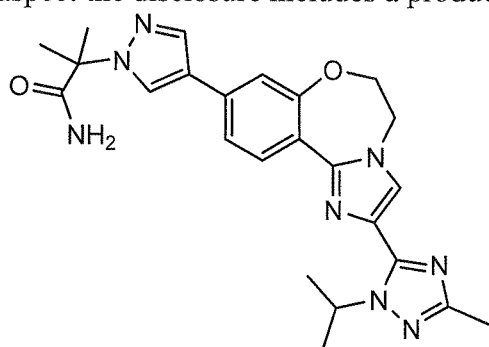


sample obtained from the patient, prior to administration of the combination to the patient, has been tested for status of a biomarker, and wherein the biomarker status is indicative of therapeutic responsiveness by the patient to GDC-0032, or a combination of GDC-0032 and a chemotherapeutic agent. In one embodiment, the biological sample has been tested by measuring functional biomarker protein level, wherein an increased level of functional biomarker indicates that the patient will be resistant to GDC-0032 or the combination. In another embodiment, the biological sample has been tested by measuring functional biomarker level, wherein an increased or decreased level of functional biomarker indicates that the patient will be resistant to GDC-0032 or the combination.

- 10 In one aspect the disclosure includes a product comprising GDC-0032 having the structure:

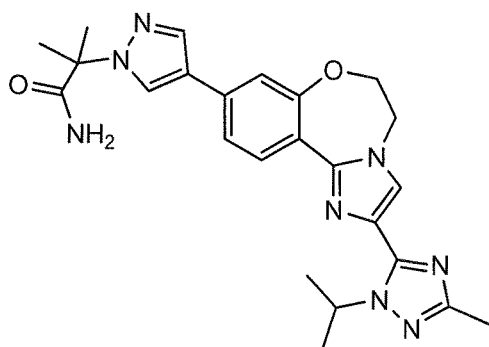


or a pharmaceutically acceptable salt thereof, and a chemotherapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, GDC-0973, GDC-0623, paclitaxel, fulvestrant, pertuzumab, trastuzumab emtansine and trastuzumab; as a combined formulation for separate, simultaneous or sequential use in the treatment of cancer selected from breast, cervical, colon, endometrial, gastric, glioma, lung, melanoma, ovarian, pancreatic, and prostate in a mammal, wherein the GDC-0032 and the chemotherapeutic agent are formulated in a single formulation for simultaneous administration of the GDC-0032 and the chemotherapeutic agent, or in separate formulations for sequential administration of the GDC-0032 and the chemotherapeutic agent.

20 The disclosure includes a pharmaceutical formulation comprising GDC-0032 and a chemotherapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, GDC-0973, GDC-0623, paclitaxel, tamoxifen, fulvestrant, dexamethasone, pertuzumab, trastuzumab emtansine, trastuzumab and letrozole. In another aspect the disclosure includes a pharmaceutical formulation comprising GDC-0032 and a chemotherapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, GDC-0973, GDC-0623, paclitaxel, fulvestrant, pertuzumab, trastuzumab emtansine, and trastuzumab.

The disclosure includes a use of a therapeutic combination of GDC-0032 and a chemotherapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, GDC-0973, GDC-0623, paclitaxel, tamoxifen, fulvestrant, dexamethasone, pertuzumab, trastuzumab emtansine, trastuzumab and letrozole in the manufacture of a medicament for the treatment of hyperproliferative disorder.

- 5 The disclosure includes a use of a therapeutic combination of GDC-0032 and a chemotherapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, GDC-0623, paclitaxel, tamoxifen, fulvestrant, dexamethasone, pertuzumab, trastuzumab emtansine, trastuzumab and letrozole in the manufacture of a medicament for the treatment of cancer selected from breast, cervical, colon, endometrial, glioma, lung, melanoma, ovarian, pancreatic, and prostate. In another aspect the disclosure includes the use of a therapeutic combination of GDC-0032 having the structure:
- 10

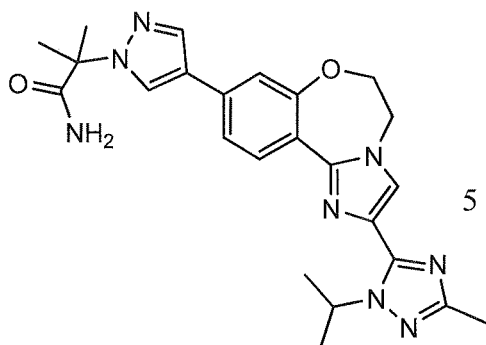


- and a chemotherapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, GDC-0973, GDC-0623, paclitaxel, fulvestrant, pertuzumab, trastuzumab emtansine, and
15 trastuzumab in the manufacture of a medicament for the treatment of cancer selected from breast, cervical, colon, endometrial, glioma, lung, melanoma, ovarian, pancreatic, and prostate.

