Inhibitors of poly(ADP-ribose) polymerases (PARP inhibitors) target the DNA repair enzyme poly(ADP-ribose) polymerase 1 (PARP1) and closely related paralogs. Several PARP inhibitors (olaparib, niraparib, rucaparib, talazoparib) have been approved for treatment of various cancers (e.g., ovarian cancer, breast cancer, fallopian tube cancer, and primary peritoneal cancer).

There is a need for new anti-cancer therapies and, in particular, effective combinations of known inhibitors with different mechanisms of action that can synergize to increase overall efficacy and treat a broader spectrum of cancers than either inhibitor alone.

SUMMARY

In general, the disclosure provides a combination of an ATR inhibitor, or a pharmaceutically acceptable salt thereof, and a PARP inhibitor, or a pharmaceutically acceptable salt thereof for the treatment of cancers or for inducing cell death in cancer cells. The cancers included herein may be, e.g., cancers having a loss of function of ATM, BRCA2, RNAse H2A, RNAse H2B, CDK12, or a combination thereof. The cancer may be, e.g., an ALT+ cancer.

In an aspect, there is provided the use of a therapeutically effective amount of an ATR inhibitor and a therapeutically effective amount of a PARP inhibitor in the manufacture of a medicament for the treatment of cancer, wherein the cancer has a loss of function of ATM, BRCA2, RNAse H2A, RNAse H2B, CDK12, or a combination thereof, or wherein the cancer has been previously identified as an ALT+ cancer.

A therapeutically effective amount of an ATR inhibitor and a therapeutically effective amount of a PARP inhibitor for use in the treatment of cancer, wherein the cancer has a loss of function of ATM, BRCA2, RNAse H2A, RNAse H2B, CDK12, or a combination thereof, or wherein the cancer has been previously identified as an ALT+ cancer.

In one example, the disclosure provides a method of treating a cancer in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of an ATR inhibitor and PARP inhibitor, where the cancer has been previously identified as a cancer having a loss of function of ATM, BRCA2, RNAse H2A, RNAse H2B, CDK12, or a combination thereof, or the cancer has been previously identified as an ALT+ cancer.

In another example, the disclosure provides a method of treating a cancer in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of an ATR inhibitor and PARP inhibitor, where the cancer has a loss of function of ATM serine/threonine kinase, BRCA2, RNAse H2A, RNAse H2B, CDK12, or a combination thereof, or the cancer is an ALT+ cancer.

In yet another example, the disclosure provides a method of treating a cancer in a subject, the method comprising:

(i) identifying the cancer as having a loss of function of ATM, BRCA2, RNAse H2A, RNAse H2B, CDK12, or a combination thereof, or as an ALT+ cancer; and

(ii) administering to the subject in need thereof a therapeutically effective amount of an ATR inhibitor and PARP inhibitor.

In some examples, the ATR inhibitor is administered before the PARP inhibitor (e.g., within 1 week, within 6 days, within 5 days, within 4 days, within 3 days, within 2 days, within 1 day, or within 12 hours). In some examples, the ATR inhibitor is administered after the PARP

inhibitor (e.g., within 1 week, within 6 days, within 5 days, within 4 days, within 3 days, within 2 days, within 1 day, or within 12 hours). In some examples, the ATR inhibitor is co-administered with the PARP inhibitor. In some examples, the ATR inhibitor is administered intermittently (e.g., 1 day/week, 2 days/week, or 3 days/week). In some examples, the PARP inhibitor is administered on a continuous daily basis.

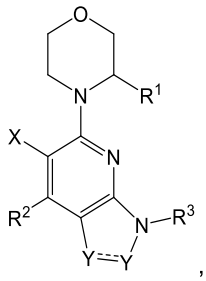
In some examples, the therapeutically effective amount is a subtherapeutic regimen of the ATR inhibitor. In some examples, the therapeutically effective amount is a subtherapeutic regimen of the PARP inhibitor. In some examples, the subtherapeutic regimen comprises a starting dosage that is at least 50% less than the lowest standard starting dosage that is used for a monotherapy. In some examples, the subtherapeutic regimen comprises a maintenance dosage that is at least 50% less than the lowest standard maintenance dosage that is used for a monotherapy. In some examples,

the maintenance dosage comprises a first reduced dosage. In some examples, the maintenance dosage comprises a second reduced dosage. In some examples, the maintenance dosage comprises a third reduced dosage. In some examples, the route of administration is an oral administration.

