

CLAIMS

~~1. Use of an ATR inhibitor in the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered to a patient with a cancer identified as having a reduced cyclin dependent kinase inhibitor 1A (CDKN1A) activity as compared to CDKN1A activity in control tissue or cell, and wherein the ATR inhibitor is in a therapeutically effective amount to sensitize the cancer to a DNA damaging agent.~~

21. 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.

32. 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.

43. The ~~use of claim 1 or the~~ method of claim 21 or claim 32, wherein the treatment with the medicament or the ATR inhibitor in the method, is to be in combination with a DNA damaging agent.

54. The ~~use of claim 1 or the~~ method of claim 21 or claim 32, 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.

65. The ~~use of claim 1 or claim 4 or claim 5, or the~~ method of any one of claims 21 to 54, 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.

~~76.~~ The ~~use of~~ method of claim ~~65~~, 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.

~~87.~~ The ~~use of claim 1 or any one of claims 4 to 7, or the method of any one of claims 2-1~~ to ~~76~~, 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.

~~98.~~ A method of identifying a patient having a cancer contraindicated (not indicated) for treatment with an ATR inhibitor, comprising:

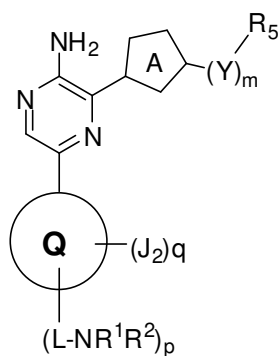
the *in vitro* measuring of the level of cyclin dependent kinase inhibitor 1A (CDKN1A) activity in a cancer of a patient;

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.

~~109.~~ The method of claim ~~98~~, wherein the contraindication is for treatment with the ATR inhibitor in combination with a DNA damaging agent.

~~1110.~~ The ~~use of claim 1 or any one of claims 4 to 8, or the method of any one of claims 2-1~~ to ~~109~~, wherein the ATR inhibitor is compound of Formula IA:

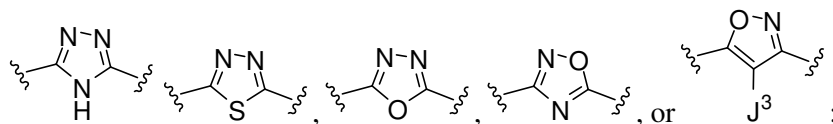


IA

or a pharmaceutically acceptable salt thereof; wherein

Y is a $\text{C}_1\text{-C}_{10}$ aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with O, NR^0 , S, $\text{C}(\text{O})$ or $\text{S}(\text{O})_2$;

Ring A is a 5 membered heteroaryl ring selected from



J^3 is H or C_1 - C_4 alkyl, wherein 1 methylene unit of the alkyl group can optionally be replaced with O, NH, $N(C_1$ - C_4 alkyl), 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;

R^5 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 R^5 is optionally substituted with 1-5 J^5 groups;

L is a C_1 - C_4 alkyl chain wherein up to two methylene units of the alkyl chain are optionally replaced with O, NR^6 , S, $-C(O)-$, $-SO-$, or $-SO_2-$;

R^0 is H or C_1 - C_6 alkyl wherein one methylene unit of the alkyl chain can be optionally replaced with O, NH, $N(C_1$ - C_4 alkyl), or S;

R^1 is H or C_1 - C_6 alkyl;

R^2 is H, C_1 - C_6 alkyl, $-(C_2$ - C_6 alkyl)-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 R^1 and R^2 , 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, C_1 - C_8 aliphatic, $-(X)_r$ -CN, or $-(X)_r$ -Z, wherein said up to two methylene units of said C_1 - C_8 aliphatic can be optionally replaced with O, NR, S, P(O), C(O), S(O), or S(O)₂, wherein said C_1 - C_8 aliphatic is optionally substituted with halo, CN, or NO₂;

X is C_1 - C_4 alkyl;

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

Z is $-NR^3R^4$;

R^3 is H or C_1 - C_2 alkyl;

R^4 is H or C_1 - C_6 alkyl;

or R^3 and R^4 , 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 ;

R^6 is H, or C_1 - C_6 alkyl;

J² 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;

X¹ is C₁-C₁₀aliphatic; wherein 1-3 methylene units of said C₁-C₁₀aliphatic are optionally replaced with -NR', -O-, -S-, C(=NR'), C(O), S(O)₂, or S(O), wherein X¹ is optionally and independently substituted with 1-4 occurrences of NH₂, NH(C₁-C₄aliphatic), N(C₁-C₄aliphatic)₂, halogen, C₁-C₄aliphatic, OH, O(C₁-C₄aliphatic), NO₂, CN, CO₂H, CO₂(C₁-C₄aliphatic), C(O)NH₂, C(O)NH(C₁-C₄aliphatic), C(O)N(C₁-C₄aliphatic)₂, SO(C₁-C₄aliphatic), SO₂(C₁-C₄aliphatic), SO₂NH(C₁-C₄aliphatic), NHC(O)(C₁-C₄aliphatic), N(C₁-C₄aliphatic)C(O)(C₁-C₄aliphatic), wherein said C₁-C₄aliphatic is optionally substituted with 1-3 occurrences of halo;

