

**[0004]** Moreover, the present disclosure describes the additional finding that CDKN1A levels below a particular threshold show a higher association to synergistic response. To this end, it is described herein that cancers having a CDKN1A level in the lower three quartiles (i.e., 1st to 3rd quartiles) as compared to the population tested displayed a higher association with a synergistic response to the ATR inhibitor combination therapy. In other words, cancers having the highest baseline CDKN1A levels were less likely to have a statistically significant association with a synergistic response to the ATR inhibitor combination therapy.

**[0005]** Accordingly, in one aspect, the present disclosure provides an ATR inhibitor for use in a method of treatment of cancer, characterized in the treatment being indicated in a cancer identified as having a reduced cyclin dependent kinase inhibitor 1A (CDKN1A) activity as compared to CDKN1A activity in a control tissue or cell. In some embodiments, the use is in a method of treating a cancer, comprising administering to a patient with a cancer identified as having a reduced CDKN1A activity as compared to CDKN1A activity in control tissue or cell a therapeutically effective amount of an ATR inhibitor to sensitize the cancer to a DNA damaging agent.

**[0006]** In some embodiments, identifying a cancer as having a reduced CDKN1A activity is by: measuring the level of CDKN1A activity in the cancer; and comparing the measured CDKN1A activity to CDKN1A activity in an appropriate control tissue or cell. As further discussed herein, in some embodiments, measuring of the CDKN1A activity is done in vitro, for example on a biological sample.

**[0007]** In some embodiments, the method of treatment further comprises detecting the presence or absence of an activity-attenuating or inactivating mutation in TP53 protein or a gene encoding the TP53 protein, wherein the cancer identified as having a reduced CDKN1A activity level 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 administered a therapeutically effective amount of the ATR inhibitor.

**[0008]** In some embodiments, the method of treatment further comprises administering to the patient a therapeutically effective amount of one or more DNA damaging agents. In some embodiments, the therapeutically effective amount of a DNA damaging agent is that amount which is therapeutically effective in combination with the ATR inhibitor. In some embodiments, the therapeutically effective amount of the DNA damaging agent is less than the therapeutically effective amount of the DNA damaging agent when used in the absence of an ATR inhibitor.

**[0009]** In another aspect, the levels of CDKN1A activity is used to identify cancers having enhanced sensitivity to an ATR inhibitor. In some embodiments, a method of identifying a cancer having enhanced sensitivity to an ATR inhibitor comprises: measuring the level of CDKN1A activity in a

**[0054]** In some embodiments, this disclosure provides the above ATR inhibitor further characterized in the treatment being in combination with a DNA damaging agent.

**[0055]** In some embodiments, this disclosure provides a method of treating a patient having cancer, comprising administering 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 a therapeutically effective amount of an ATR inhibitor to sensitize the cancer to a DNA damaging agent.

**[0056]** In some embodiments, identifying a cancer as having a reduced CDKN1A activity is by: (a) measuring the level of CDKN1A activity in the cancer; and (b) comparing the measured CDKN1A activity to CDKN1A activity in a control tissue or cell. As further discussed herein, in some embodiments, measuring of the CDKN1A activity is done in vitro, for example on a biological sample.

**[0057]** In some embodiments, the method of treatment further comprises administering to the patient a therapeutically effective amount of a DNA damaging agent.

**[0058]** In some embodiments, a method of treating a patient having cancer comprises administering to a patient having a cancer identified as having a reduced CDKN1A activity as compared to CDKN1A activity in control tissue or cell a therapeutically effective amount of an ATR inhibitor in combination with a DNA damaging agent. As noted above, in some embodiments, the therapeutically effective amount of a DNA damaging agent is that amount which is therapeutically effective in combination with the ATR inhibitor. In some embodiments, the therapeutically effective amount of the DNA damaging agent is less than the therapeutically effective amount of the DNA damaging agent when used in the absence of an ATR inhibitor.

**[0059]** In some embodiments, a method of treating a patient having cancer comprises: measuring the level of CDKN1A activity in a cancer of a patient afflicted with the cancer; comparing the measured CDKN1A activity to CDKN1A activity in a control tissue or cell; and administering to the patient with the cancer identified as having a reduced CDKN1A activity as compared to CDKN1A activity in control tissue or cell a therapeutically effective amount of an ATR inhibitor to sensitize the cancer to a DNA damaging agent.

**[0060]** In some embodiments, the method of treating a subject with cancer based on measuring the level of CDKN1A activity in the cancer further comprises administering to the patient a therapeutically effective amount of a DNA damaging agent.