In still another example, the disclosure provides a method of inducing cell death in an aberrant cancer cell having a loss of function of ATM, BRCA2, RNAse H2A, RNAse H2B, CDK12, or a combination thereof, or in an ALT+ cancer cell, the method comprising contacting the cell with an effective amount of an ATR inhibitor and an effective amount of a PARP inhibitor, the effective amounts being sufficient to induce cell death in the aberrant cancer cell.

In some examples, the loss of function is a loss of function of ATM. In some examples, the loss of function is a loss of function of RNAse H2A. In some examples, the loss of function is a loss of function of RNAse H2B. In some examples, the loss of function is a loss of function of CDK12. In some examples, the loss of function is a loss of function of BRCA2. In some examples, the cancer is an ALT+ cancer.

In some examples, the ATR inhibitor is a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

⁼⁼⁼⁼⁼⁼ is a double bond, and each Y is independently N or CR^4; or ⁼⁼⁼⁼⁼⁼ is a single bond, and each Y is independently NR^Y, carbonyl, or $C(R^Y)_2$; wherein each R^Y is independently H or optionally substituted C_{1-6} alkyl;

R^1 is optionally substituted C_{1-6} alkyl or H;

R^2 is optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{2-9} heterocyclyl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, optionally substituted C_{1-9} heteroaryl C_{1-6} alkyl, halogen, $–N(R^5)_2$, $–OR^5$, $–CON(R^6)_2$, $–SO_2N(R^6)_2$,$–SO_2R^{5A}$, or $–Q–R^{5B}$;

R^3 is optionally substituted C_{1-9} heteroaryl or optionally substituted C_{1-9} heteroaryl C_{1-6} alkyl;

each R^4 is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, or optionally substituted C_{2-6} alkynyl;

each R^5 is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, or $–SO_2R^{5A}$; or both R^5, together with the atom to which they are attached, combine to form an optionally substituted C_{2-9} heterocyclyl;

each R^{5A} is independently optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, or optionally substituted C_{6-10} aryl;

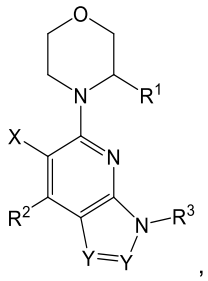
R^{5B} is hydroxyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, $–N(R^5)_2$, $–CON(R^6)_2$, $–SO_2N(R^6)_2$, $–SO_2R^{5A}$, or optionally substituted alkoxy;

each R^6 is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkoxyalkyl, optionally substituted C_{6-10} aryl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{3-8} cycloalkyl, or optionally substituted C_{1-9} heteroaryl; or both R^6, together with the atom to which they are attached, combine to form an optionally substituted C_{2-9} heterocyclyl;

Q is optionally substituted C_{2-9} heterocyclylene, optionally substituted C_{3-8} cycloalkylene, optionally substituted C_{1-9} heteroarylene, or optionally substituted C_{6-10} arylene; and

X is hydrogen or halogen.

In some examples, the ATR inhibitor is a compound of formula (II):



,

(II)

or a pharmaceutically acceptable salt thereof,

wherein

each Y is independently N or CR^4;

R^1 is optionally substituted C_{1-6} alkyl or H;

R^2 is optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{2-9} heterocyclyl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, optionally substituted C_{1-9} heteroaryl C_{1-6} alkyl, halogen, $–N(R^5)_2$, $–OR^5$, $–CON(R^6)_2$, $–SO_2N(R^6)_2$,$–SO_2R^{5A}$, or $–Q–R^{5B}$;

