allosteric pocket 1 and may be utilized in combination therapies, for example, combination therapies in which the disclosed PI3Kα inhibitors are used in combination with PI3Kα inhibitors that target other pockets of PI3Kα, such as the PI3Kα orthosteric pocket.

[11] The present invention also provides a characterization of another non-ATP binding pocket of PI3Kα, which is referred to as "the PI3Kα allosteric pocket 2," and the interaction of inhibitors of PI3Kα with the PI3Kα allosteric pocket 2. The disclosed kinase inhibitors which target PI3Kα allosteric pocket 1 may be used in combination therapies with PI3Kα inhibitors that target the PI3Kα allosteric pocket 2.

Summary

[12] The disclosure relates to the use of inhibitors of phosphoinositide 3-kinase (PI3K) that target allosteric and orthosteric pockets of PI3K in methods of treating, preventing, or ameliorating a disease, or disorder, (or uses in the treatment, prevention, or amelioration of a disease, or disorder), in which PI3K plays a role. The PI3K inhibitors may be utilized in combination and may target an allosteric pocket of phosphatidylinositol 3-kinase alpha (PI3Kα) referred to herein as "PI3Kα allosteric pocket 1,," an allosteric pocket of PI3Kα referred to herein as "PI3Kα allosteric pocket 2," or the PI3Kα orthosteric pocket. (*See* Fig. 1). In some examples of the disclosed methods, a PI3Kα inhibitor may target the PI3Kα allosteric pocket 1, the PI3Kα allosteric pocket 2, or the PI3Kα orthosteric pocket of a PI3Kα mutant that is resistant to treatment with another PI3Kα inhibitor, for example a PI3Kα inhibitor that targets a different pocket of PI3Kα.

[13] The methods may include administering to a patient in need thereof a therapeutically effective amount of a PI3K inhibitor of the present disclosure or combinations of PI3K inhibitors of the present disclosure and other PI3K inhibitors, which may include other allosteric inhibitors of PI3K and orthosteric inhibitors of PI3K. The methods and PI3K inhibitors of the present disclosure can be used in the treatment of a variety of PI3K-dependent or PI3K-associated diseases, and disorders.

[14] In some examples, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3Kα. The methods may comprise administering to a patient in need thereof: (i) a therapeutically effective amount of a first PI3Kα selective inhibitor, wherein the first

PI3Kα selective inhibitor binds to the PI3Kα allosteric pocket 1; and (ii) a therapeutically effective amount of a second PI3Kα selective inhibitor, wherein the second PI3Kα selective inhibitor binds to the PI3Kα orthosteric pocket.

[15] In some examples, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3Kα. The methods may comprise administering to a patient in need thereof: (i) a therapeutically effective amount of a first PI3Kα selective inhibitor, wherein the first PI3Kα selective inhibitor binds to the PI3Kα allosteric pocket 2; and (ii) a therapeutically effective amount of a second PI3Kα selective inhibitor, wherein the second PI3Kα selective inhibitor binds to the PI3Kα orthosteric pocket.

[16] In some examples, the disclosed methods may comprise administering to the patient: (i) a therapeutically effective amount of a first PI3Kα selective inhibitor, wherein the first PI3Kα selective inhibitor binds to PI3Kα allosteric pocket 1; and (ii) a therapeutically effective amount of a second PI3Kα selective inhibitor, wherein the second PI3Kα selective inhibitor binds to PI3Kα allosteric pocket 2.

[17] In some examples, the disclosed methods may comprise administering to the patient: (i) a therapeutically effective amount of a first PI3Kα selective inhibitor, wherein the first PI3Kα selective inhibitor binds to PI3Kα allosteric pocket 1; and (ii) a therapeutically effective amount of a second PI3Kα selective inhibitor which is different from the first PI3Kα selective inhibitor, wherein the second different PI3Kα selective inhibitor binds to the PI3Kα allosteric pocket 1. In some examples, the first PI3Kα selective inhibitor and the second PI3Kα selective inhibitor competitively bind to PI3Kα allosteric pocket 1.

[18] In the disclosed methods, the first PI3Kα selective inhibitor and the second PI3Kα selective inhibitor are administered simultaneously, separately, or sequentially. In some examples, the second PI3Kα selective inhibitor is administered to the patient if the patient has a disease or disorder that is resistant to treatment with the first PI3Kα selective inhibitor. In some examples, the second PI3Kα selective inhibitor is administered to the patient after the disease or disorder of the patient has acquired resistance to treatment with the first PI3Kα selective inhibitor.

