CLAIMS

1. Use of a compound that inhibits ATR protein kinase in the manufacture of a medicament for treating cancer, where said ATR inhibitor is used in combination with a compound that inhibits Chk1 protein kinase.

2. Use of a compound that inhibits Chk1 protein kinase in the manufacture of a medicament for treating cancer, wherein said Chk1 inhibitor is used in combination with a compound that inhibits ATR protein kinase.

3. Use of a compound that inhibits ATR protein kinase and a compound that inhibits Chk1 protein kinase in the manufacture of a medicament for treating cancer.

4. The use of claim 3, wherein the compound which inhibits ATR protein kinase is prepared as a first medicament and the compound which inhibits Chk1 protein kinase is prepared as a second medicament.

5. The use of any one of claims 1-4, wherein treating cancer further comprises administering to said patient 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 administered together with the compound as a single dosage form or separately from the compound as part of a multiple dosage form.

6. The use of claim 5, wherein said DNA-damaging agent is selected from chemotherapy or radiation treatment.

7. The use of claim 6, wherein said DNA-damaging agent is independently selected from ionizing radiation, radiomimetic neocarzinostatin, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, an antimetabolite, an alkylating agent, an alkyl sulphonate, and an antibiotic.

8. The use of claim 7, 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.~~

~~9. The use of claim 8, wherein said platinating agent is Cisplatin, Oxaliplatin, Carboplatin, Nedaplatin, or Satraplatin; said Topo I inhibitor is Camptothecin, Topotecan, or irinotecan/SN38, rubitecan; said Topo II inhibitor is Etoposide; said antimetabolite is methotrexate, pemetrexed, Thioguanine, Fludarabine, Cladribine, Cytarabine, gemcitabine, 6-Mercaptopurine, or 5-Fluorouracil; said alkylating agent is nitrogen mustards, nitrosoureas, triazenes, alkyl sulfonates, Procarbazine, or aziridines; and said antibiotic is Anthracyclines, Anthracenediones, or Streptomyces family.~~

~~10. The use of any one of claims 7-9, wherein said DNA-damaging agent is a platinating agent.~~

~~11. The use of claim 10, wherein the platinating agent is Cisplatin.~~

~~12. The use of claim 10, wherein the DNA-damaging agent is Carboplatin.~~

~~13. The use of claim 7, wherein said DNA-damaging agent is ionizing radiation.~~

~~14. The use of claim 7, wherein said DNA-damaging agent is gemcitabine.~~

~~15. The use of claim 7, wherein the DNA-damaging agent is a Topo I inhibitor selected from Camptothecin, Topotecan, Irinotecan/SN38, Rubitecan and Belotecan.~~

~~16. The use of claim 7, wherein the DNA-damaging agent is Etoposide.~~

~~17. The use of claim 7, wherein the DNA-damaging agent is Temozolomide.~~

~~18. The use of claim 7, wherein said DNA-damaging agent is selected from one or more of the following: Cisplatin, Carboplatin, Gemcitabine, Etoposide, Temozolomide, and ionizing radiation.~~

~~19. The use of claim 1, wherein said cancer has a defect in a base excision repair protein.~~

~~20. The use of claim 19, wherein said cancer has a defect in a base excision repair protein selected from 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) and Aprataxin.~~

~~21. The use of claim 20, wherein said cancer has a defect in base excision repair protein PARP1 or PARP2.~~

~~22. The use of claim 1, further comprising use with an agent which inhibits PARP1 or PARP2.~~

~~23. The use of claim 22, wherein the agent which inhibits PARP1 or PARP2 is selected from Olaparib (also known as AZD2281 or KU-0059436), Iniparib (also known as BSI-201 or SAR240550), Veliparib (also known as ABT-888), Rucaparib (also known as PF-01367338),CEP-9722, INO-1001, MK-4827, E7016, BMN673, or AZD2461.~~

~~24. The use of claim 23, wherein the agent which inhibits PARP1 or PARP2 is Olaparib, Veliparib, Rucaparib, CEP-9722, INO-1001, MK-4827, E7016, BMN673, or AZD2461.~~

25. The use of any one of claims 1-24, 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, and adrenal gland.

26. The use of claim 25, wherein said cancer is a solid tumor selected from the following cancers: Oral: buccal cavity, lip, tongue, mouth, pharynx; Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell or epidermoid, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, larynx, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel or small intestines (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel or large intestines (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colon, colon-rectum, colorectal; rectum, Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma, biliary passages; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma,

meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, keratoacanthoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis, Thyroid gland: papillary thyroid carcinoma, follicular thyroid carcinoma; medullary thyroid carcinoma, multiple endocrine neoplasia type 2A, multiple endocrine neoplasia type 2B, familial medullary thyroid cancer, pheochromocytoma, paraganglioma; and Adrenal glands: neuroblastoma.