Q⁴ 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 Q⁴ is optionally substituted with 1-5 J^{Q4};

J^{Q4} is halo, CN, or C₁-C₄alkyl 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 C₁-C₄alkyl wherein said C₁-C₄alkyl is optionally substituted with 1-4 halo;

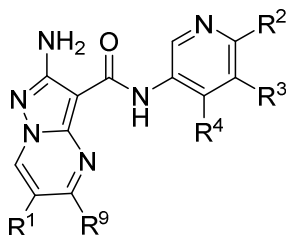
J² is halo; CN; a 5-6 membered aromatic or nonaromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, and sulfur; or a C₁-C₁₀aliphatic group wherein up to 2 methylene units are optionally replaced with O, NR'', C(O), S, S(O), or S(O)₂; wherein said C₁-C₁₀aliphatic group is optionally substituted with 1-3 halo or CN; and said monocyclic ring is optionally substituted with 1-3 occurrences of halo; CN; a C₃-C₆cycloalkyl; a 3-7 membered heterocyclyl containing 0-2 heteroatoms selected from oxygen, nitrogen, and sulfur; or a C₁-C₄alkyl wherein up to one methylene unit of the alkyl chain is optionally replaced with O, NR'', or S; and wherein said C₁-C₄alkyl 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, C₁-C₄alkyl, or is absent; wherein said C₁-C₄alkyl is optionally substituted with 1-4 halo.

~~1211.~~ The use of claim 1 or any one of claims 4 to 8 or claim 11, or the method of any one of claims ~~2-1~~ to ~~11~~10, wherein the ATR inhibitor is a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is independently selected from -C(J¹)₂CN, halo, -(L)_k-W, and M;

R⁹ is independently selected from H, -C(J¹)₂CN, halo, -(L)_k-W, and M;

J¹ is independently selected from H and C₁-C₂alkyl; or

two occurrences of J¹, 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 C₁-C₈aliphatic, 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 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-;

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 C₁-C₄aliphatic 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;

R² is independently selected from H; halo; -CN; NH₂; a C₁-C₂alkyl optionally substituted with 0-3 occurrences of fluoro; and a C₁-C₃aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)_n;

R³ is independently selected from H; halo; C₁-C₄alkyl optionally substituted with 1-3 occurrences of halo; C₃-C₄cycloalkyl; 3-4 membered heterocyclyl; -CN; and a C₁-C₃aliphatic 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 ;

Q^1 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 C_1 - C_6 aliphatic, =O, halo, and $\rightarrow O$;

J^Q is independently selected from -CN; halo; =O; Q^2 ; and a C_1 - C_8 aliphatic 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 Q^1 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^2 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; $\rightarrow O$; Q^3 ; and a C_1 - C_6 aliphatic 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 Q^2 , form a 6-10 membered saturated or partially unsaturated bridged ring system;

Q^3 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 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-;

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 Q³, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J^M is independently selected from halo and C₁-C₆aliphatic;

n is 0, 1 or 2; and

R is independently selected from H and C₁-C₄aliphatic.

~~1312. The use of claim 1 or any one of claims 4 to 8 or claim 11 or claim 12, or the method of any one of claims 2-1 to 1211, wherein the DNA damaging agent when present comprises ionizing radiation, platinating agent, topoisomerase I (Topo I) inhibitor, topoisomerase II (Topo II) inhibitor, anti-metabolite, alkylating agent, anti-cancer antibiotic, or combinations thereof.~~

~~1413. The use or method of claim 1312, wherein the DNA damaging agent comprises a platinating agent.~~

~~1514. The use or method of claim 1413, wherein the platinating agent comprises cisplatin, oxaliplatin, or carboplatin.~~

~~1615. The use or method of claim 1312, wherein the DNA damaging agent comprises an anti-metabolite.~~

~~1716. The use or method of claim 1615, wherein the anti-metabolite comprises cytarabine, gemcitabine, capecitabine, or 5-fluorouracil (5-FU).~~

~~18. — An article of manufacture comprising:~~
~~—— (a) — a packaging material;~~
~~—— (b) — an ATR inhibitor, or a pharmaceutically acceptable salt thereof; and~~
~~—— (c) — a label, a package insert, or directions for obtaining the label or the package insert, contained within the packaging material, wherein the label or package insert provides prescribing information based on level of CDKN1A activity, or based on the level of CDKN1A activity and TP53 mutations status, determined for the cancer in a patient.~~