R^3 is optionally substituted C_{1-9} heteroaryl or optionally substituted C_{1-9} heteroaryl C_{1-6} alkyl;

each R^4 is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, or optionally substituted C_{2-6} alkynyl;

each R^5 is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, or $–SO_2R^{5A}$; or both R^5, together with the atom to which they are attached, combine to form an optionally substituted C_{2-9} heterocyclyl;

each R^{5A} is independently optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, or optionally substituted C_{6-10} aryl;

R^{5B} is hydroxyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, $–N(R^5)_2$, $–CON(R^6)_2$, $–SO_2N(R^6)_2$, $–SO_2R^{5A}$, or optionally substituted alkoxy;

each R^6 is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkoxyalkyl, optionally substituted C_{6-10} aryl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{3-8} cycloalkyl, or optionally substituted C_{1-9} heteroaryl; or both R^6, together with the atom to which they are attached, combine to form an optionally substituted C_{2-9} heterocyclyl;

Q is optionally substituted C_{2-9} heterocyclylene, optionally substituted C_{3-8} cycloalkylene, optionally substituted C_{1-9} heteroarylene, or optionally substituted C_{6-10} arylene; and

X is hydrogen or halogen.

In some examples, the ATR inhibitor is selected from the group consisting of compounds 43, 57, 62, 87, 93, 94, 95, 99, 100, 106, 107, 108, 109, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 123, 135, 147, 148, and pharmaceutically acceptable salts thereof.

In some examples, the ATR inhibitor is compound 43 or a pharmaceutically acceptable salt thereof. In some examples, the ATR inhibitor is compound 121 or a pharmaceutically acceptable salt thereof. In some examples, the ATR inhibitor is compound 122 or a pharmaceutically acceptable salt thereof. In some examples, the PARP inhibitor is talazoparib or a pharmaceutically acceptable salt thereof. In some examples, the PARP inhibitor is niraparib or a pharmaceutically acceptable salt thereof. In some examples, the PARP inhibitor is rucaparib or a pharmaceutically acceptable salt thereof. In some examples, the PARP inhibitor is olaparib or a pharmaceutically acceptable salt thereof. In some examples, the cancer is renal cell carcinoma, mature B-cell neoplasms, endometrial cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, colorectal cancer, skin cancer, small bowel cancer, non-small cell lung cancer, melanoma, bladder cancer, pancreatic cancer, head and neck cancer, mesothelioma, glioma, prostate cancer, breast cancer, or esophagogastric cancer.

Definitions

The term "aberrant," as used herein, refers to different from normal. When used to describe enzymatic activity, aberrant refers to activity that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, where returning the aberrant activity to a normal or non-disease-associated amount (e.g. by administering a compound or using a method as described herein), results in reduction of the disease or one or more disease symptoms. The aberrant activity can be measured by measuring the modification of a substrate of the enzyme in question; a difference of greater or equal to a 2-fold change in activity could be considered as aberrant. Aberrant activity could also refer to an increased dependence on a particular signaling pathway as a result of a deficiency in a separate complementary pathway

The term “acyl,” as used herein, represents a group –C(=O)–R, where R is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, or heterocyclyl. Acyl may be optionally substituted as described herein for each respective R group.

The term “adenocarcinoma,” as used herein, represents a malignancy of the arising from the glandular cells that line organs within an organism. Non-limiting examples of adenocarcinomas include non-small cell lung cancer, prostate cancer, pancreatic cancer, esophageal cancer, and colorectal cancer.

The term “alkanoyl,” as used herein, represents a hydrogen or an alkyl group that is attached to the parent molecular group through a carbonyl group and is exemplified by formyl (i.e., a carboxyaldehyde group), acetyl, propionyl, butyryl, and iso-butyryl. Unsubstituted alkanoyl groups contain from 1 to 7 carbons. The alkanoyl group may be unsubstituted of substituted (e.g., optionally substituted C1-7 alkanoyl) as described herein for alkyl group. The ending “-oyl” may be added to

another group defined herein, e.g., aryl, cycloalkyl, and heterocyclyl, to define “aryloyl,” “cycloalkanoyl,” and “(heterocyclyl)oyl.” These groups represent a carbonyl group substituted by aryl, cycloalkyl, or

Claims

1. Use of a therapeutically effective amount of an ATR inhibitor and a therapeutically effective amount of a PARP inhibitor in the manufacture of a medicament for the treatment of cancer, wherein the cancer has a loss of function of ATM, BRCA2, RNAse H2A, RNAse H2B, CDK12, or a combination thereof, or wherein the cancer has been previously identified as an ALT+ cancer.

