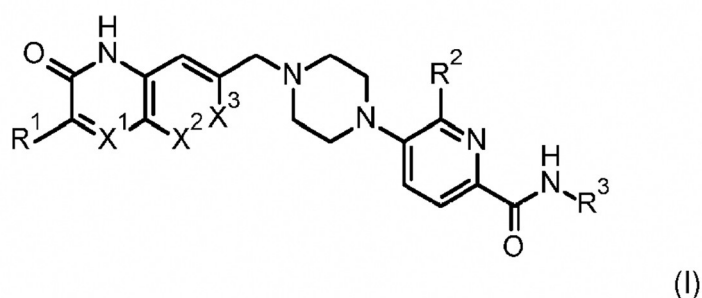


Claims

1. Use of a selective PARP1 inhibitor or a pharmaceutically acceptable salt thereof and an ATR inhibitor or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating ovarian cancer, breast cancer, gastrointestinal cancer, lung cancer, cancer of the brain or prostate cancer in a subject in need thereof, wherein a first amount of the selective PARP1 inhibitor or a pharmaceutically acceptable salt thereof, and a second amount of the ATR inhibitor or a pharmaceutically acceptable salt thereof are to be administered to the subject, wherein the first amount and the second amount together comprise a therapeutically effective amount.

2. The use according to claim 1, wherein the selective PARP1 inhibitor is selected from the group consisting of:

(a) a compound of formula (I):



wherein:

X^1 and X^2 are each independently selected from N and C(H),

X^3 is independently selected from N and C(R^4), wherein R^4 is H or fluoro,

R^1 is C_{1-4} alkyl or C_{1-4} fluoroalkyl,

R^2 is independently selected from H, halo, C_{1-4} alkyl, and C_{1-4} fluoroalkyl, and

R^3 is H or C_{1-4} alkyl,

or a pharmaceutically acceptable salt thereof

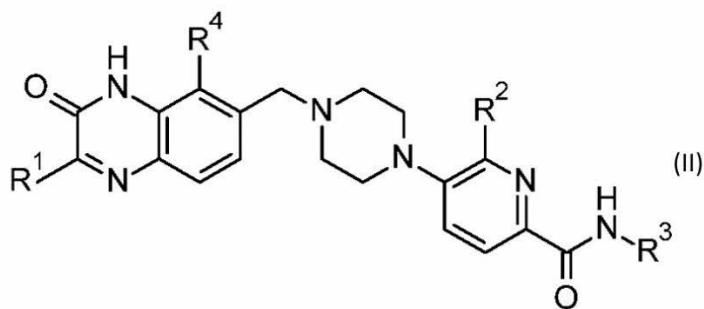
provided that:

when X^1 is N, then X^2 is C(H), and X^3 is C(R^4),

when X^2 is N, then X^1 = C(H), and X^3 is C(R^4), and

when X^3 is N, then X^1 and X^2 are both C(H); and

(b) a compound of formula (II):



wherein:

R¹ is independently selected from H, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, and C₁₋₄ alkyloxy;

R² is independently selected from H, halo, C₁₋₄ alkyl, and C₁₋₄ fluoroalkyl; and

5 R³ is H or C₁₋₄ alkyl;

R⁴ is halo or C₁₋₄ alkyl,

or a pharmaceutically acceptable salt thereof.

3. The use according to either claim 1 or claim 2, wherein the selective PARP1 inhibitor
10 is selected from:

(a) AZD5305; and

(b) AZD9574.

4. The use according any one of claims 1 to 3, wherein the selective PARP1 inhibitor is
15 AZD5305.

5. The use according any one of claims 1 to 3, wherein the selective PARP1 inhibitor is
AZD9574.

20 6. The use according to any one of claims 1 to 5, wherein the ATR inhibitor is selected
from the group consisting of:

(a) ceralasertib;

(b) berzosertib;

(c) elimusertib;

25 (d) VE-821;

(e) gartisertib;

(f) camonsertib;

(g) AZ20;

(h) ATRN-119;

30 (i) ART-0380;

- (j) IMP-9064;
- (k) SC-0245;
- (l) ATG-018; and
- (m) LR-02.