**[0061]** Thus, in some embodiments, a method of treating a patient having cancer comprises: measuring the level of cyclin dependent kinase inhibitor 1A (CDKN1A) activity in a cancer of a patient afflicted with the cancer; comparing the measured CDKN1A activity to CDKN1A activity in a

## 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.

2. 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.

3. 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.

4. The use of claim 1 or the method of claim 2 or claim 3, wherein the treatment with the medicament or the ATR inhibitor in the method, is to be in combination with a DNA damaging agent.

5. The use of claim 1 or the method of claim 2 or claim 3, 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.

6. The use of claim 1 or claim 4 or claim 5, or the method of any one of claims 2 to 5, 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.

7. The use or method of claim 6, 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.

8. The use of claim 1 or any one of claims 4 to 7, or the method of any one of claims 2 to 7, 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.

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

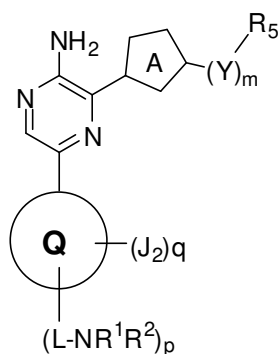
the *in vitro* measuring of the level of cyclin dependent kinase inhibitor 1A (CDKN1A) activity in a cancer of a patient;

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.

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

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

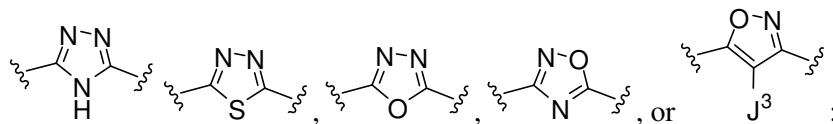


IA

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,  $\text{NR}^0$ , 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,  $-(X)_t$ -CN, or  $-(X)_t$ -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)<sub>2</sub>, wherein said  $C_1$ - $C_8$ aliphatic is optionally substituted with halo, CN, or NO<sub>2</sub>;

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;

$J^Z$  is independently  $NH_2$ ,  $NH(C_1-C_4\text{aliphatic})$ ,  $N(C_1-C_4\text{aliphatic})_2$ , halogen,  $C_1-C_4\text{aliphatic}$ ,  $OH$ ,  $O(C_1-C_4\text{aliphatic})$ ,  $NO_2$ ,  $CN$ ,  $CO_2H$ ,  $CO(C_1-C_4\text{aliphatic})$ ,  $CO_2(C_1-C_4\text{aliphatic})$ ,  $O(\text{halo}C_1-C_4\text{aliphatic})$ , or  $\text{halo}C_1-C_4\text{aliphatic}$ ;

$J^5$  is halo, oxo,  $CN$ ,  $NO_2$ ,  $X^1-R$ , or  $-(X^1)_p-Q^4$ ;

$X^1$  is  $C_1-C_{10}\text{aliphatic}$ ; wherein 1-3 methylene units of said  $C_1-C_{10}\text{aliphatic}$  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  $NH_2$ ,  $NH(C_1-C_4\text{aliphatic})$ ,  $N(C_1-C_4\text{aliphatic})_2$ , halogen,  $C_1-C_4\text{aliphatic}$ ,  $OH$ ,  $O(C_1-C_4\text{aliphatic})$ ,  $NO_2$ ,  $CN$ ,  $CO_2H$ ,  $CO_2(C_1-C_4\text{aliphatic})$ ,  $C(O)NH_2$ ,  $C(O)NH(C_1-C_4\text{aliphatic})$ ,  $C(O)N(C_1-C_4\text{aliphatic})_2$ ,  $SO(C_1-C_4\text{aliphatic})$ ,  $SO_2(C_1-C_4\text{aliphatic})$ ,  $SO_2NH(C_1-C_4\text{aliphatic})$ ,  $NHC(O)(C_1-C_4\text{aliphatic})$ ,  $N(C_1-C_4\text{aliphatic})C(O)(C_1-C_4\text{aliphatic})$ , wherein said  $C_1-C_4\text{aliphatic}$  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  $C_1-C_4\text{alkyl}$  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  $C_1-C_4\text{alkyl}$  wherein said  $C_1-C_4\text{alkyl}$  is optionally substituted with 1-4 halo;

