

CLAIMS

1. A method of selecting a cancer for treatment with an ATR inhibitor, comprising:
the *in vitro* measuring of the level of cyclin dependent kinase inhibitor 1A (CDKN1A) activity in a cancer;
comparing the measured CDKN1A activity to CDKN1A activity in a control tissue or cell;
and
selecting the cancer having a reduced CDKN1A activity as compared to CDKN1A activity in a control tissue or cell for treatment with an ATR inhibitor.
2. A method of selecting a patient with cancer for treatment with an ATR inhibitor, comprising:
the *in vitro* measuring of the level of CDKN1A activity in a cancer of a patient;
comparing the measured CDKN1A activity to CDKN1A activity in a control tissue or cell;
and
selecting the patient with a cancer identified as having a reduced CDKN1A activity as compared to CDKN1A activity of a control tissue or cell for treatment with the ATR inhibitor.
3. The method of claim 1 or claim 2, wherein the treatment with the medicament or the ATR inhibitor in the method, is to be in combination with a DNA damaging agent.
4. The method of claim 1 or claim 2, wherein the cancer identified as having a reduced CDKN1A activity is characterized by a synergistic growth inhibition response to the ATR inhibitor and a DNA damaging agent.
5. The method of any one of claims 1 to 4, further comprising detecting the presence or absence of an activity-attenuating or inactivating mutation in TP53 protein or a gene encoding the TP53 protein, and wherein the patient with the cancer having a reduced CDKN1A activity compared to the CDKN1A activity in the control tissue or cell, and the presence of an activity-attenuating or inactivating mutation in the TP53 protein or the gene encoding the TP53 protein is selected for treatment with the ATR inhibitor.
6. The method of claim 5, wherein the activity attenuating or inactivating mutation of TP53 is a loss of function mutation in the DNA binding domain, homo-oligomerization domain, or transactivation domain of TP53.

7. The method of any one of claims 1 to 6, wherein the reduced CDKN1A activity is a CDKN1A activity level which is in the lower three quartiles of the CDKN1A activity in the control tissue or cell.

8. A method of identifying a patient having a cancer contraindicated (not indicated) for treatment with an ATR inhibitor, comprising:

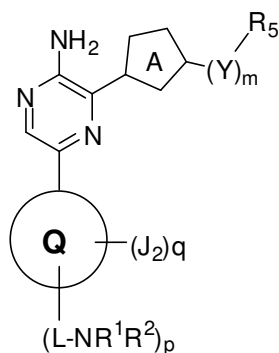
the *in vitro* measuring of the level of cyclin dependent kinase inhibitor 1A (CDKN1A) activity in a cancer of a patient;

comparing the measured CDKN1A activity to CDKN1A activity in a control tissue or cell; and

identifying the patient having a cancer with a CDKN1A activity which is substantially similar to CDKN1A activity in control tissue or cell as being contraindicated for treatment with the ATR inhibitor.

9. The method of claim 8, wherein the contraindication is for treatment with the ATR inhibitor in combination with a DNA damaging agent.

10. The method of any one of claims 1 to 9, wherein the ATR inhibitor is compound of Formula IA:

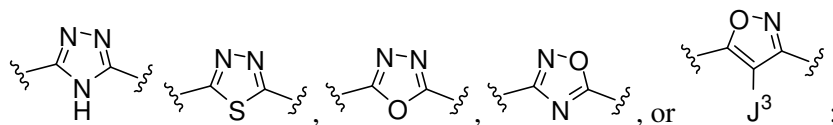


IA

or a pharmaceutically acceptable salt thereof; wherein

Y is a C₁-C₁₀aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with O, NR⁰, S, C(O) or S(O)₂;

Ring A is a 5 membered heteroaryl ring selected from



J³ is H or C₁-C₄alkyl, wherein 1 methylene unit of the alkyl group can optionally be replaced with O, NH, N(C₁-C₄alkyl), or S and optionally substituted with 1-3 halo;

Q is a 5-6 membered monocyclic aromatic ring containing 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or an 8-10 membered bicyclic aromatic ring containing 0-6 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R⁵ is H; a 3-7 membered monocyclic fully saturated, partially unsaturated, or aromatic ring containing 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic fully saturated, partially unsaturated, or aromatic ring containing 0-6 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein R⁵ is optionally substituted with 1-5 J⁵ groups;

L is a C₁-C₄alkyl chain wherein up to two methylene units of the alkyl chain are optionally replaced with O, NR⁶, S, -C(O)-, -SO-, or -SO₂-;

R⁰ is H or C₁-C₆alkyl wherein one methylene unit of the alkyl chain can be optionally replaced with O, NH, N(C₁-C₄alkyl), or S;

R¹ is H or C₁-C₆alkyl;