The disclosure includes a therapeutic combination of GDC-0032 having the structure:

Claims

1. A product comprising GDC-0032 having the structure:



or a pharmaceutically acceptable salt thereof, and a chemotherapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, GDC-0973, GDC-0623, paclitaxel, fulvestrant, pertuzumab, trastuzumab emtansine and trastuzumab; as a combined formulation for ~~separate, simultaneous~~ or sequential use in the treatment of cancer selected from breast, cervical, colon, endometrial, gastric, glioma, lung, melanoma, ovarian, pancreatic, and prostate in a mammal, wherein the GDC-0032 and the chemotherapeutic agent are formulated in a single formulation for simultaneous administration of the GDC-0032 and the chemotherapeutic agent, or in separate formulations for sequential administration of the GDC-0032 and the chemotherapeutic agent.

2. The product of claim 1 wherein the chemotherapeutic agent is 5-FU.
3. The product of claim 1 wherein the chemotherapeutic agent is docetaxel.
4. The product of claim 1 wherein the chemotherapeutic agent is eribulin.
5. The product of claim 1 wherein the chemotherapeutic agent is gemcitabine.
6. The product of claim 1 wherein the chemotherapeutic agent is GDC-0973.
7. The product of claim 1 wherein the chemotherapeutic agent is GDC-0623.
8. The product of claim 1 wherein the chemotherapeutic agent is paclitaxel.
9. The product of claim 1 wherein the chemotherapeutic agent is fulvestrant.

10. The product of claim 1 wherein the chemotherapeutic agent is pertuzumab.

11. The product of claim 1 wherein the chemotherapeutic agent is trastuzumab emtansine.

12. The product of claim 1 wherein the chemotherapeutic agent is trastuzumab.

5 13. The product of claim 1 wherein the combined formulation further includes carboplatin.

14. The product of claim 1 wherein the combined formulation further includes an anti-VEGF antibody.

15. The product of claim 14 wherein the anti-VEGF antibody is bevacizumab.

10 16. The product of any one of claims 1-15 wherein the pharmaceutically acceptable salt of GDC-0032 is selected from a salt formed with hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, benzenesulfonic acid, formic acid, acetic acid, trifluoroacetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric
15 acid, ethanesulfonic acid, aspartic acid and glutamic acid.

~~17. The product of any one of claims 1-16 wherein the GDC-0032, and the chemotherapeutic agent are to be administered to a mammal by alternation.~~

~~18. The product of claim 17 wherein the mammal is to be administered the chemotherapeutic agent and subsequently to be administered GDC-0032.~~

20 ~~19. The product of claim 17 wherein the combined formulation is to be administered by a dosing regimen where the GDC-0032 is to be administered in a range from twice daily to once every three weeks, and the chemotherapeutic agent is to be administered in a range from twice daily to once every three weeks.~~

20. — The product of claim 19 wherein the dosing regimen is repeated one or more times.

21. — The product of any one of claims 1-16 wherein administration of the combined formulation results in a synergistic effect.

22. — The product of claim 22 wherein administration of the combined formulation results in a Combination Index value of less than about 0.7.

23. — The product of claim 1 wherein the cancer expresses a PIK3CA mutant selected from E542K, E545K, Q546R, H1047L and H1047R.

24. — The product of claim 1 wherein the cancer expresses a PTEN mutant.

25. — The product of claim 1 wherein the cancer is HER2 positive.

26. — The product of claim 1 wherein the mammal is a breast cancer patient wherein the patient is HER2 negative, ER (estrogen receptor) negative, and PR (progesterone receptor) negative.

27. — The product of claim 26 wherein the breast cancer subtype is Basal or Luminal.

28. — The product of claim 26 wherein the patient is to be administered GDC-0032 and eribulin.

29. — The product of any one of claims 1-16 wherein GDC-0032 and the chemotherapeutic agent are each to be administered in an amount from about 1 mg to about 1000 mg per unit dosage form.