5

7. The use according to claim 6, wherein the ATR inhibitor is ceralasertib.

8. The use according to any one of claims 1 to 7, wherein the ovarian cancer is selected from the group consisting of:

- 10 (a) advanced epithelial ovarian cancer;
- (b) high-grade serous ovarian cancer;
- (c) high-grade endometrioid ovarian cancer;
- (d) epithelial ovarian cancer comprising a gBRCA1 or a gBRCA2 mutation; and
- (e) platinum-sensitive relapsed ovarian cancer, following treatment with a PARP inhibitor.

15

9. The use according to any one of claims 1 to 7, wherein the ovarian cancer is platinum-sensitive relapsed ovarian cancer, following treatment with a PARP inhibitor.

10. The use according to any one of claims 1 to 7, wherein the breast cancer is selected from the group consisting of:

20

- (a) deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer;
- (b) deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer and has been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting;
- (c) deleterious or suspected deleterious gBRCAm, HER2 -negative, hormone receptor (HR)-
- 25 positive breast cancer and has been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting and has been treated with a prior endocrine therapy or been considered inappropriate for endocrine therapy; and
- (d) triple negative breast cancer.

25

11. The use according to any one of claims 1 to 7, wherein the gastrointestinal cancer is selected from the group consisting of:

30

- (a) gastric cancer;
- (b) colorectal cancer
- (c) stomach cancer;
- 35 (d) liver cancer;
- (e) gallbladder cancer;
- (f) anal cancer;

35

- (g) pancreatic adenocarcinoma;
 - (h) deleterious or suspected deleterious gBRCAm pancreatic adenocarcinoma; and
 - (i) deleterious or suspected deleterious gBRCAm pancreatic adenocarcinoma and the disease has not progressed on at least 16 weeks for a first-line platinum-based
- 5 chemotherapy regimen.

12. The use according to any one of claims 1 to 7, wherein the lung cancer is selected from the group consisting of:

- (a) small cell lung cancer; and
- 10 (b) non-small cell lung cancer.

13. The use according to any one of claims 1 to 7, wherein the cancer of the brain is selected from the group consisting of:

- (a) glioma; and
- 15 (b) glioblastoma.

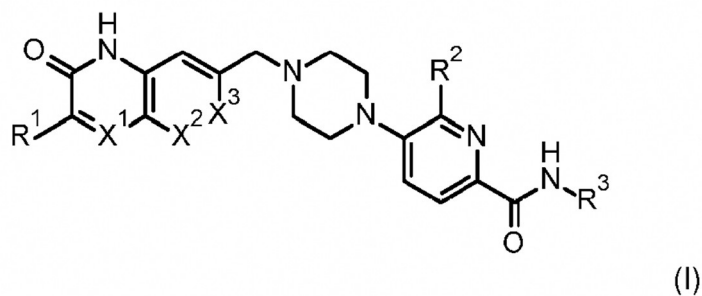
14. The use according to any one of claims 1 to 7, wherein the prostate cancer is selected from the group consisting of:

- (a) metastatic prostate cancer;
- 20 (b) hormone sensitive prostate cancer;
- (c) castrate resistant prostate cancer;
- (d) metastatic hormone sensitive prostate cancer; and
- (e) metastatic castrate resistant prostate cancer.

- 25 15. A selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of ovarian cancer, breast cancer, gastrointestinal cancer, lung cancer, cancer of the brain or prostate cancer, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, and ii) an ATR inhibitor, or a pharmaceutically acceptable salt
- 30 thereof, to said subject.

16. A selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, for use according to claim 15, wherein the selective PARP1 inhibitor is selected from the group consisting of:

- 35 (a) a compound of formula (I):



wherein:

X¹ and X² are each independently selected from N and C(H),

X³ is independently selected from N and C(R⁴), wherein R⁴ is H or fluoro,

5 R¹ is C₁₋₄ alkyl or C₁₋₄ fluoroalkyl,

R² is independently selected from H, halo, C₁₋₄ alkyl, and C₁₋₄ fluoroalkyl, and

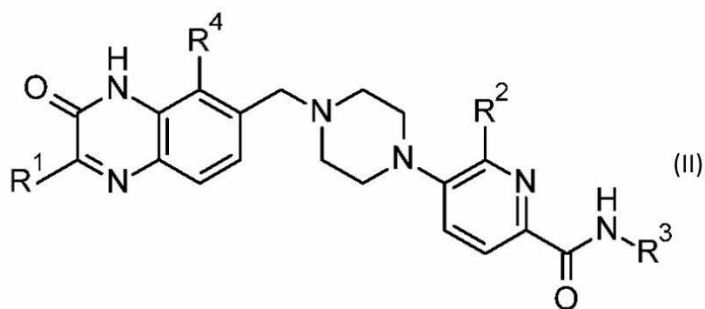
R³ is H or C₁₋₄ alkyl,

or a pharmaceutically acceptable salt thereof

provided that:

- 10 when X¹ is N, then X² is C(H), and X³ is C(R⁴),
 when X² is N, then X¹ = C(H), and X³ is C(R⁴), and
 when X³ is N, then X¹ and X² are both C(H); and

(b) a compound of formula (II):



15

wherein:

R¹ is independently selected from H, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, and C₁₋₄ alkyloxy;

R² is independently selected from H, halo, C₁₋₄ alkyl, and C₁₋₄ fluoroalkyl; and

R³ is H or C₁₋₄ alkyl;

20 R⁴ is halo or C₁₋₄ alkyl,

or a pharmaceutically acceptable salt thereof.

17. A selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, for use according to either claim 15 or claim 16, wherein the selective PARP1 inhibitor is selected from:

(a) AZD5305; and

5 (b) AZD9574.

18. A selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 15 to 17, wherein the selective PARP1 inhibitor is AZD5305.

10 19. A selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 15 to 17, wherein the selective PARP1 inhibitor is AZD9574.

20. A selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claim 15 to 19, wherein the ATR inhibitor is selected from the group
15 consisting of:

(a) ceralasertib;

(b) berzosertib;

(c) elimusertib;

(d) VE-821;

20 (e) gartisertib;

(f) camonsertib;

(g) AZ20;

(h) ATRN-119;

(i) ART-0380;

25 (j) IMP-9064;

(k) SC-0245;

(l) ATG-018; and

(m) LR-02.

30 21. A selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, for use according to claim 20, wherein the ATR inhibitor is ceralasertib.

22. A selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 15 to 21, wherein the ovarian cancer is selected from the
35 group consisting of:

(a) advanced epithelial ovarian cancer;

(b) high-grade serous ovarian cancer;

- (c) high-grade endometrioid ovarian cancer;
- (d) epithelial ovarian cancer comprising a gBRCA1 or a gBRCA2 mutation; and
- (e) platinum-sensitive relapsed ovarian cancer, following treatment with a PARP inhibitor.

5 23. A selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 15 to 21, wherein the ovarian cancer is platinum-sensitive relapsed ovarian cancer, following treatment with a PARP inhibitor.

24. A selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, for use
 10 according to any one of claims 15 to 21, wherein the breast cancer is selected from the group consisting of:
 (a) deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer;
 (b) deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer and has been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting;
 15 (c) deleterious or suspected deleterious gBRCAm, HER2 -negative, hormone receptor (HR)-positive breast cancer and has been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting and has been treated with a prior endocrine therapy or been considered inappropriate for endocrine therapy; and
 (d) triple negative breast cancer.

20

25. A selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 15 to 21, wherein the gastrointestinal cancer is selected from the group consisting of:

- (a) gastric cancer;
- 25 (b) colorectal cancer
- (c) stomach cancer;
- (d) liver cancer;
- (e) gallbladder cancer;
- (f) anal cancer;
- 30 (g) pancreatic adenocarcinoma;
- (h) deleterious or suspected deleterious gBRCAm pancreatic adenocarcinoma; and
- (i) deleterious or suspected deleterious gBRCAm pancreatic adenocarcinoma and the disease has not progressed on at least 16 weeks for a first-line platinum-based chemotherapy regimen.

35

26. A selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 15 to 21, wherein the lung cancer is selected from the group consisting of:

- (a) small cell lung cancer; and
- 5 (b) non-small cell lung cancer.

