Claims

1. 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 a therapeutically effective amount of a PARP inhibitor, wherein 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 wherein the cancer has been previously identified as an ALT+ cancer.

2. 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 a therapeutically effective amount of a PARP inhibitor, wherein the cancer has a loss of function of ATM, BRCA2, RNAse H2A, RNAse H2B, CDK12, or a combination thereof, or wherein the cancer is an ALT+ cancer.

3. 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 a therapeutically effective amount of a PARP inhibitor.

4. The method of any one of claims 1 to 3, wherein the ATR inhibitor is administered before the PARP inhibitor.

5. The method of any one of claims 1 to 3, wherein the ATR inhibitor is administered after the PARP inhibitor.

6. The method of any one of claims 1 to 3, wherein the ATR inhibitor is co-administered with the PARP inhibitor.

7. The method of any one of claims 1 to 6, wherein the therapeutically effective amount is a subtherapeutic regimen of the ATR inhibitor.

8. The method of any one of claims 1 to 7, wherein the therapeutically effective amount is a subtherapeutic regimen of the PARP inhibitor.

9. The method of claim 7 or 8, 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.

10. The method of any one of claims 7 to 9, 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.

11. The method of claim 10, wherein the maintenance dosage comprises a first reduced dosage.

12. The method of claim 10 or 11, wherein the maintenance dosage comprises a second reduced dosage.

13. The method of any one of claims 10 to 12, wherein the maintenance dosage comprises a third reduced dosage.

14. The method of any one of claims 1 to 13, wherein the route of administration is an oral administration.

15. The method of any one of claims 1 to 14, wherein the ATR inhibitor is administered 1 day/week, 2 days/week, or 3 days/week.

16. The method of any one of claims 1 to 15, wherein the PARP inhibitor is administered daily.

17. 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.

18. The method of any one of claims 1 to 17, wherein the loss of function is a loss of function of ATM.

19. The method of any one of claims 1 to 17, wherein the loss of function is a loss of function of RNAse H2A.

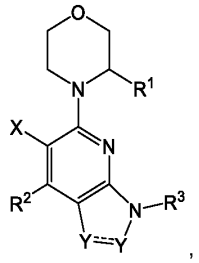
20. The method of any one of claims 1 to 17, wherein the loss of function is a loss of function of RNAse H2B.

21. The method of any one of claims 1 to 17, wherein the loss of function is a loss of function of CDK12.

22. The method of any one of claims 1 to 17, wherein the loss of function is a loss of function of BRCA2.

23. The method of any one of claims 1 to 17, wherein the cancer is an ALT+ cancer.

24. The method of any one of claims 1 to 23, wherein 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;

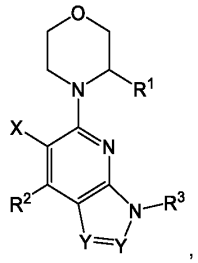
R^{5B} is hydroxyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, $–N(R^5)_2$, $–CON(R^6)_2$, $–SO_2N(R^6)_2$, $–SO_2R^{5A}$, or optionally substituted alkoxy;

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.

25. The method of claim 24, 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.

26. The method of claim 24, 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.

27. The method of claim 26, wherein the ATR inhibitor is compound 43 or a pharmaceutically acceptable salt thereof.

28. The method of claim 26, wherein the ATR inhibitor is compound 121 or a pharmaceutically acceptable salt thereof.

29. The method of claim 26, wherein the ATR inhibitor is compound 122 or a pharmaceutically acceptable salt thereof.

30. The method of any one of claims 1 to 29, wherein the PARP inhibitor is talazoparib or a pharmaceutically acceptable salt thereof.

31. The method of any one of claims 1 to 29, wherein the PARP inhibitor is niraparib or a pharmaceutically acceptable salt thereof.

32. The method of any one of claims 1 to 29, wherein the PARP inhibitor is rucaparib or a pharmaceutically acceptable salt thereof.

33. The method of any one of claims 1 to 29, wherein the PARP inhibitor is olaparib or a pharmaceutically acceptable salt thereof.

34. The method of any one of claims 1 to 33, 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.