27. The use of any one of claims 1-24, 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.

28. The use of claim 27, wherein said cancer is selected from non-small cell lung cancer, small cell lung cancer, and triple negative breast cancer.

29. The use of clam 27, wherein the additional therapeutic agent is gemcitabine or cisplatin, and the cancer is the squamous subtype of non-small cell lung cancer.

30. Use of a compound that inhibits ATR protein kinase in the manufacture of a medicament for promoting cell death in cancer cells in a patient, where said ATR inhibitor is used in combination with a compound that inhibits Chk1 protein kinase.

31. The use of claim 30, wherein said cancer has a defect in ATM signaling cascade.

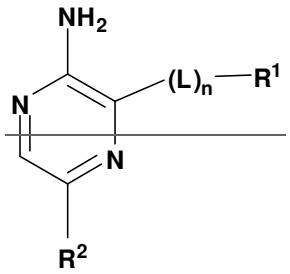
32. The use of claim 31, wherein said cancer has altered expression or activity of one or more of the following: ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1, H2AX, MCPH1/BRIT1, CTIP, or SMC1.

33. The use of claim 30, wherein said cancer express a DNA damaging oncogene.

34. The use of claim 33, wherein said cancer has altered expression or activity of one or more of the following: K-Ras, N-Ras, H-Ras, Raf, Myc, Mos, E2F, Cdc25A, CDC4, CDK2, Cyclin E, Cyclin A and Rb.

35. The use of any one of claims 1-34, wherein the compound that inhibits Chk1 is AZD7762, LY2603618, MK-8776, CHIR-124, or PF-477736.

36. The use of any one of claims 1-35, wherein the compound that inhibits ATR protein kinase is represented by Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is a 5-6 membered monocyclic aryl or heteroaryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said monocyclic aryl or heteroaryl ring is optionally fused to another ring to form an 8-10 membered bicyclic aryl or heteroaryl ring having 0-6 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each R^1 is optionally substituted with 1-5 J^1 groups;

R^2 is a 5-6 membered monocyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said monocyclic aryl or heteroaryl ring is optionally fused to another ring to form an 8-10 membered bicyclic aryl or heteroaryl ring

having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each R^2 is optionally substituted with 1-5 J^2 groups;

L is $C(O)NH$ or $C(O)N(C_{1-6}alkyl)$;

n is 0 or 1;

each J^1 and J^2 is independently halo, CN, NO_2, V^1-R, or $(V^2)_m$-Q;

V^1 is a C_{1-10}aliphatic chain wherein 0-3 methylene units are optionally and independently replaced with O, NR", S, C(O), S(O), or $S(O)_2$; V^1 is optionally substituted with 1-6 occurrences of J^{V1};

V^2 is a C_{1-10}aliphatic chain wherein 0-3 methylene units are optionally and independently replaced with O, NR", S, C(O), S(O), or $S(O)_2$; V^2 is optionally substituted with 1-6 occurrences of J^{V2};

m is 0 or 1;

Q is a 3-8 membered saturated or unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 9-10 membered saturated or unsaturated bicyclic ring having 0-6 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each Q is optionally substituted with 0-5 J^Q;

each J^{V1} or J^{V2} is independently halogen, CN, NH_2, NO_2, C_{1-4}aliphatic, $NH(C_{1-4}aliphatic)$, $N(C_{1-4}aliphatic)_2$, OH, $O(C_{1-4}aliphatic)$, CO_2H, $CO_2(C_{1-4}aliphatic)$, $C(O)NH_2$, $C(O)NH(C_{1-4}aliphatic)$, $C(O)N(C_{1-4}aliphatic)_2$, $NHCO(C_{1-4}aliphatic)$, $N(C_{1-4}aliphatic)CO(C_{1-4}aliphatic)$, $SO_2(C_{1-4}aliphatic)$, $NHSO_2(C_{1-4}aliphatic)$, or $N(C_{1-4}aliphatic)SO_2(C_{1-4}aliphatic)$, wherein said C_{1-4}aliphatic is optionally substituted with halo;

R is H or C_{1-6}aliphatic wherein said C_{1-6}aliphatic is optionally substituted with 1-4 occurrences of NH_2, $NH(C_{1-4}aliphatic)$, $N(C_{1-4}aliphatic)_2$, halogen, C_{1-4}aliphatic, OH, $O(C_{1-4}aliphatic)$, NO_2, CN, CO_2H, $CO_2(C_{1-4}aliphatic)$, $CO(C_{1-4}aliphatic)$, $O(haloC_{1-4}aliphatic)$, or $haloC_{1-4}aliphatic$;

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

p is 0 or 1;

