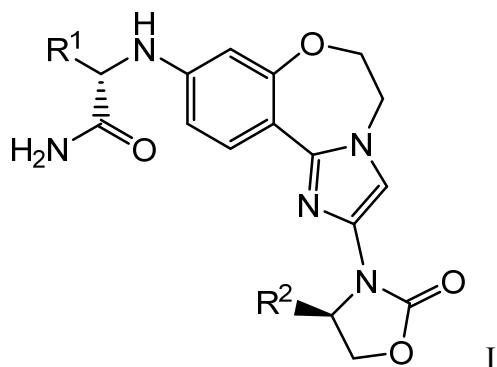


chronic lymphoid leukemia, CLL (Somoza, J.R. et al (2015) J. Biol. Chem. 290:8439-8446; US 6800620; US 6949535; US 8138195; US 8492389; US 8637533; US 8865730; US 8980901; RE44599; RE44638). Diarrhea and colitis are among the most common adverse events reported after idelalisib treatment (Brown et al “Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110d, for relapsed/refractory chronic lymphocytic leukemia” (2014) Blood 123(22):3390-3397; Zydelig® Prescribing Information 2014; Zydelig® REMS Fact Sheet). The significant GI toxicities observed after treatment with idelalisib are consistent with the hypothesis that inhibition of PI3K δ (delta) is a source of gastrointestinal toxicities. Additional serious side effects were seen in clinical trials of idelalisib (Zydelig®) in combination with other therapies. Adverse events, including deaths have been tied to infections such as pneumonia. In March 2016, the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) issued a provisional warning and a recommendation that patients receive antibiotic co-treatment and are routinely monitored for infection when taking Zydelig (idelalisib). In March 2016, the US Food and Drug Administration issued an alert that “six clinical trials exploring idelalisib (Zydelig®) in combination with other therapies have been halted due to reports of an increased rate of adverse events, including death”.

There is a need for additional modulators of PI3K α that are useful for treating cancers, particularly an inhibitor of PI3K α that is selective for mutant PI3K α expressing tumors relative to non-mutant PI3K α expressing cells. There is especially a need for such an agent that selectively inhibits the PI3K α isoform relative to the PI3K β , PI3K δ , and PI3K γ isoforms, which may be expected to result in an enhanced therapeutic window.

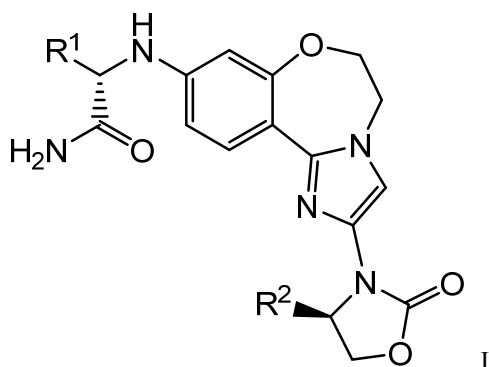
SUMMARY

The disclosure relates generally to benzoxazepin oxazolidinone compounds with selective activity in modulating mutant forms of the PI3K α (alpha) isoform, and having the Formula I structure:



and stereoisomers, geometric isomers, tautomers, and pharmaceutically acceptable salts thereof. The various substituents are defined herein.

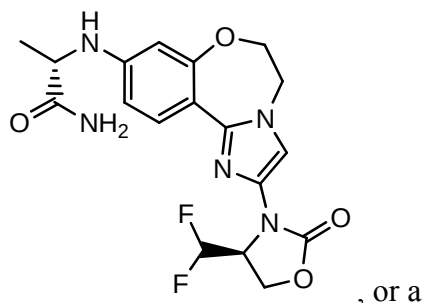
In one aspect, the present disclosure relates to a compound selected from Formula I:



5

or a stereoisomer, a tautomer, and a pharmaceutically acceptable salt thereof, wherein: R^1 is selected from $-CH_3$, $-CH_2CH_3$, cyclopropyl, and cyclobutyl; R^2 is selected from $-CH_3$, $-CHF_2$, $-CH_2F$, and $-CF_3$.