[19] In some examples of the disclosed methods which comprise administering a therapeutically

effective amount of a first PI3Kα selective inhibitor and a therapeutically effective amount of a second PI3Kα selective inhibitor, an additive effect or synergistic effect may be observed. In some examples of the disclosed methods, the therapeutically effective amount of the first PI3Kα selective inhibitor administered in the disclosed methods may be less than a therapeutically effective amount of the first PI3Kα selective inhibitor that is required in a treatment method where the second PI3Kα selective inhibitor is not administered. In some examples of the disclosed methods, the therapeutically effective amount of the second PI3Kα selective inhibitor administered in the disclosed methods may be less than a therapeutically effective amount of the second PI3Kα selective inhibitor that is required in a treatment method where the first PI3Kα selective inhibitor is not administered.

[20] In some examples of the disclosed methods, the therapeutically effective amount of the first PI3Kα selective inhibitor is effective for reducing PI3Kα activity in the patient without inducing adverse events, or while minimizing the risk of adverse events. In some examples of the disclosed methods, the therapeutically effective amount of the second PI3Kα selective inhibitor is effective for reducing PI3Kα activity in the patient without inducing adverse events, or while minimizing the risk of adverse events. Adverse events may include, but are not limited to hyperglycemia, hyperinsulinemia, diarrhea, dehydration, skin rash, lymphopenia, increased alanine transaminase, fatigue, anemia, elevated serum lipase, anorexia, stomatitis, vomiting, weight loss, hypocalcemia, hypoglycemic disorder, alopecia, prolonged activated partial thromboplastin time, kidney disease with reduction in glomerular filtration rate (GFR), acute abdominal pain, and abnormal hepatic function tests.

[21] In some examples, the disclosed methods relate to methods for treating a disease or disorder that is associated with modulation of PI3Kα in a patient that has a disease or disorder that is resistant to treatment with a PI3Kα selective inhibitor, which may be a PI3Kα selective allosteric inhibitor or a PI3Kα selective orthosteric inhibitor. The methods may comprise administering to the patient a different PI3Kα selective inhibitor to which the disease or disorder is not resistant, such as a PI3Kα selective allosteric inhibitor or a PI3Kα selective orthosteric inhibitor.

[22] In some examples, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3Kα in a patient that has a disease or disorder that is resistant to

treatment with a PI3Kα selective orthosteric inhibitor. In some examples, the disclosed methods relate to treating a disease or disorder associated with modulation of PI3Kα in a patient that is identified as having a disease or disorder that is resistant to treatment with a PI3Kα selective orthosteric inhibitor or in a patient that is identified as having a disease or disorder which exhibits an incomplete response to treatment with a PI3Kα selective orthosteric inhibitor. In some examples, the methods may comprise administering to a patient that is identified as having a disease or disorder that is resistant to treatment with a PI3Kα selective orthosteric inhibitor or that is identified as having a disease or disorder that exhibits an incomplete response to treatment with a PI3Kα selective orthosteric inhibitor, a therapeutically effective amount of a PI3Kα selective allosteric inhibitor, wherein the PI3Kα selective allosteric inhibitor binds to the PI3Kα allosteric pocket 1. In some examples, the methods may comprise administering to a patient that is identified as having a disease or disorder that is resistant to treatment with a PI3Kα selective orthosteric inhibitor or that is identified as having a disease or disorder which exhibits an incomplete response to treatment with a PI3Kα selective orthosteric inhibitor, a therapeutically effective amount of a PI3Kα selective allosteric inhibitor, wherein the PI3Kα selective allosteric inhibitor binds to the PI3Kα allosteric pocket 2.

[23] In some examples, the disclosed methods relate to treating a disease or disorder associated with modulation of PI3Kα that is resistant to treatment with a first PI3Kα selective allosteric inhibitor, wherein the first PI3Kα selective allosteric inhibitor binds to the PI3Kα allosteric pocket 1. In some examples, the methods may comprise administering to a patient having the resistant disease or disorder a therapeutically effective amount of a second different PI3Kα selective allosteric inhibitor that binds to the PI3Kα allosteric pocket 1. In some examples, the methods may comprise administering to a patient having the resistant disease or disorder a therapeutically effective amount of a second different PI3Kα selective allosteric inhibitor that binds to the PI3Kα allosteric pocket 2. In some examples, the methods may comprise administering to a patient having the resistant disease or disorder a therapeutically effective amount of a PI3Kα selective inhibitor that binds to the PI3Kα orthosteric pocket.