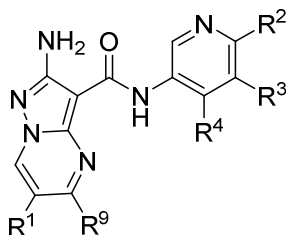
$J^2$  is halo;  $CN$ ; a 5-6 membered aromatic or nonaromatic monocyclic ring having 0-3 heteroatoms selected from oxygen, nitrogen, and sulfur; or a  $C_1-C_{10}\text{aliphatic}$  group wherein up to 2 methylene units are optionally replaced with  $O$ ,  $NR''$ ,  $C(O)$ ,  $S$ ,  $S(O)$ , or  $S(O)_2$ ; wherein said  $C_1-C_{10}\text{aliphatic}$  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  $C_3-C_6\text{cycloalkyl}$ ; a 3-7 membered heterocyclyl containing 0-2 heteroatoms selected from oxygen, nitrogen, and sulfur; or a  $C_1-C_4\text{alkyl}$  wherein up to one methylene unit of the alkyl chain is optionally replaced with  $O$ ,  $NR''$ , or  $S$ ; and wherein said  $C_1-C_4\text{alkyl}$  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  $H$ ,  $C_1-C_4\text{alkyl}$ , or is absent; wherein said  $C_1-C_4\text{alkyl}$  is optionally substituted with 1-4 halo.

12. 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 to 11, wherein the ATR inhibitor is a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R<sup>1</sup> is independently selected from -C(J<sup>1</sup>)<sub>2</sub>CN, halo, -(L)<sub>k</sub>-W, and M;

R<sup>9</sup> is independently selected from H, -C(J<sup>1</sup>)<sub>2</sub>CN, halo, -(L)<sub>k</sub>-W, and M;

J<sup>1</sup> is independently selected from H and C<sub>1</sub>-C<sub>2</sub>alkyl; or

two occurrences of J<sup>1</sup>, 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<sub>1</sub>-C<sub>8</sub>aliphatic, wherein up to three methylene units are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)<sub>n</sub>-, each M and L<sup>1</sup> is optionally substituted with 0-3 occurrences of J<sup>LM</sup>;

J<sup>LM</sup> is independently selected from halo, -CN, and a C<sub>1</sub>-C<sub>4</sub>aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)<sub>n</sub>-;

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<sup>W</sup>;

J<sup>W</sup> is independently selected from -CN, halo, -CF<sub>3</sub>; a C<sub>1</sub>-C<sub>4</sub>aliphatic wherein up to two methylene units are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)<sub>n</sub>-; and a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, and sulfur; or two occurrences of J<sup>W</sup> 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<sup>W</sup>, together with W, form a 6-10 membered saturated or partially unsaturated bridged ring system;

R<sup>2</sup> is independently selected from H; halo; -CN; NH<sub>2</sub>; a C<sub>1</sub>-C<sub>2</sub>alkyl optionally substituted with 0-3 occurrences of fluoro; and a C<sub>1</sub>-C<sub>3</sub>aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)<sub>n</sub>;

R<sup>3</sup> is independently selected from H; halo; C<sub>1</sub>-C<sub>4</sub>alkyl optionally substituted with 1-3 occurrences of halo; C<sub>3</sub>-C<sub>4</sub>cycloalkyl; 3-4 membered heterocyclyl; -CN; and a C<sub>1</sub>-C<sub>3</sub>aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)<sub>n</sub>;

$R^4$  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)<sub>n</sub>-; 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)<sub>n</sub>-; 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)<sub>n</sub>-; 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)<sub>n</sub>-;

J<sup>T</sup> is independently selected from halo, -CN; →O; =O; -OH; a C<sub>1</sub>-C<sub>6</sub>aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR-, -C(O)-, or -S(O)<sub>n</sub>-; and a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, and sulfur; each occurrence of J<sup>T</sup> is optionally substituted with 0-3 occurrences of J<sup>M</sup>; or two occurrences of J<sup>T</sup> 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<sup>T</sup>, together with Q<sup>3</sup>, form a 6-10 membered saturated or partially unsaturated bridged ring system;

J<sup>M</sup> is independently selected from halo and C<sub>1</sub>-C<sub>6</sub>aliphatic;

n is 0, 1 or 2; and

R is independently selected from H and C<sub>1</sub>-C<sub>4</sub>aliphatic.

13. 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 to 12, 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.

14. The use or method of claim 13, wherein the DNA damaging agent comprises a platinating agent.

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

16. The use or method of claim 13, wherein the DNA damaging agent comprises an antimetabolite.

17. The use or method of claim 16, 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.