R² is H, C₁-C₆alkyl, -(C₂-C₆alkyl)-Z or a 4-8 membered cyclic ring containing 0-2 nitrogen atoms; wherein said ring is bonded via a carbon atom and is optionally substituted with one occurrence of J^Z;

or R¹ and R², taken together with the atom to which they are bound, form a 4-8 membered heterocyclic ring containing 1-2 heteroatoms selected from oxygen, nitrogen, and sulfur; wherein said heterocyclic ring is optionally substituted with one occurrence of J^{Z1};

J^{Z1} is halo, CN, C₁-C₈aliphatic, -(X)_t-CN, or -(X)_t-Z, wherein said up to two methylene units of said C₁-C₈aliphatic can be optionally replaced with O, NR, S, P(O), C(O), S(O), or S(O)₂, wherein said C₁-C₈aliphatic is optionally substituted with halo, CN, or NO₂;

X is C₁-C₄alkyl;

each t, r and m is independently 0 or 1;

Z is -NR³R⁴;

R³ is H or C₁-C₂alkyl;

R⁴ is H or C₁-C₆alkyl;

or R³ and R⁴, taken together with the atom to which they are bound, form a 4-8 membered heterocyclic ring containing 1-2 heteroatoms selected from oxygen, nitrogen, and sulfur; wherein said ring is optionally substituted with one occurrence of J^Z;

R⁶ is H, or C₁-C₆alkyl;

J^Z is independently NH₂, NH(C₁-C₄aliphatic), N(C₁-C₄aliphatic)₂, halogen, C₁-C₄aliphatic, OH, O(C₁-C₄aliphatic), NO₂, CN, CO₂H, CO(C₁-C₄aliphatic), CO₂(C₁-C₄aliphatic), O(haloC₁-C₄aliphatic), or haloC₁-C₄aliphatic;

J⁵ is halo, oxo, CN, NO₂, X¹-R, or -(X¹)_p-Q⁴;

X^1 is C_1 - C_{10} aliphatic; wherein 1-3 methylene units of said C_1 - C_{10} aliphatic are optionally replaced with $-NR'$ -, $-O$ -, $-S$ -, $C(=NR')$, $C(O)$, $S(O)_2$, or $S(O)$, wherein X^1 is optionally and independently substituted with 1-4 occurrences of NH_2 , $NH(C_1-C_4aliphatic)$, $N(C_1-C_4aliphatic)_2$, halogen, $C_1-C_4aliphatic$, OH , $O(C_1-C_4aliphatic)$, NO_2 , CN , CO_2H , $CO_2(C_1-C_4aliphatic)$, $C(O)NH_2$, $C(O)NH(C_1-C_4aliphatic)$, $C(O)N(C_1-C_4aliphatic)_2$, $SO(C_1-C_4aliphatic)$, $SO_2(C_1-C_4aliphatic)$, $SO_2NH(C_1-C_4aliphatic)$, $NHC(O)(C_1-C_4aliphatic)$, $N(C_1-C_4aliphatic)C(O)(C_1-C_4aliphatic)$, wherein said $C_1-C_4aliphatic$ is optionally substituted with 1-3 occurrences of halo;

Q^4 is a 3-8 membered saturated or unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 8-10 membered saturated or unsaturated bicyclic ring having 0-6 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each Q^4 is optionally substituted with 1-5 J^{Q^4} ;

J^{Q^4} is halo, CN , or C_1-C_4alkyl wherein up to 2 methylene units are optionally replaced with O , NR^* , S , $C(O)$, $S(O)$, or $S(O)_2$;

R is H or C_1-C_4alkyl wherein said C_1-C_4alkyl is optionally substituted with 1-4 halo;

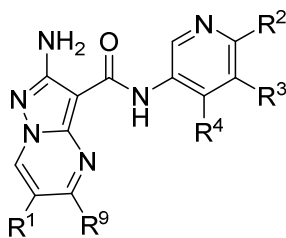
J^2 is halo; CN ; a 5-6 membered aromatic or nonaromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, and sulfur; or a $C_1-C_{10}aliphatic$ group wherein up to 2 methylene units are optionally replaced with O , NR'' , $C(O)$, S , $S(O)$, or $S(O)_2$; wherein said $C_1-C_{10}aliphatic$ group is optionally substituted with 1-3 halo or CN ; and said monocyclic ring is optionally substituted with 1-3 occurrences of halo; CN ; a $C_3-C_6cycloalkyl$; a 3-7 membered heterocyclyl containing 0-2 heteroatoms selected from oxygen, nitrogen, and sulfur; or a C_1-C_4alkyl wherein up to one methylene unit of the alkyl chain is optionally replaced with O , NR'' , or S ; and wherein said C_1-C_4alkyl is optionally substituted with 1-3 halo;

q is 0, 1, or 2;

p is 0 or 1;

R' , R'' , and R^* are each independently H , C_1-C_4alkyl , or is absent; wherein said C_1-C_4alkyl is optionally substituted with 1-4 halo.