[24] In some examples, the disclosed methods relate to treating a disease or disorder associated with modulation of PI3Kα that is resistant to treatment with a first PI3Kα selective allosteric inhibitor,

wherein the first PI3Kα selective allosteric inhibitor binds to PI3Kα allosteric pocket 2. In some examples, the methods may comprise administering to a patient having the resistant disease or disorder a therapeutically effective amount of a second different PI3Kα selective allosteric inhibitor that binds to the PI3Kα allosteric pocket 1. In some examples, the methods may comprise administering to a patient having the resistant disease or disorder a therapeutically effective amount of a PI3Kα selective inhibitor that binds to the PI3Kα orthosteric pocket.

[25] In some examples, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3Kα in a patient in need thereof, wherein the patient has been treated previously with a therapeutically effective amount of a PI3Kα selective inhibitor, and the disease or disorder of the patient has acquired resistance to treatment with the PI3Kα selective inhibitor. The method may include administered to the patient a different PI3Kα selective inhibitor to which the disease or disorder is not resistant.

[26] In some examples, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3Kα in a patient in need thereof, wherein the patient previously has been treated with a therapeutically effective amount of a PI3Kα selective allosteric inhibitor, wherein the PI3Kα selective allosteric inhibitor binds to the PI3Kα allosteric pocket 1 or the PI3Kα allosteric pocket 2. In the disclosed methods, the disease or disorder of the patient may have acquired resistance to treatment with the PI3Kα selective allosteric inhibitor, and the methods may comprise administering to the patient a therapeutically effective amount of a PI3Kα selective orthosteric inhibitor. In the disclosed methods, the disease or disorder of the patient may have acquired resistance to treatment with the PI3Kα selective allosteric inhibitor that binds to the PI3Kα allosteric pocket 1, and the methods may comprise administering to the patient a therapeutically effective amount of a different PI3Kα selective allosteric inhibitor that binds to the PI3Kα allosteric pocket 2. In the disclosed methods, the disease or disorder of the patient may have acquired resistance to treatment with the PI3Kα selective allosteric inhibitor that binds to the PI3Kα allosteric pocket 2, and the methods may comprise administering to the patient a therapeutically effective amount of a different PI3Kα selective allosteric inhibitor that binds to the PI3Kα allosteric pocket 1. In the disclosed methods, the disease or disorder of the patient may have acquired resistance to

treatment with the PI3Kα selective allosteric inhibitor that binds to the PI3Kα allosteric pocket 1, and the methods may comprise administering to the patient a therapeutically effective amount of a different PI3Kα selective allosteric inhibitor that binds to the PI3Kα allosteric pocket 1.

[27] In some examples, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3Kα in a patient in need thereof, wherein the patient previously has been treated with a therapeutically effective amount of a PI3Kα selective allosteric inhibitor, wherein the PI3Kα selective allosteric inhibitor binds to the PI3Kα allosteric pocket 1 or the PI3Kα allosteric pocket 2. In the disclosed methods, the disease or disorder of the patient may have acquired resistance to treatment with the PI3Kα selective allosteric inhibitor, and the methods may comprise administering to the patient a therapeutically effective amount of a PI3Kα selective orthosteric inhibitor. In the disclosed methods, the disease or disorder of the patient may have acquired resistance to treatment with the PI3Kα selective allosteric inhibitor that binds to the PI3Kα allosteric pocket 1, and the methods may comprise administering to the patient a therapeutically effective amount of a different PI3Kα selective allosteric inhibitor that binds to the PI3Kα allosteric pocket 2. In the disclosed methods, the disease or disorder of the patient may have acquired resistance to treatment with the PI3Kα selective allosteric inhibitor that binds to the PI3Kα allosteric pocket 2, and the methods may comprise administering to the patient a therapeutically effective amount of a different PI3Kα selective allosteric inhibitor that binds to the PI3Kα allosteric pocket 1. In the disclosed methods, the disease or disorder of the patient may have acquired resistance to treatment with the PI3Kα selective allosteric inhibitor that binds to the PI3Kα allosteric pocket 1, and the methods may comprise administering to the patient a therapeutically effective amount of a different PI3Kα selective allosteric inhibitor that binds to the PI3Kα allosteric pocket 1.