30. — The product of any one of claims 1-16 wherein GDC-0032 and the chemotherapeutic agent are to be administered in a ratio of about 1:50 to about 50:1 by weight.

3117. A pharmaceutical formulation comprising GDC-0032 and a chemotherapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, GDC-0973, GDC-0623, paclitaxel, fulvestrant, pertuzumab, trastuzumab emtansine, and trastuzumab.

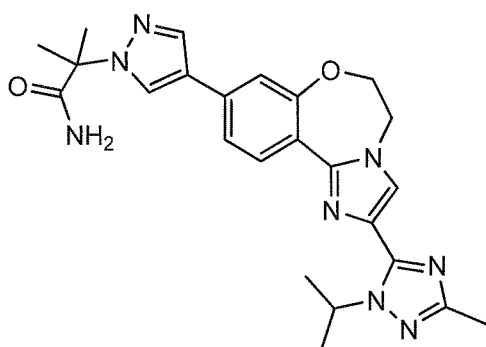
3218. The pharmaceutical formulation of claim 3117 further comprising a pharmaceutically acceptable glidant selected from silicon dioxide, powdered cellulose, microcrystalline cellulose, metallic stearates, sodium aluminosilicate, sodium benzoate, calcium

carbonate, calcium silicate, corn starch, magnesium carbonate, asbestos free talc, stearowet C, starch, starch 1500, magnesium lauryl sulfate, magnesium oxide, and combinations thereof.

3319. The pharmaceutical formulation of claim 31-17 wherein GDC-0032 and the chemotherapeutic agent each comprise an amount from about 1 mg to about 1000 mg per unit dosage form.

3420. The pharmaceutical formulation of claim 33-19 for use in a method of treatment of cancer.

3521. The use of a therapeutic combination of GDC-0032 having the structure:



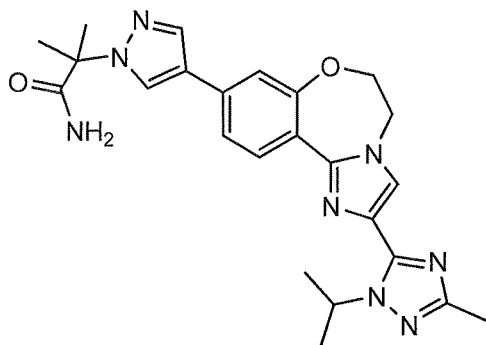
and a chemotherapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, GDC-0973, GDC-0623, paclitaxel, fulvestrant, pertuzumab, trastuzumab emtansine, and trastuzumab in the manufacture of a medicament for the treatment of cancer selected from breast, cervical, colon, endometrial, glioma, lung, melanoma, ovarian, pancreatic, and prostate.

3622. An article of manufacture for treating cancer selected from breast, cervical, colon, endometrial, gastric, glioma, lung, melanoma, ovarian, pancreatic, and prostate comprising:

- a) a combined formulation of any one of claims 1-16; and
- b) instructions for use.

3723. A method for determining compounds to be used in combination for the treatment of cancer comprising:

a) treating an in vitro tumor cell line with a K-ras mutation with a therapeutic combination of GDC-0032 having the structure



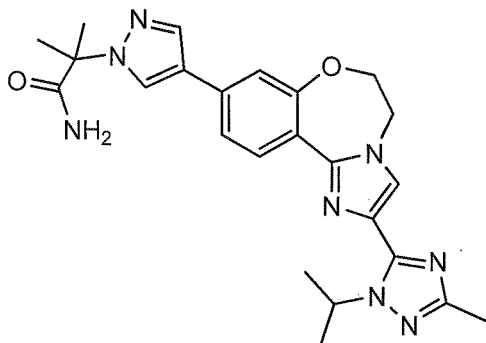
and a chemotherapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, GDC-0973, GDC-0623, paclitaxel, fulvestrant, pertuzumab, trastuzumab emtansine, and trastuzumab, and

b) measuring a synergistic or non-synergistic effect;

whereby a synergistic therapeutic combination for the treatment of cancer is determined.

3824. A method for selecting compounds to be used in combination for the treatment of cancer comprising:

a) measuring a change in pAkt level in a tumour cell that had been administered a therapeutic combination of GDC-0032 having the structure



and a chemotherapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, GDC-0973, GDC-0623, paclitaxel, fulvestrant, pertuzumab, trastuzumab emtansine, and trastuzumab; and

b) selecting a synergistic therapeutic combination which shows an increase in pAkt levels.

