about 1.9 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, about 2000 mg, about 2100 mg, about 2200 mg, about 2300 mg, and about 2400 mg per day.

20. The method of any one of claims 1 to 19, wherein Compound (I), or a pharmaceutically acceptable form thereof, is administered 1, 2, 3, or 4 times per day, or is administered once per day, or administered twice per day.

21. The method of any one of claims 1 to 9 or 11 to 20, wherein the PI3K inhibitor is administered orally.

22. The method of any one of claims 1 to 9 and 11 to 21, wherein the PI3K inhibitor is administered to the patient at a dose of 10 to 400 mg per day, or at a dose of about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg or about 300 mg per day.

23. The method of any one of claims 1 to 9 and 11 to 22, wherein the PI3K inhibitor is administered once or twice per day.

24. The method of any one of claims 1 to 23, wherein Compound (I), or a pharmaceutically acceptable form thereof, is administered once or twice per day on days 1-7 of a 28-day cycle, or on days 1-7 and 15-21 of a 28-day cycle, or on days 1-21 of a 28-day cycle, or on days 1-28 of a 28-day cycle, and, where the PI3K inhibitor is administered, said PI3K inhibitor is administered once per day of a 28-day cycle.
25. The method of any one of claims 1 to 24, wherein the method delays, halts, or prevents progression of SCC and/or SCC tumor growth.
26. The method of any one of claims 1 to 25, wherein the method increases Time to Progression (TTP), Progression Free Survival (PFS), Event-free survival (EFS), Overall Survival (OS), overall response rate (ORR), disease control rate (DCR), or duration of response (DoR), or increases Time to Response (TTR), or any combination thereof, compared to no therapy, chemotherapy, single agent therapy, first-line therapy, second-line therapy, anti-EGFR antibody therapy, immunotherapy, or localized and loco-regional disease therapies.
27. The method of any one of claims 1 to 9 and 11 to 26, wherein the PI3K inhibitor is a PI3K α inhibitor, or is selected from alpelisib (PIQRAY®; BYL719), AMG319, AZD8168, AZD8835, buparlisib, B591, CH5132799, copanlisib (aliqopa), delalisib (zydelig), duvelisib (copiktra), eganelisib, GSK2636771, leniolisib, linperlisib, parsacalisib, pictilisib, pilaralisib, RIDR-PI-103, serabelisib, sonolisib, taselisib, tenalisib, TG-100-115, umbralisib, zandelisib, ZSTK474, STX-478, RLY-2608, LOXO-783, or inavolisib, or a pharmaceutically acceptable form thereof.
28. The method of claim 27, wherein the PI3K inhibitor is alpelisib.
29. The method of any one of claims 1 to 28, wherein the SCC is early stage, advanced, relapsed, refractory, or metastatic, or is recurrent and/or metastatic.
30. The method of any one of claims 1 to 29, wherein the SCC is HNSCC, oral cavity HNSCC, pharynx HNSCC, larynx HNSCC, tonsil HNSCC, sinonasal HNSCC, nasopharyngeal HNSCC, esophageal SCC, lung SCC, thyroid SCC, cervical SCC, urothelial SCC, bladder SCC, vaginal SCC, or prostate SCC; or the SCC is cutaneous SCC.

31. A pharmaceutical kit, comprising (a) a pharmaceutical composition comprising Compound (I), or a pharmaceutically acceptable form thereof, and a pharmaceutically acceptable carrier, diluent, or excipient, and (b) a pharmaceutical composition comprising a PI3K inhibitor and a pharmaceutically acceptable carrier, diluent, or excipient.
32. The pharmaceutical kit of claim 31, wherein the pharmaceutical kit comprises instructions for administering the contents of the kit to a patient having SCC.
33. The pharmaceutical kit of claim 31 or claim 32, wherein the PI3K inhibitor is alpelisib.
34. The pharmaceutical kit of claim 32 or claim 33, wherein the SCC is early stage, advanced, relapsed, refractory, or metastatic, or is recurrent and/or metastatic.
35. The pharmaceutical kit of any one of claims 32 to 34, wherein the SCC is HNSCC, oral cavity HNSCC, pharynx HNSCC, larynx HNSCC, tonsil HNSCC, sinonasal HNSCC, nasopharyngeal HNSCC, esophageal SCC, lung SCC, thyroid SCC, cervical SCC, urothelial SCC, bladder SCC, vaginal SCC, or prostate SCC.