[28] In some examples, the disclosed methods relate to methods for treating a disease or disorder associated with modulation of PI3Kα in a patient in need thereof, wherein the patient has a disease or disorder comprising an M1043 mutation (e.g., M1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with an H1047R mutation). The methods may comprise administering to the patient having the disease or disorder a therapeutically effective amount of a PI3Kα selective orthosteric inhibitor. The methods may comprise

administering to the patient having the disease or disorder comprising an M1043 mutation (e.g., M1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with an H1047R mutation) a therapeutically effective amount of a PI3Kα allosteric inhibitor, wherein the PI3Kα allosteric inhibitor binds to the PI3Kα allosteric pocket 1. The methods may comprise administering to the patient having the disease or disorder comprising an M1043 mutation (e.g., M1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with an H1047R mutation) a therapeutically effective amount of a PI3Kα selective allosteric inhibitor that binds the PI3Kα allosteric pocket 2.

[29] In some examples, the methods related to methods for treating a disease or disorder associated with modulation of PI3Kα in a patient in need thereof, such as a patient having a disease or disorder comprising an M1043 mutation (e.g., M1043I/L optionally in *cis* with an H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in cis with an H1047R mutation). The methods may comprise determining that the patient has a disease or disorder comprising the M1043 mutation (e.g., M1043I/L optionally in *cis* with the H1047R mutation) and/or the C901 mutation (e.g., C901F optionally in *cis* with the H1047R mutation), for example, by ordering or performing a genomic analysis. If the patient is found to have a disease or disorder comprising the M1043 mutation (e.g., M1043I/L optionally in *cis* with the H1047R mutation) and/or the C901 mutation (e.g., C901F optionally in *cis* with the H1047R mutation), the methods further may comprise administering treatment to the patient, which may include administering one or more PI3Kα selective inhibitors to the patient, which may include allosteric inhibitors (e.g., an allosteric inhibitor that binds to the PI3Kα allosteric pocket 1 and/or an allosteric inhibitor that binds to the PI3Kα allosteric pocket 2), orthosteric inhibitors, or combinations thereof as disclosed herein.

[30] In some examples, the disclosed methods comprise selecting a patient for treatment with one or more PI3Kα selective inhibitors. In some examples, the patient is selected based on the patient having disease or disorder comprising a M1043 mutation (e.g., M1043I/L optionally in *cis* with the H1047R mutation) and/or a C901 mutation (e.g., C901F optionally in *cis* with the H1047R mutation). Optionally, a selected patient may be administered treatment, which may include administering one or more PI3Kα selective inhibitors to the patient, which may include allosteric inhibitors (e.g.,

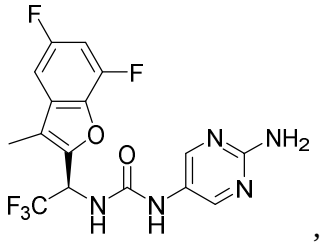
allosteric inhibitor that binds to the PI3Kα allosteric pocket 1 or an allosteric inhibitor that binds to the PI3Kα allosteric pocket 2), orthosteric inhibitors, or combinations thereof as disclosed herein.

[31] In the disclosed methods, a patient in need thereof may have cancer. In some examples, the patient in need thereof may have breast cancer. In some examples, the patient in need thereof may have PIK3CA-mutated, advanced, or metastatic breast cancer. In some examples, the patient in need thereof may have PIK3CA H1047R-mutant advanced, or metastatic breast cancer that is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-).

[32] In the disclosed methods, a patient in need thereof may have cancer and may have been previously administered one or more therapeutic agents for treating the cancer, which may include a PI3Kα selective inhibitor. In some examples, the patient may have a cancer which exhibits *de novo* resistance or acquired resistance to treatment with a therapeutic agent, which may include a PI3Kα selective inhibitor, and the patient may be administered a different therapeutic agent, which may include a different PI3Kα selective inhibitor.

[33] In the disclosed methods, the patient may have not been previously administered a therapeutic agent for treating the cancer, which may include a PI3Kα selective inhibitor. In some examples, the patient may be characterized as naïve to treatment with a PI3Kα selective inhibitor.