X is C_{1-10}aliphatic; wherein 1-3 methylene units of said C_{1-6}aliphatic are optionally replaced with -NR, -O-, -S-, C(O), $S(O)_2$, or S(O); wherein X is optionally and independently substituted with 1-4 occurrences of NH_2, $NH(C_{1-4}$aliphatic), $N(C_{1-4}$aliphatic$)_2$, halogen, C_{1-4}aliphatic, OH, $O(C_{1-4}$aliphatic), NO_2, CN, $CO(C_{1-4}$aliphatic), CO_2H, $CO_2(C_{1-4}$aliphatic), $C(O)NH_2$, $C(O)NH(C_{1-4}$aliphatic), $C(O)N(C_{1-4}$aliphatic$)_2$, $SO(C_{1-4}$aliphatic), $SO_2(C_{1-4}$aliphatic), $SO_2NH(C_{1-4}$aliphatic), $SO_2N(C_{1-4}$aliphatic$)_2$, $NHC(O)(C_{1-4}$aliphatic), $N(C_{1-4}$aliphatic$)C(O)(C_{1-4}$aliphatic), wherein said C_{1-4}aliphatic is optionally substituted with 1-3 occurrences of halo;

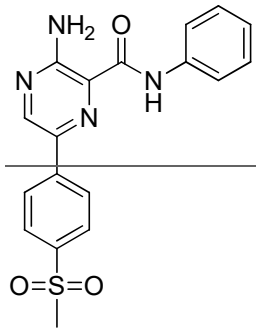
Q^4 is a 3-8 membered saturated or unsaturated monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 8-10 membered saturated or unsaturated bicyclic ring having 0-6 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each Q^4 is optionally substituted with 1-5 J^{Q4};

J^{Q4} is halo, CN, or C_{1-4}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_{1-4}alkyl wherein said C_{1-4}alkyl is optionally substituted with 1-4 halo; and

R", and R* are each independently H, C_{1-4}alkyl, or is absent; wherein said C_{1-4}alkyl is optionally substituted with 1-4 halo.

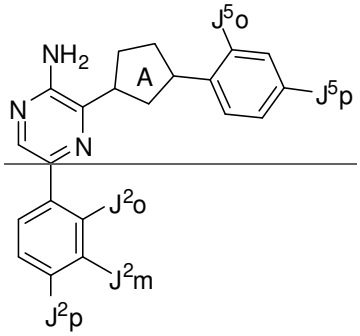
37. The use of any one of claims 1-35, wherein the compound which inhibits ATR protein kinase is



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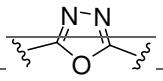
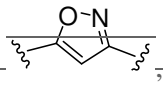
or a pharmaceutically acceptable salt thereof.

38. The use of any one of claims 1-35, wherein the compound that inhibits ATR protein kinase is represented by Formula **I-a:**

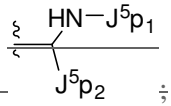


I-a:

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;

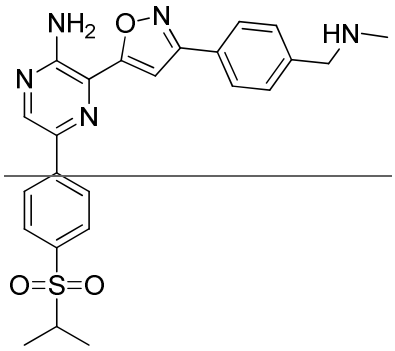
J^5p2 is H, methyl, ethyl, CH_2F, CF_3, or CH_2OH;

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 occurences halo, OH, or $O(C_{1-4}$alkyl).

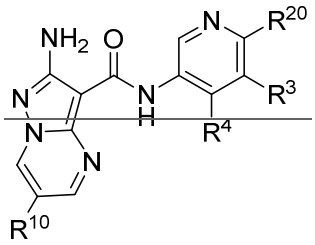
39. The use of any one of claims 1-35, wherein the compound that inhibits ATR protein kinase is



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or a pharmaceutically acceptable salt thereof.

40. The use of any one of claims 1-35, 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_{1-2}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 $-\rightarrow O$;

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; $\rightarrow$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; $\rightarrow$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;

J is H or Cl;

z is 0, 1 or 2; and

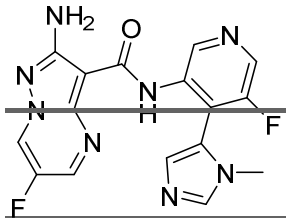
R^a is independently H and C_{1-4}aliphatic.