27. A selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 15 to 21, wherein the cancer of the brain is selected from the group consisting of:

- 10 (a) glioma; and
- (b) glioblastoma.

28. A selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 15 to 21, wherein the prostate cancer is selected from the group consisting of:

- 15 (a) metastatic prostate cancer;
- (b) hormone sensitive prostate cancer;
- (c) castrate resistant prostate cancer;
- (d) metastatic hormone sensitive prostate cancer; and
- 20 (e) metastatic castrate resistant prostate cancer.

29. An ATR inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of ovarian cancer, breast cancer, gastrointestinal cancer, lung cancer, cancer of the brain or prostate cancer in a subject, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said ATR inhibitor, or a pharmaceutically acceptable salt thereof, and ii) a selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, to said subject.

30. An ATR inhibitor, or a pharmaceutically acceptable salt thereof, for use according to claim 29, wherein the ATR inhibitor is selected from the group consisting of:

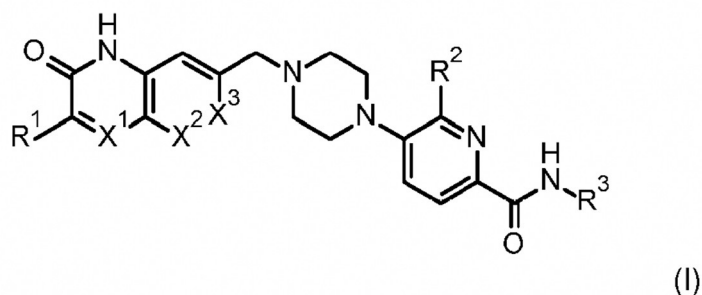
- (a) ceralasertib;
- (b) berzosertib;
- (c) elimusertib;
- (d) VE-821;
- 35 (e) gartisertib;
- (f) camonsertib;
- (g) AZ20;

- (h) ATRN-119;
 (i) ART-0380;
 (j) IMP-9064;
 (k) SC-0245;
 5 (l) ATG-018; and
 (m) LR-02.

31. An ATR inhibitor, or a pharmaceutically acceptable salt thereof, for use according to claim 30, wherein the ATR inhibitor is ceralasertib.

32. An ATR inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 29 to 31, wherein the selective PARP1 inhibitor is selected from the group consisting of:

(a) a compound of formula (I):



wherein:

X^1 and X^2 are each independently selected from N and C(H),

X^3 is independently selected from N and C(R^4), wherein R^4 is H or fluoro,

R^1 is C_{1-4} alkyl or C_{1-4} fluoroalkyl,

R^2 is independently selected from H, halo, C_{1-4} alkyl, and C_{1-4} fluoroalkyl, and

R^3 is H or C_{1-4} alkyl,

or a pharmaceutically acceptable salt thereof

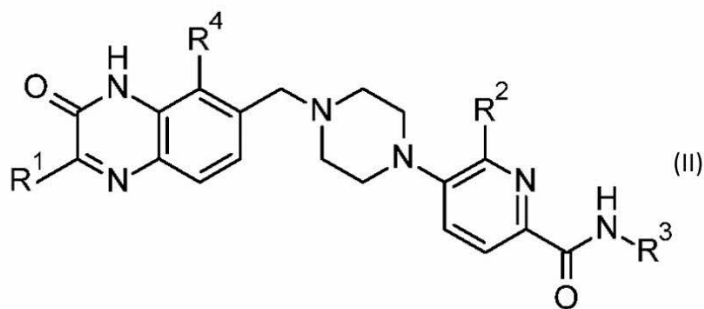
provided that:

when X^1 is N, then X^2 is C(H), and X^3 is C(R^4),

when X^2 is N, then X^1 = C(H), and X^3 is C(R^4), and

when X^3 is N, then X^1 and X^2 are both C(H); and

(b) a compound of formula (II):



wherein:

R¹ is independently selected from H, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, and C₁₋₄ alkyloxy;

R² is independently selected from H, halo, C₁₋₄ alkyl, and C₁₋₄ fluoroalkyl; and

5 R³ is H or C₁₋₄ alkyl;

R⁴ is halo or C₁₋₄ alkyl,

or a pharmaceutically acceptable salt thereof.

