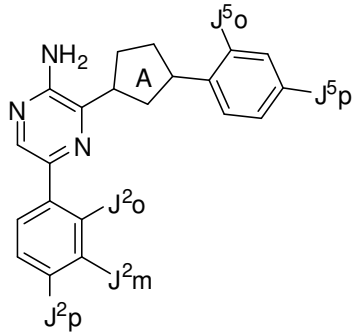
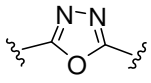
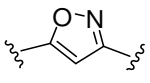
CLAIMS

1. Use of a compound that inhibits ATR protein kinase in the manufacture of a medicament for treating cancer in a patient, wherein the compound that inhibits ATR protein kinase is used in combination with a compound that inhibits Chk1 protein kinase, wherein the compound that inhibits ATR protein kinase is represented by Formula **I-a:**

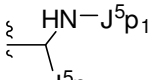


I-a:

or a pharmaceutically acceptable salt thereof, wherein

Ring A is  or ,

J^5o is H, F, Cl, C_{1-4}aliphatic, O(C_{1-3}aliphatic), or OH;

J^5p is ;

J^5p1 is H, C_{1-4}aliphatic, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl; wherein J^5p1 is optionally substituted with 1-2 occurrences of OH or halo;

J^5p2 is H, methyl, ethyl, CH_2F, CF_3, or CH_2OH;

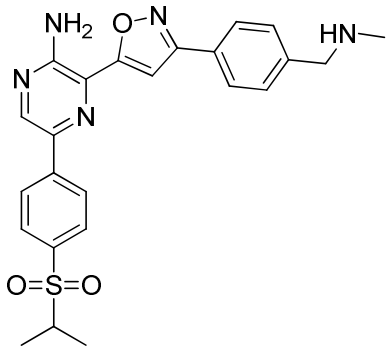
J^2o is H, CN, or SO_2CH_3;

J^2m is H, F, Cl, or methyl;

J^2p is -SO_2(C_{1-6}alkyl), -SO_2(C_{3-6}cycloalkyl), -SO_2(4-6 membered heterocyclyl), -SO_2(C_{1-4}alkyl)N(C_{1-4}alkyl)$_2$, or -SO_2(C_{1-4}alkyl)-(4-6 membered heterocyclyl), wherein said heterocyclyl contains 1 heteroatom selected from oxygen, nitrogen, and sulfur; and wherein said J^2p is optionally substituted with 1-3 occurrences halo, OH, or O(C_{1-4}alkyl).

2. The use of claim 1, wherein the cancer has one or more defects in the ATM signaling pathway.

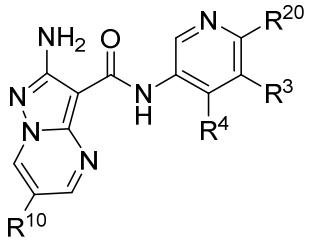
3. The use of claim 1, wherein the compound that inhibits ATR protein kinase is



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or a pharmaceutically acceptable salt thereof.

4. Use of a compound that inhibits ATR protein kinase in the manufacture of a medicament for treating cancer in a patient, wherein the compound that inhibits ATR protein kinase is used in combination with a compound that inhibits Chk1 protein kinase, wherein the compound that inhibits ATR protein kinase is represented by Formula **II**:



II

or a pharmaceutically salt thereof, wherein:

R^{10} is independently selected from fluoro, chloro, and $–C(J^{10})_2CN$;

J^{10} is independently selected from H and $C_{1\text{-}2}$alkyl; or

two occurrences of J^{10} ,together with the carbon atom to which they are attached, form a 3-4 membered optionally substituted carbocyclic ring;

R^{20} is independently selected from H; halo; -CN; NH_2; a C_{1-2}alkyl optionally substituted with 0-3 occurrences of fluoro; and a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR^a-, -C(O)-, or –$S(O)_z$;

R^3 is independently selected from H; halo; C_{1-4}alkyl optionally substituted with 1-3 occurrences of halo; C_{3-4}cycloalkyl; -CN; and a C_{1-3}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR^a-, -C(O)-, or –$S(O)_z$;

R^4 is independently selected from Q^1 and a C_{1-10}aliphatic chain wherein up to four methylene units of the aliphatic chain are optionally replaced with -O-, -NR^a-, -C(O)-, or -$S(O)_z$-; each R^4 is optionally substituted with 0-5 occurrences of J^{Q1}; 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_{1-6}aliphatic, =O, halo, and →O;

J^{Q1} is independently selected from –CN; halo; =O; Q^2; and a C_{1-8}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR^a-, -C(O)-, or -$S(O)_z$-; each occurrence of J^{Q1} is optionally substituted by 0-3 occurrences of J^R; or

two occurrences of J^{Q1} 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^{Q1} is optionally substituted with 0-3 occurrences of J^X; or

two occurrences of J^{Q1}, 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; →O; Q^3; and a C_{1-6}aliphatic chain wherein up to three methylene units of the aliphatic chain are optionally replaced with -O-, -NR^a-, -C(O)-, or -$S(O)_z$-; 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, and 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_{1-4}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR^a-, -C(O)-, or -$S(O)_z$-;

J^T is independently selected from halo, -CN; →O; =O; -OH; a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR^a-, -C(O)-, or -$S(O)_z$-; 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_{1-6}aliphatic;

z is 0, 1 or 2; and

R^a is independently selected from H and C_{1-4}aliphatic.