2. The use of claim 1, wherein the ATR inhibitor is to be administered before the PARP inhibitor.

3. The use of claim 1, wherein the ATR inhibitor is to be administered after the PARP inhibitor.

4. The use of claim 1, wherein the ATR inhibitor is to be co-administered with the PARP inhibitor.

5. The use of any one of claims 1 to 4, wherein the therapeutically effective amount is a subtherapeutic regimen of the ATR inhibitor.

6. The use of any one of claims 1 to 5, wherein the therapeutically effective amount is a subtherapeutic regimen of the PARP inhibitor.

7. The use of claim 5 or 6, wherein the subtherapeutic regimen comprises a starting dosage that is at least 50% less than the lowest standard starting dosage that is used for a monotherapy.

8. The use of any one of claims 5 to 7, wherein the subtherapeutic regimen comprises a maintenance dosage that is at least 50% less than the lowest standard maintenance dosage that is used for a monotherapy.

9. The use of claim 8, wherein the maintenance dosage comprises a first, second, and/or third reduced dosage.

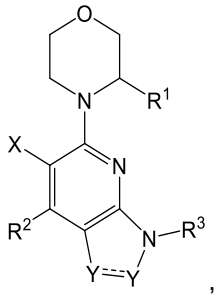
10. The use of any one of claims 1 to 9, wherein the ATR inhibitor is to be administered 1 day/week, 2 days/week, or 3 days/week.

11. The use of any one of claims 1 to 10, wherein the PARP inhibitor is to be administered daily.

12. The use of any one of claims 1 to 11, wherein the loss of function is:
    (i) a loss of function of ATM;
    (ii) a loss of function of RNAse H2A;
    (iii) a loss of function of RNAse H2B;
    (iv) a loss of function of CDK12; or
    (v) a loss of function of BRCA2.

13. The use of any one of claims 1 to 11, wherein the cancer is an ALT+ cancer.

14. The use of any one of claims 1 to 13, wherein the ATR inhibitor is a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

$\overline{\text{------}}$ is a double bond, and each Y is independently N or CR^4; or $\overline{\text{------}}$ is a single bond, and each Y is independently NR^Y, carbonyl, or $C(R^Y)_2$; wherein each R^Y is independently H or optionally substituted C_{1-6} alkyl;

R^1 is optionally substituted C_{1-6} alkyl or H;

R^2 is optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{2-9} heterocyclyl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, optionally substituted C_{1-9} heteroaryl C_{1-6} alkyl, halogen, $–N(R^5)_2$, $–OR^5$, $–CON(R^6)_2$, $–SO_2N(R^6)_2$,$–SO_2R^{5A}$, or $–Q–R^{5B}$;

R^3 is optionally substituted C_{1-9} heteroaryl or optionally substituted C_{1-9} heteroaryl C_{1-6} alkyl;

each R^4 is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, or optionally substituted C_{2-6} alkynyl;

each R^5 is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, or $–SO_2R^{5A}$; or both R^5, together with the atom to which they are attached, combine to form an optionally substituted C_{2-9} heterocyclyl;

each R^{5A} is independently optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, or optionally substituted C_{6-10} aryl;

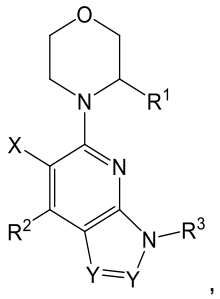
R^{5B} is hydroxyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, $–N(R^5)_2$, $–CON(R^6)_2$, $–SO_2N(R^6)_2$, $–SO_2R^{5A}$, or optionally substituted alkoxy;

each R^6 is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkoxyalkyl, optionally substituted C_{6-10} aryl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{3-8} cycloalkyl, or optionally substituted C_{1-9} heteroaryl; or both R^6, together with the atom to which they are attached, combine to form an optionally substituted C_{2-9} heterocyclyl;

Q is optionally substituted C_{2-9} heterocyclylene, optionally substituted C_{3-8} cycloalkylene, optionally substituted C_{1-9} heteroarylene, or optionally substituted C_{6-10} arylene; and

X is hydrogen or halogen.