3925. A use of a combination of GDC-0032 and a chemotherapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, GDC-0973, GDC-0623, paclitaxel, fulvestrant, pertuzumab, trastuzumab emtansine, and trastuzumab in the manufacture of a medicament for the treatment of cancer selected from breast, cervical, colon, endometrial, gastric, glioma, lung, melanoma, ovarian, pancreatic, and prostate in a patient, wherein a biological sample obtained from the patient, prior to administration of the combination to the patient, has been tested for PIK3CA or PTEN mutation status, and wherein PIK3CA or PTEN mutation status is indicative of therapeutic responsiveness by the patient to the combination.

4026. The use of claim 39-26 wherein the patient is to be administered a therapeutically effective amount of the combination of GDC-0032 and a chemotherapeutic agent.

4127. The use of claim 39-25 wherein the cancer is HER2 expressing breast cancer.

4227. The use of claim 39-25 wherein the cancer is estrogen receptor positive (ER+) breast cancer.

4328. The use of claim 39-25 wherein a biological sample has been tested by measuring functional PI3K protein level after administration of the combination of GDC-0032 and the chemotherapeutic agent, wherein a change in the level of functional PI3K protein indicates that the patient will be resistant or responsive to the combination of GDC-0032 and a chemotherapeutic agent.

29. The use of any one of claims 25-28 wherein the GDC-0032 and the chemotherapeutic agent are to be administered to a mammal by alternation.

30. The use of claim 29 wherein the mammal is to be administered the chemotherapeutic agent and subsequently to be administered GDC-0032.

31. The use of claim 29 wherein the GDC-0032 and the chemotherapeutic agent are to be administered by a dosing regimen where the GDC-0032 is to be administered in a range from twice daily to once every three weeks, and the chemotherapeutic agent is to be administered in a range from twice daily to once every three weeks.

32. The use of claim 31 wherein the dosing regimen is repeated one or more times.

33. The use of any one of claims 25-28 wherein administration of the GDC-0032 and the chemotherapeutic agent results in a synergistic effect.

34. The use of claim 33 wherein administration of the GDC-0032 and the chemotherapeutic agent results in a Combination Index value of less than about 0.7.

35. The use of claim 25 wherein the cancer expresses a PIK3CA mutant selected from E542K, E545K, Q546R, H1047L and H1047R.

36. The use of claim 25 wherein the cancer expresses a PTEN mutant.

37. The use of claim 25 wherein the cancer is HER2 positive.

38. The use of claim 25 wherein the mammal is a breast cancer patient wherein the patient is HER2 negative, ER (estrogen receptor) negative, and PR (progesterone receptor) negative.

39. The use of claim 38 wherein the breast cancer subtype is Basal or Luminal.

40. The use of claim 38 wherein the patient is to be administered GDC-0032 and eribulin.

41. The use of any one of claims 25-28 wherein GDC-0032 and the chemotherapeutic agent are each to be administered in an amount from about 1 mg to about 1000 mg per unit dosage form.

42. The use of any one of claims 25-28 wherein GDC-0032 and the chemotherapeutic agent are to be administered in a ratio of about 1:50 to about 50:1 by weight.

43. The use of any one of claims 25 to 28 wherein the GDC-0032 and the chemotherapeutic agent are formulated in a single formulation for simultaneous administration of the GDC-0032 and the chemotherapeutic agent, or in separate formulations for sequential administration of the GDC-0032 and the chemotherapeutic agent.

44. A method of monitoring whether a patient with cancer selected from breast, cervical, colon, endometrial, gastric, glioma, lung, melanoma, ovarian, pancreatic, and prostate will respond to treatment with a combination of GDC-0032 and a chemotherapeutic agent, the method comprising:

(a) detecting a PIK3CA or PTEN mutation in a biological sample obtained from the patient following administration of the at least one dose of the combination of GDC-0032 and a chemotherapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, GDC-0973, GDC-0623, paclitaxel, fulvestrant, pertuzumab, trastuzumab emtansine, and trastuzumab; and

(b) comparing PIK3CA or PTEN mutation status in a biological sample obtained from the patient prior to administration of the combination of GDC-0032 and a chemotherapeutic agent to the patient,

wherein a change or modulation of PIK3CA or PTEN mutation status in the sample obtained following administration of the combination of GDC-0032 and a chemotherapeutic agent identifies a patient who will respond to treatment with the combination of GDC-0032 and a chemotherapeutic agent.