41. The use of claim 40, wherein R^1 and R^3 are fluoro.

42. The use of claim 40, wherein R^4 is Q^1.

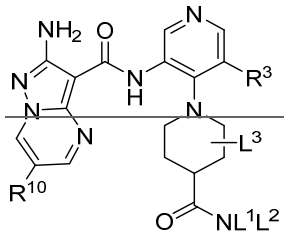
43. The use of claim 40, wherein Q^1 is independently selected from piperidinyl and imidazolyl.

44. The use of any one of claim 1-35, wherein the compound that inhibits ATR protein kinase is represented by the structure:



or a pharmaceutically acceptable salt thereof.

45. The use of claim 40, wherein the compound that inhibits ATR protein kinase 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_{1-2}alkyl; or

two occurrences of J^1, 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_{1-4}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)$_z$–;

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_{1-6}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;

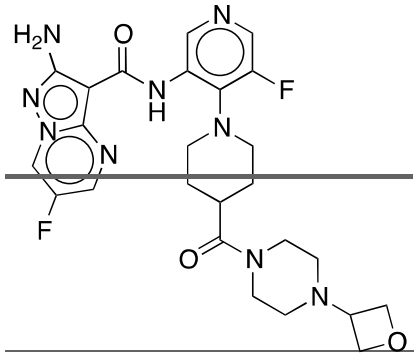
J^K is a 3–7 membered aromatic or non-aromatic ring having 0–2 heteroatoms selected from oxygen, nitrogen, and sulfur;

~~z is 0, 1, or 2; and~~

~~R^a and R° are H or C_{1-4}alkyl.~~

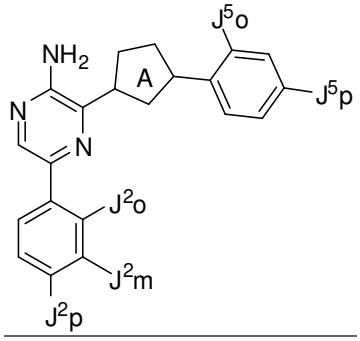
~~46. The use of claim 45, wherein R^1 and R^3 are fluoro.~~

~~47. The use of claim 46, wherein the compound that inhibits ATR protein kinase is represented by the structure:~~



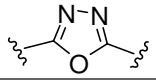
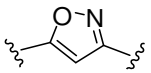
~~or a pharmaceutically acceptable salt thereof.~~

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:**

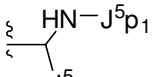


I-a:

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;

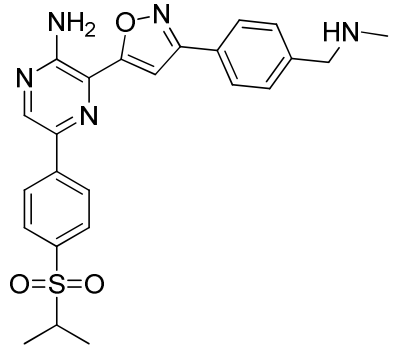
J^2o is H, CN, or SO_2CH_3;

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.

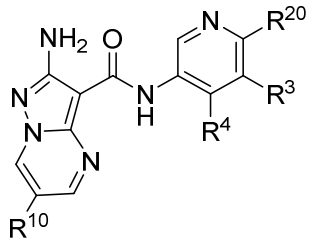
3. The use of claim 1, wherein the compound that inhibits ATR protein kinase is



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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_{1-2}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.

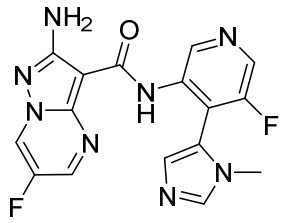
5. The use of claim 4, wherein R^{10} and R^3 are fluoro.

6. The use of claim 5, wherein

R^4 is Q^1; or

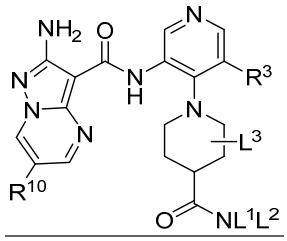
R^4 is Q^1, wherein Q^1 is independently selected from piperidinyl and imidazolyl.

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_{1-2}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_{1-4}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 $-S(O)_z-$;

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_{1-6}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;

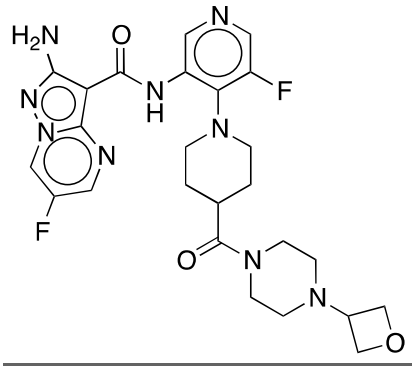
J^K is a 3-7 membered aromatic or non-aromatic ring having 0-2 heteroatoms selected from oxygen, nitrogen, and sulfur;

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.