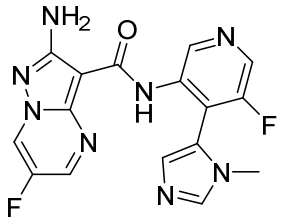
5. The use of claim 4, wherein R^{10} and R^3 are fluoro.

6. The use of claim 5, wherein

R^4 is Q^1; or

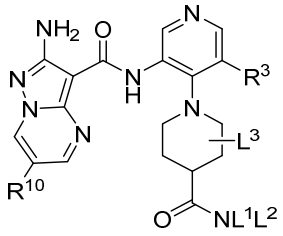
R^4 is Q^1, wherein Q^1 is independently selected from piperidinyl and imidazolyl.

7. The use of claim 6, wherein the compound that inhibits ATR is represented by the structure:



or a pharmaceutically acceptable salt thereof.

8. The use of claim 4, wherein the compound that inhibits ATR is represented by Formula **II-a**:



II-a

or a pharmaceutically acceptable salt thereof, wherein:

R^{10} is independently selected from fluoro, chloro, and $–C(J^{10})_2CN$;

J^{10} is independently selected from H and $C_{1\text{-}2}$alkyl; or

two occurrences of J^{10} ,together with the carbon atom to which they are attached, form an optionally substituted 3-4 membered carbocyclic ring;

R^3 is independently selected from H; chloro; fluoro; $C_{1\text{-}4}$alkyl optionally substituted with 1-3 occurrences of halo; $C_{3\text{-}4}$cycloalkyl; -CN; and a $C_{1\text{-}3}$aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, $-NR^a$-, -C(O)-, or $–S(O)_z$;

L^1 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen and sulfur; or a $C_{1\text{-}6}$aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, $-NR^a$-, -C(O)-, or $–S(O)_z$; each L^1 is

optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, and sulfur;

L^2 is H; a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen nitrogen and sulfur; or a C_{1-6}aliphatic chain wherein up to two methylene units of the aliphatic chain are optionally replaced with -O-, -NR^a-, -C(O)-, or –$S(O)_z$; each L^2 is optionally substituted with C_{1-4}aliphatic; -CN; halo; -OH; or a 3-6 membered non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, and sulfur; or

L^1 and L^2, together with the nitrogen to which they are attached, form a Ring D; Ring D is optionally substituted with 0-5 occurrences of J^G;

L^3 is H; C_{1-3}aliphatic; or CN;

Ring D is independently selected from a 3-7 membered heterocyclyl ring having 1-2 heteroatoms selected from oxygen, nitrogen and sulfur; and an 7-12 membered fully saturated or partially unsaturated bicyclic ring having 1-5 heteroatoms selected from oxygen, nitrogen, and sulfur;

J^G is independently selected from halo; -CN; -$N(R°)_2$; →O; a 3-6 membered carbocycyl; a 3-6 membered heterocyclyl having 1-2 heteroatoms selected from oxygen nitrogen, and sulfur; and a C_{1-4}alkyl chain wherein up to two methylene units of the alkyl chain are optionally replaced with -O-, -NR^a-, -C(O)-, or –$S(O)_z$; each J^G is optionally substituted with 0-2 occurrences of J^K.

two occurrences of J^G 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^G, together with Ring D, form a 6-10 membered saturated or partially unsaturated bridged ring system;

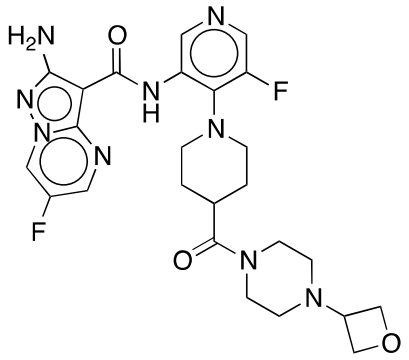
J^K is a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, and sulfur;

z is 0, 1, or 2; and

R^a and R° are H or C_{1-4}alkyl.

9. The use of claim 8, wherein R^{10} and R^3 are fluoro.

10. The use of claim 9, wherein the compound that inhibits ATR is represented by the structure:



or a pharmaceutically acceptable salt thereof.

11. The use of any one of claims 1-10, wherein the compound that inhibits ATR protein kinase is used in manufacture as a first medicament and the compound that inhibits Chk1 protein kinase is used in manufacture as a second medicament.

12. The use of any one of claims 1-10, further comprising use with one or more additional therapeutic agents independently selected from a DNA-damaging agent; wherein said additional therapeutic agent is appropriate for the disease being treated; and said additional therapeutic agent is used together with said compounds as a single dosage form or separately from said compounds as part of a multiple dosage form.