In another aspect, the present disclosure relates to a compound (S)-2-((2-((S)-4-
10 (difluoromethyl)-2-oxooxazolidin-3-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-



yl)amino)propanamide, having the structure
pharmaceutically acceptable salt thereof.

The present disclosure relates to a pharmaceutical composition comprising a benzoxazepin oxazolidinone compound of Formula I, and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

5 In another aspect, the present disclosure relates to a pharmaceutical composition comprised of a compound or a pharmaceutically acceptable salt thereof as defined herein, and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

10 In another aspect, the present disclosure relates to a pharmaceutical composition comprised of a compound or a pharmaceutically acceptable salt thereof as defined herein, and one or more additional therapeutic agents selected from palbociclib, fulvestrant and letrozole, and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

In another aspect, the present disclosure relates to a process for making a pharmaceutical composition comprising combining a compound or a pharmaceutically acceptable salt thereof as defined herein, with a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

15 The present disclosure relates to a method of treating cancer in a patient having cancer comprising administering to said patient a therapeutically effective amount of a benzoxazepin oxazolidinone compound of Formula I.

20 In another aspect, the present disclosure relates to the use of a compound or a pharmaceutically acceptable salt thereof as defined herein in the manufacture of a medicament for treating cancer in a patient wherein the cancer is selected from breast cancer and non-small cell lung cancer.

The present disclosure relates to a kit for the therapeutic treatment of breast cancer, comprising:

- a) a benzoxazepin oxazolidinone compound of Formula I; and
- 25 b) instructions for use in the therapeutic treatment of breast cancer

In another aspect, the present disclosure relates to a kit for the therapeutic treatment of breast cancer, comprising:

- a) the pharmaceutical composition as defined herein; and
- b) instructions for use in the therapeutic treatment of breast cancer.

5 In another aspect, the present disclosure relates to the compound or a pharmaceutically acceptable salt thereof as defined herein for use for treating cancer in a patient wherein the cancer is selected from breast cancer and non-small cell lung cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

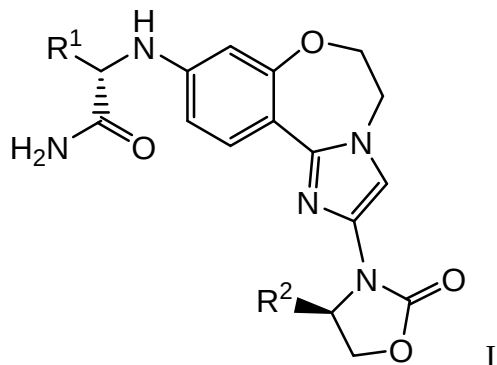
Figure 1 shows the x-ray co-crystal structures of PI3K α with: A) taselisib (GDC-
10 0032), B) Compound 529 of US 8242104, C) Compound **101**, and D) Compound **103**.

Figure 2 shows the x-ray co-crystal structures of PI3K α with: A) taselisib (GDC-0032), and B) Compound **101**.

Figure 3A shows Western-blot data depicting p110 α (p110a, p110 alpha) levels after 24 hour treatment with Compound **101**, Compound **103** and Compound 436 of US 8242104
15 in HCC-1954 cells (PI3K α mutant H1047R).

CLAIMS

1. A compound selected from Formula I:



or a stereoisomer, a tautomer, and a pharmaceutically acceptable salt thereof,

5 wherein:

R^1 is selected from $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, cyclopropyl, and cyclobutyl;

R^2 is selected from $-\text{CH}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, and $-\text{CF}_3$.

2. The compound of claim 1 wherein R^1 is CH_3 or cyclopropyl.

3. The compound of claim 1 or 2, wherein R^2 is $-\text{CHF}_2$.

10

4. The compound of any one of claims 1-3 wherein Formula I is:

(*S*)-2-cyclobutyl-2-((2-((*R*)-4-methyl-2-oxooxazolidin-3-yl)-5,6-dihydrobenzo[*f*]imidazo[1,2-*d*][1,4]oxazepin-9-yl)amino)acetamide, or a pharmaceutically acceptable salt thereof.