11. The method of any one of claims 1 to 10, wherein the ATR inhibitor is a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is independently selected from $-C(J^1)_2CN$, halo, $-(L)_k-W$, and M;

R^9 is independently selected from H, $-C(J^1)_2CN$, halo, $-(L)_k-W$, and M;

J^1 is independently selected from H and C_1-C_2 alkyl; or
 two occurrences of J^1 , together with the carbon atom to which they are attached, form a 3-4 membered optionally substituted carbocyclic ring;

k is 0 or 1;

M and L are a C_1-C_8 aliphatic, wherein up to three methylene units are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-, each M and L¹ is optionally substituted with 0-3 occurrences of J^{LM} ;

J^{LM} is independently selected from halo, -CN, and a C_1-C_4 aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-;

W is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen and sulfur; and a 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, and sulfur; wherein W is optionally substituted with 0-5 occurrences of J^W ;

J^W is independently selected from -CN, halo, -CF₃; a C_1-C_4 aliphatic wherein up to two methylene units are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-; and a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, and sulfur; or two occurrences of J^W on the same atom, together with atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, and sulfur; or two occurrences of J^W , together with W, form a 6-10 membered saturated or partially unsaturated bridged ring system;

R^2 is independently selected from H; halo; -CN; NH₂; a C_1-C_2 alkyl optionally substituted with 0-3 occurrences of fluoro; and a C_1-C_3 aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-;

R^3 is independently selected from H; halo; C_1-C_4 alkyl optionally substituted with 1-3 occurrences of halo; C_3-C_4 cycloalkyl; 3-4 membered heterocyclyl; -CN; and a C_1-C_3 aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-;

R^4 is independently selected from Q^1 and a C_1-C_{10} aliphatic chain wherein up to four methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-; each R^4 is optionally substituted with 0-5 occurrences of J^Q ; or

R^3 and R^4 , taken together with the atoms to which they are bound, form a 5-6 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen and sulfur; the ring formed by R^3 and R^4 is optionally substituted with 0-3 occurrences of J^Z ;

Q¹ is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring, the 3-7 membered ring having 0-3 heteroatoms selected from oxygen, nitrogen and sulfur; and an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, and sulfur;

J^z is independently selected from C₁-C₆aliphatic, =O, halo, and →O;

J^Q is independently selected from -CN; halo; =O; Q²; and a C₁-C₈aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-; each occurrence of J^Q is optionally substituted by 0-3 occurrences of J^R; or two occurrences of J^Q on the same atom, taken together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, and sulfur; wherein the ring formed by two occurrences of J^Q is optionally substituted with 0-3 occurrences of J^X; or two occurrences of J^Q, together with Q¹, form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q² is independently selected from a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, and sulfur; and an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, and sulfur;

J^R is independently selected from -CN; halo; =O; →O; Q³; and a C₁-C₆aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-; each J^R is optionally substituted with 0-3 occurrences of J^T; or two occurrences of J^R on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, and sulfur; wherein the ring formed by two occurrences of J^R is optionally substituted with 0-3 occurrences of J^X; or two occurrences of J^R, together with Q², form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q³ is a 3-7 membered fully saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, or sulfur; or an 7-12 membered fully saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, and sulfur;

J^X is independently selected from -CN; =O; halo; and a C₁-C₄aliphatic chain, wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-;

J^T is independently selected from halo, -CN; →O; =O; -OH; a C₁-C₆aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n-; and a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, and sulfur; each occurrence of J^T is optionally substituted with 0-3 occurrences of J^M; or two occurrences of J^T on the same atom, together with the atom to which they are joined, form a 3-6 membered ring having 0-2 heteroatoms selected from oxygen, nitrogen, and sulfur; or two

occurrences of J^T , together with Q^3 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^M is independently selected from halo and C_1-C_6 aliphatic;

n is 0, 1 or 2; and

R is independently selected from H and C_1-C_4 aliphatic.

12. The method of any one of claims 1 to 11, wherein the DNA damaging agent comprises platinating agent, anti-metabolite, or combinations thereof.

13. The method of claim 12, wherein the DNA damaging agent comprises a platinating agent.

14. The method of claim 13, wherein the platinating agent comprises cisplatin, oxaliplatin, or carboplatin.

15. The method of claim 12, wherein the DNA damaging agent comprises an anti-metabolite.

16. The method of claim 15, wherein the anti-metabolite comprises cytarabine, gemcitabine, capecitabine, or 5-fluorouracil (5-FU).