45. The method of claim 44 wherein the cancer is HER2 expressing breast cancer.

46. A method of optimizing therapeutic efficacy of the combination of GDC-0032 and a chemotherapeutic agent in the treatment of cancer selected from breast, cervical, colon, endometrial, gastric, glioma, lung, melanoma, ovarian, pancreatic, and prostate, the method comprising:

- 5 (a) detecting a PIK3CA or PTEN mutation in a biological sample obtained from a patient following administration of at least one dose of the combination of GDC-0032 and a chemotherapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, GDC-0973, GDC-0623, paclitaxel, fulvestrant, pertuzumab, trastuzumab emtansine, and trastuzumab; and

0623, paclitaxel, fulvestrant, pertuzumab, trastuzumab emtansine, and trastuzumab in the manufacture of a medicament for the treatment of cancer selected from breast, cervical, colon, endometrial, gastric, glioma, lung, melanoma, ovarian, pancreatic, and prostate in a patient, wherein treatment is based upon a sample from the patient having a PIK3CA or PTEN mutation.

5 51. The use of claim 50 wherein the biomarker mutation is the H1047R or H1047L mutation of PIK3CA.

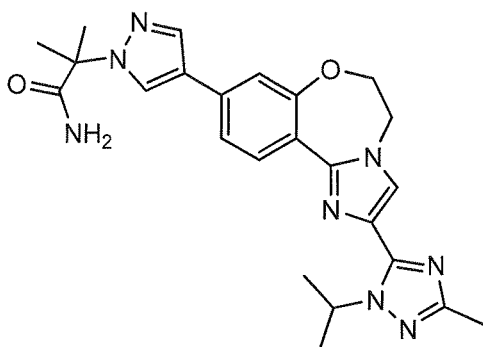
 52. The use of claim 50 wherein the biomarker mutation is the E542K, E545K or Q546R mutation of PIK3CA.

 53. The use of claim 50 wherein the cancer is HER2 expressing breast cancer.

10 54. The use of claim 50 wherein the cancer is estrogen receptor positive (ER+) breast cancer.

 55. The use of any one of claims 50 to 54 wherein the GDC-0032 and the chemotherapeutic agent are formulated in a single formulation for simultaneous administration of the GDC-0032 and the chemotherapeutic agent, or in separate formulations for sequential
15 administration of the GDC-0032 and the chemotherapeutic agent.

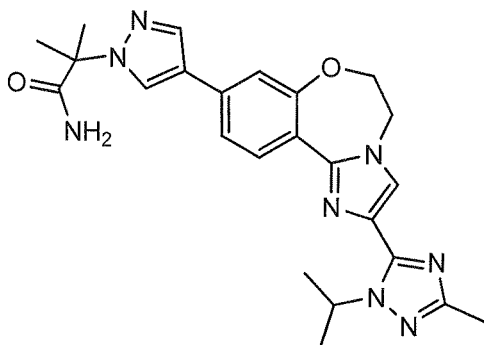
~~55~~56. A therapeutic combination of GDC-0032 having the structure:



and a chemotherapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, GDC-0973, GDC-0623, paclitaxel, fulvestrant, pertuzumab, trastuzumab emtansine, and trastuzumab for use in the treatment of cancer selected from breast, cervical, colon, endometrial, glioma, lung, melanoma, ovarian, pancreatic, and prostate.

57. The therapeutic combination of claim 56 wherein the GDC-0032 and the chemotherapeutic agent are formulated in a single formulation for simultaneous administration of the GDC-0032 and the chemotherapeutic agent, or in separate formulations for sequential administration of the GDC-0032 and the chemotherapeutic agent.

58. The use of a therapeutic combination of GDC-0032 having the structure:



and a chemotherapeutic agent selected from 5-FU, docetaxel, eribulin, gemcitabine, GDC-0973, GDC-0623, paclitaxel, fulvestrant, pertuzumab, trastuzumab emtansine, and trastuzumab in the manufacture of a medicament for the treatment of cancer selected from breast, cervical, colon, endometrial, glioma, lung, melanoma, ovarian, pancreatic, and prostate.

59. The use of claim 58, wherein the GDC-0032 and the chemotherapeutic agent are formulated in a single formulation for simultaneous administration of the GDC-0032 and the chemotherapeutic agent, or in separate formulations for sequential administration of the GDC-0032 and the chemotherapeutic agent.