15

5. The compound of any one of claims 1-3 wherein Formula I is:

(S)-2-cyclopropyl-2-((2-((S)-4-(difluoromethyl)-2-oxooxazolidin-3-yl)-5,6-dihydrobenzo[f]imidazo[1,2-*d*][1,4]oxazepin-9-yl)amino)acetamide, or a pharmaceutically acceptable salt thereof.

5 6. The compound of any one of claims 1-3 wherein Formula I is:

(S)-2-cyclopropyl-2-((2-((R)-4-methyl-2-oxooxazolidin-3-yl)-5,6-dihydrobenzo[f]imidazo[1,2-*d*][1,4]oxazepin-9-yl)amino)acetamide, or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1-3 wherein Formula I is:

10 (S)-2-cyclopropyl-2-((2-((S)-4-(fluoromethyl)-2-oxooxazolidin-3-yl)-5,6-dihydrobenzo[f]imidazo[1,2-*d*][1,4]oxazepin-9-yl)amino)acetamide, or a pharmaceutically acceptable salt thereof.

8. The compound of any one claims 1-3 wherein Formula I is:

15 (S)-2-((2-((S)-4-(fluoromethyl)-2-oxooxazolidin-3-yl)-5,6-dihydrobenzo[f]imidazo[1,2-*d*][1,4]oxazepin-9-yl)amino)propanamide, or a pharmaceutically acceptable salt thereof.

9. The compound of any one of claims 1-3 wherein Formula I is:

20 (S)-2-((2-((S)-4-(difluoromethyl)-2-oxooxazolidin-3-yl)-5,6-dihydrobenzo[f]imidazo[1,2-*d*][1,4]oxazepin-9-yl)amino)butanamide, or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprised of a compound or a pharmaceutically acceptable salt thereof of any one of claims 1-9 and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

11. The pharmaceutical composition of claim 10 wherein the pharmaceutically acceptable carrier, glidant, diluent, or excipient is selected from silicon dioxide, powdered cellulose, microcrystalline cellulose, metallic stearates, sodium aluminosilicate, sodium benzoate, calcium carbonate, calcium silicate, corn starch, magnesium carbonate, asbestos
5 free talc, stearowet C, starch, starch 1500, magnesium lauryl sulfate, magnesium oxide, and combinations thereof.

12. A process for making a pharmaceutical composition comprising combining a compound or a pharmaceutically acceptable salt thereof of any one of claims 1-9 with a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

13. The use of a compound or a pharmaceutically acceptable salt thereof of any one of claims 1-9 in the manufacture of a medicament for treating cancer in a patient wherein the cancer is selected from breast cancer and non-small cell lung cancer.

14. The use of claim 13 further comprising an additional therapeutic agent
5 selected from 5-FU, docetaxel, eribulin, gemcitabine, cobimetinib, ipatasertib, paclitaxel, tamoxifen, fulvestrant, GDC-0810, dexamethasone, palbociclib, bevacizumab, pertuzumab, trastuzumab emtansine, trastuzumab and letrozole.

15. The use of claim 13 wherein the cancer is breast cancer.

16. The use of claim 15 wherein the breast cancer is estrogen receptor positive
10 (ER+) breast cancer.

17. The use of claim 15 wherein the breast cancer subtype is Basal or Luminal.

18. The use of claim 13 wherein the cancer expresses a PIK3CA mutant selected from E542K, E545K, Q546R, H1047L and H1047R.

19. The use of claim 13 wherein the cancer expresses a PTEN mutant.

20. The use of claim 15 wherein the cancer is HER2 positive.
15

21. The use of claim 15 wherein the patient is HER2 negative, ER (estrogen receptor) negative, and PR (progesterone receptor) negative.