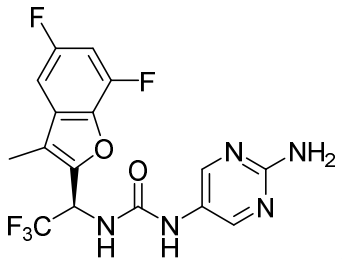
[33a] In an aspect, there is provided use of a PI3Kα selective inhibitor that binds to PI3Kα allosteric pocket 2 in the manufacture of a medicament for treating a cancer associated with modulation of phosphatidylinositol 3-kinase alpha (PI3Kα) that is resistant to treatment with alpelisib or inavolisib in a patient, wherein the PI3Kα selective inhibitor is:



,

or a pharmaceutically acceptable salt thereof.

[33b] In another aspect, there is provided use of a PI3Kα selective inhibitor in the manufacture of a medicament for treating a cancer associated with modulation of phosphatidylinositol 3-kinase alpha (PI3Kα) in a patient, wherein the patient has a cancer comprising an M1043I/L mutation in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047R mutation, and wherein the PI3Kα selective inhibitor is:



,

or a pharmaceutically acceptable salt thereof.

Brief Description of the Figures

[34] Fig. 1. Schematic illustration of PI3Kα (H1047R) showing Orthosteric pocket, Allosteric pocket 1, and Allosteric pocket 2.

[35] Fig. 2. Dose response curve for alpelisib in a T47D (M1043I+H1047R) (double, in *cis*, 6×) cell proliferation assay.

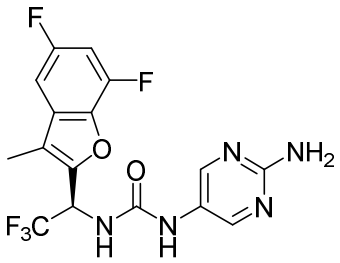
[36] Fig. 3. Dose response curve for Compound 21 in a T47D (M1043I+H1047R) (double, in *cis*, 6×) cell proliferation assay.

[37] Fig. 4. Dose response curve for Compound N1 in a T47D (M1043I+H1047R) (double, in *cis*, 6×) cell proliferation assay.

[38] Fig. 5. Dose response curve for Compound N2 in a T47D (M1043I+H1047R) (double, in *cis*, 6×) cell proliferation assay.

CLAIMS

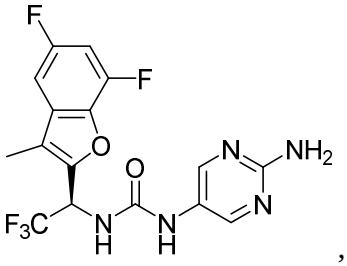
1. Use of a PI3Kα selective inhibitor that binds to PI3Kα allosteric pocket 2 in the manufacture of a medicament for treating a cancer associated with modulation of phosphatidylinositol 3-kinase alpha (PI3Kα) that is resistant to treatment with alpelisib or inavolisib in a patient, wherein the PI3Kα selective inhibitor is:



,

or a pharmaceutically acceptable salt thereof.

2. Use of a PI3Kα selective inhibitor in the manufacture of a medicament for treating a cancer associated with modulation of phosphatidylinositol 3-kinase alpha (PI3Kα) in a patient, wherein the patient has a cancer comprising an M1043I/L mutation in *cis* with an H1047R mutation and/or a C901F mutation in *cis* with an H1047R mutation, and wherein the PI3Kα selective inhibitor is:



,

or a pharmaceutically acceptable salt thereof.

3. The use of claim 1 or 2, wherein the cancer is breast cancer.

4. The use of claim 1 or 2, wherein the cancer is PIK3CA-mutated, advanced or metastatic breast cancer.

5. The use of claim 1 or 2, wherein the cancer is PIK3CA H1047R-mutant advanced or metastatic breast cancer.

6. The use of claim 1 or 2, wherein the cancer is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-), PIK3CA H1047R-mutant advanced or metastatic breast cancer.

7. The use of claim 1 or 2, wherein the patient is a postmenopausal female.

8. The use of claim 1 or 2, wherein the patient has type II diabetes mellitus.

9. The use of claim 1 or 2, wherein the PI3Kα selective inhibitor is to be administered with a selective estrogen receptor degrader (SERD).

10. The use of claim 9, wherein the SERD is selected from imlunestrant, fulvestrant, giredestrant, amcenestrant, rintodestrant, elacestrant, and camizestrant.

11. The use of claim 10, wherein the SERD is to be administered at a 500 mg dose on days 1, 15, and 29.