13. The use of claim 12, wherein:

said DNA-damaging agent is a chemotherapeutic agent or ionizing radiation; or said DNA-damaging agent is ionizing radiation, radiomimetic neocarzinostatin, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, an antimetabolite, an alkylating agent, an alkyl sulphonate, or an antibiotic.

14. The use of claim 13, wherein said DNA damaging agent is Cisplatin, Oxaliplatin, Carboplatin, Nedaplatin, Lobaplatin, Triplatin Tetranitrate, Picoplatin, Satraplatin, ProLindac, Aroplatin, Camptothecin, Topotecan, Irinotecan/SN38, Rubitecan, Belotecan, Etoposide, Daunorubicin, Doxorubicin, Aclarubicin, Epirubicin, Idarubicin, Amrubicin, Pirarubicin, Valrubicin, Zorubicin, Teniposide, Aminopterin, Methotrexate, Pemetrexed, Raltitrexed, Pentostatin, Cladribine, Clofarabine, Fludarabine, Thioguanine, Mercaptopurine, Fluorouracil, Capecitabine, Tegafur, Carmofur, Floxuridine, Cytarabine, Gemcitabine, Azacitidine, Hydroxyurea, Mechlorethamine, Cyclophosphamide, Ifosfamide, Trofosfamide, Chlorambucil,

Melphalan, Prednimustine, Bendamustine, Uramustine, Estramustine, Carmustine, Lomustine, Semustine, Fotemustine, Nimustine, Ranimustine, Streptozocin, Busulfan, Mannosulfan, Treosulfan, Carboquone, ThioTEPA, Triaziquone, Triethylenemelamine, Procarbazine, Dacarbazine, Temozolomide, Altretamine, Mitobronitol, Actinomycin, Bleomycin, Mitomycin or Plicamycin.

15. The use of claim 13, wherein said platinating agent is independently selected from Cisplatin, Oxaliplatin, Carboplatin, Nedaplatin, and Satraplatin; said Topo I inhibitor is selected from Camptothecin, Topotecan, irinotecan/SN38, and rubitecan; said Topo II inhibitor is selected from Etoposide; said antimetabolite is selected from methotrexate, pemetrexed, Thioguanine, Fludarabine, Cladribine, Cytarabine, gemcitabine, 6-Mercaptopurine, and 5-Fluorouracil; said alkylating agent is selected from nitrogen mustards, nitrosoureas, triazenes, alkyl sulfonates, Procarbazine, and aziridines; and said antibiotic is selected from Hydroxyurea, Anthracyclines, Anthracenediones, and Streptomyces family.

16. The use of claim 13, wherein the DNA-damaging agent is

a) a platinating agent selected from Cisplatin;

b) a platinating agent selected from Carboplatin;

c) ionizing radiation;

d) an antimetabolite selected from gemcitabine;

e) a Topo I inhibitor selected from Camptothecin, Topotecan, Irinotecan/SN38, Rubitecan and Belotecan;

f) a Topo II inhibitor selected from Etoposide; and

g) an alkyating agent selected from Temozolomide; or

h) selected from one or more of the following: Cisplatin, Carboplatin, Gemcitabine, Etoposide, Temozolomide, and ionizing radiation.

17. The use of any one of claims 1-16,

wherein the cancer has a defect in a base excision repair protein; or

wherein the cancer has a defect in a base excision repair protein, wherein the base excision repair protein is UNG, SMUG1, MBD4, TDG, OGG1, MYH, NTH1, MPG, NEIL1, NEIL2, NEIL3 (DNA glycosylases); APE1, APEX2 (AP endonucleases); LIG1, LIG3 (DNA

ligases I and III); XRCC1 (LIG3 accessory); PNK, PNKP (polynucleotide kinase and phosphatase); PARP1, PARP2(Poly(ADP-Ribose) Polymerases); PolB, PolG (polymerases); FEN1 (endonuclease) or Aprataxin; or

wherein the cancer has a defect in a base excision repair protein, wherein the base excision repair protein is PARP1 or PARP2.

18. The use of claim 17,

further comprising use with an inhibitor or modulator of a base excision repair protein; or

further comprising use with an inhibitor or modulator of a base excision repair protein, wherein the base excision repair protein is PARP1 or PARP2.

19. The use of any one of claims 1-18, wherein said cancer is a solid tumor selected from the following cancers: oral, lung, gastrointestinal: genitourinary tract, liver, bone, nervous system, gynecological, skin, thyroid gland, or adrenal gland.

20. The use of any one of claims 1-18, wherein

said cancer is selected from non-small cell lung cancer, small cell lung cancer, pancreatic cancer, biliary tract cancer, head and neck cancer, bladder cancer, colorectal cancer; glioblastoma, esophageal cancer, breast cancer, hepatocellular carcinoma, and ovarian cancer; or

said cancer is selected from non-small cell lung cancer, small cell lung cancer, and triple negative breast cancer; or

the additional therapeutic agent is gemcitabine or cisplatin and said cancer is the squamous subtype of non-small cell lung cancer.

21. The use of any one of claims 1-20, wherein the compound that inhibits Chk1 is AZD7762, LY2603618, MK-8776, CHIR-124, or PF-477736.