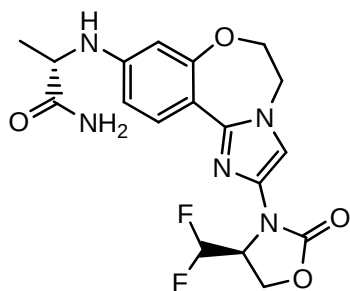
22. A kit for the therapeutic treatment of breast cancer, comprising:

a) the pharmaceutical composition of claims 10 or 11; and

b) instructions for use in the therapeutic treatment of breast cancer.
20

23. The compound of any one of claims 1-9 for use for treating cancer in a patient wherein the cancer is selected from breast cancer and non-small cell lung cancer.

24. A compound (S)-2-((2-((S)-4-(difluoromethyl)-2-oxooxazolidin-3-yl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)amino)propanamide, having the structure



, or a pharmaceutically acceptable salt thereof.

25. A pharmaceutical composition comprised of a compound or a pharmaceutically acceptable salt thereof of claim 24, and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

26. The pharmaceutical composition of claim 25 wherein the pharmaceutically acceptable carrier, glidant, diluent, or excipient is selected from silicon dioxide, powdered cellulose, microcrystalline cellulose, metallic stearates, sodium aluminosilicate, sodium benzoate, calcium carbonate, calcium silicate, corn starch, magnesium carbonate, asbestos free talc, stearowet C, starch, starch 1500, magnesium lauryl sulfate, magnesium oxide, and combinations thereof.

27. The pharmaceutical composition of claim 25 or 26, further comprising one or more additional therapeutic agents selected from 5-FU, docetaxel, eribulin, gemcitabine, cobimetinib, ipatasertib, paclitaxel, tamoxifen, fulvestrant, GDC-0810, dexamethasone, palbociclib, bevacizumab, pertuzumab, trastuzumab emtansine, trastuzumab and letrozole.

28. The pharmaceutical composition of any one of claims 25 to 27, for use in treating a PIK3CA-mutant cancer.

29. The pharmaceutical composition of claim 28, wherein said cancer is breast cancer.

30. A pharmaceutical composition comprised of a compound or a pharmaceutically acceptable salt thereof of claim 24, and one or more additional therapeutic agents selected from palbociclib, fulvestrant and letrozole, and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

5 31. The pharmaceutical composition of claim 30 for use in for treating PIK3CA-mutant and estrogen receptor positive (ER+) breast cancer.

32. A process for making a pharmaceutical composition comprising combining a compound or a pharmaceutically acceptable salt thereof of claim 24 with a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

10 33. The use of a compound or a pharmaceutically acceptable salt thereof of claim 24 in the manufacture of a medicament for treating cancer in a patient wherein the cancer is selected from breast cancer and non-small cell lung cancer.

34. The use of claim 33 further comprising an additional therapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, cobimetinib, ipatasertib, paclitaxel,
15 tamoxifen, fulvestrant, GDC-0810, dexamethasone, palbociclib, bevacizumab, pertuzumab, trastuzumab emtansine, trastuzumab and letrozole.

35. The use of claim 33 wherein the cancer is breast cancer.

36. The use of claim 35 wherein the breast cancer is estrogen receptor positive (ER+) breast cancer.

20 37. The use of claim 35 wherein the breast cancer subtype is Basal or Luminal.

38. The use of claim 33 wherein the cancer expresses a PIK3CA mutant selected from E542K, E545K, Q546R, H1047L and H1047R.

39. The use of claim 33 wherein the cancer expresses a PTEN mutant.

40. The use of claim 35 wherein the breast cancer is HER2 positive.

41. The use of claim 35 wherein the patient is HER2 negative, ER (estrogen receptor) negative, and PR (progesterone receptor) negative.

42. A kit for the therapeutic treatment of breast cancer, comprising:

a) the pharmaceutical composition of any one of claims 25 to 27 or 30; and

5 b) instructions for use in the therapeutic treatment of breast cancer.

43. The compound or a pharmaceutically acceptable salt thereof of claim 24 for use for treating cancer in a patient wherein the cancer is selected from breast cancer and non-small cell lung cancer.