33. An ATR inhibitor, or a pharmaceutically acceptable salt thereof, for use according to claim 32, wherein the selective PARP1 inhibitor is selected from:

(a) AZD5305; and

(b) AZD9574.

34. An ATR inhibitor, or a pharmaceutically acceptable salt thereof, for use according to either claim 32 or claim 33, wherein the selective PARP1 inhibitor is AZD5305.

35. An ATR inhibitor, or a pharmaceutically acceptable salt thereof, for use according to either claim 32 or claim 33, wherein the selective PARP1 inhibitor is AZD9574.

36. An ATR inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 29 to 35, wherein the ovarian cancer is selected from the group consisting of:

(a) advanced epithelial ovarian cancer;

(b) high-grade serous ovarian cancer;

25 (c) high-grade endometrioid ovarian cancer;

(d) epithelial ovarian cancer comprising a gBRCA1 or a gBRCA2 mutation; and

(e) platinum-sensitive relapsed ovarian cancer, following treatment with a PARP inhibitor.

37. An ATR inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 29 to 35, wherein the ovarian cancer is platinum-sensitive relapsed ovarian cancer, following treatment with a PARP inhibitor.

- 5 38. An ATR inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 29 to 35, wherein the breast cancer is selected from the group consisting of:
- (a) deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer;
 - (b) deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer
 - 10 and has been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting;
 - (c) deleterious or suspected deleterious gBRCAm, HER2 -negative, hormone receptor (HR)-positive breast cancer and has been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting and has been treated with a prior endocrine therapy or been considered inappropriate for endocrine therapy; and
 - 15 (d) triple negative breast cancer.

39. An ATR inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 29 to 35, wherein the gastrointestinal cancer is selected from the group consisting of:

- 20 (a) gastric cancer;
- (b) colorectal cancer
 - (c) stomach cancer;
 - (d) liver cancer;
 - (e) gallbladder cancer;
 - 25 (f) anal cancer;
 - (g) pancreatic adenocarcinoma;
 - (h) deleterious or suspected deleterious gBRCAm pancreatic adenocarcinoma; and
 - (i) deleterious or suspected deleterious gBRCAm pancreatic adenocarcinoma and the disease has not progressed on at least 16 weeks for a first-line platinum-based
 - 30 chemotherapy regimen.

40. An ATR inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 29 to 35, wherein the lung cancer is selected from the group consisting of:

- (a) small cell lung cancer; and
- 35 (b) non-small cell lung cancer.

41. An ATR inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 29 to 35, wherein the cancer of the brain is selected from the group consisting of:

(a) glioma; and

5 (b) glioblastoma.

42. An ATR inhibitor, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 29 to 35, wherein the prostate cancer is selected from the group consisting of:

10 (a) metastatic prostate cancer;

(b) hormone sensitive prostate cancer;

(c) castrate resistant prostate cancer;

(d) metastatic hormone sensitive prostate cancer; and

(e) metastatic castrate resistant prostate cancer.

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43. The use of a selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of ovarian cancer, breast cancer, gastrointestinal cancer, lung cancer, cancer of the brain or prostate cancer, wherein said treatment comprises the separate, sequential or simultaneous administration of i) said medicament comprising said selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, and ii) an ATR inhibitor, or a pharmaceutically acceptable salt thereof, to said subject.

20

44. The use of a selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof, according to claim 43, wherein the selective PARP1 inhibitor is selected from:

25

(a) AZD5305; and

(b) AZD9574;

and the ATR inhibitor is ceralasertib.

30

45. A pharmaceutical product comprising i) a selective PARP1 inhibitor or a pharmaceutically acceptable salt thereof, and ii) an ATR inhibitor or a pharmaceutically acceptable salt thereof.

35

46. A kit comprising: a first pharmaceutical composition comprising a selective PARP1 inhibitor, or a pharmaceutically acceptable salt thereof; a second pharmaceutical composition comprising an ATR inhibitor, or a pharmaceutically acceptable salt thereof; and instructions for using the first and second pharmaceutical compositions in combination.

47. The pharmaceutical product according to claim 45 for use in therapy.