15. The use of claim 14, wherein the ATR inhibitor is a compound of formula (II):



(II)

or a pharmaceutically acceptable salt thereof,

wherein

each Y is independently N or CR^4;

R^1 is optionally substituted C_{1-6} alkyl or H;

R^2 is optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{2-9} heterocyclyl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, optionally substituted C_{1-9} heteroaryl C_{1-6} alkyl, halogen, $–N(R^5)_2$, $–OR^5$, $–CON(R^6)_2$, $–SO_2N(R^6)_2$,$–SO_2R^{5A}$, or $–Q–R^{5B}$;

R^3 is optionally substituted C_{1-9} heteroaryl or optionally substituted C_{1-9} heteroaryl C_{1-6} alkyl;

each R^4 is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, or optionally substituted C_{2-6} alkynyl;

each R^5 is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, or $–SO_2R^{5A}$; or both R^5, together with the atom to which they are attached, combine to form an optionally substituted C_{2-9} heterocyclyl;

each R^{5A} is independently optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, or optionally substituted C_{6-10} aryl;

R^{5B} is hydroxyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, $–N(R^5)_2$, $–CON(R^6)_2$, $–SO_2N(R^6)_2$, $–SO_2R^{5A}$, or optionally substituted alkoxy;

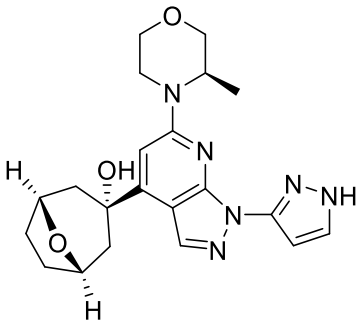
each R^6 is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkoxyalkyl, optionally substituted C_{6-10} aryl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{3-8} cycloalkyl, or optionally substituted C_{1-9} heteroaryl; or both R^6, together with the atom to which they are attached, combine to form an optionally substituted C_{2-9} heterocyclyl;

Q is optionally substituted C_{2-9} heterocyclylene, optionally substituted C_{3-8} cycloalkylene, optionally substituted C_{1-9} heteroarylene, or optionally substituted C_{6-10} arylene; and

X is hydrogen or halogen.

16. The use of claim 14, wherein the ATR inhibitor is selected from the group consisting of compounds 43, 57, 62, 87, 93, 94, 95, 99, 100, 106, 107, 108, 109, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 123, 135, 147, 148, and pharmaceutically acceptable salts thereof.

17. The use of claim 16, wherein the ATR inhibitor is a compound having the formula:



, or a pharmaceutically acceptable salt thereof.

18. The use of any one of claims 1 to 17, wherein the PARP inhibitor is talazoparib, niraparib, rucaparib, olaparib or a pharmaceutically acceptable salt thereof.

19. The use of any one of claims 1 to 18, wherein the cancer is renal cell carcinoma, mature B-cell neoplasms, endometrial cancer, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, colorectal cancer, skin cancer, small bowel cancer, non-small cell lung cancer, melanoma, bladder cancer, pancreatic cancer, head and neck cancer, mesothelioma, glioma, prostate cancer, breast cancer, or esophagogastric cancer.

20. A therapeutically effective amount of an ATR inhibitor and a therapeutically effective amount of a PARP inhibitor for use in the treatment of cancer, wherein the cancer has a loss of function of ATM, BRCA2, RNAse H2A, RNAse H2B, CDK12, or a combination thereof, or wherein the cancer has been previously identified as an ALT+ cancer.