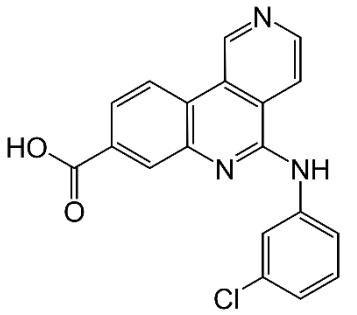
Claims

What is claimed is:

1. Use of ~~A~~a combination of ~~an~~ anti-cancer agents, a CK2 inhibitor and ~~optionally~~ an immune checkpoint inhibitor ~~for use~~ in the ~~treatment of~~ manufacture of a medicament for treating a cancer or refractory cancer and/or inhibiting cancer metastasis, recurrence or progression in a subject or increasing the likelihood of survival over a relevant period in a subject diagnosed with a cancer, wherein:

the anti-cancer agents comprise cisplatin, and gemcitabine, and

the CK2 inhibitor is CX-4945, which has the following structure:



.

2. The use of Claim 1, wherein the combination is to be administered to increase the likelihood of survival over a relevant period in the subject.

~~2.~~ 3. The ~~combination for~~ use of Claim 1, wherein the ~~administration increases~~ combination is to be administered to increase tumor-specific T cells in the tumor microenvironment in a subject.

~~3.~~ 4. The ~~combination for~~ use of Claim 1, wherein the combination of the anticancer agents and ~~a~~ the CK2 inhibitor ~~can~~ are to be administered concurrently, sequentially, intermittently or periodically.

~~4.~~ 5. The ~~combination for~~ use of Claim 1, wherein the ~~method comprises~~ combination is to be administered for at least one administration cycle, wherein the cycle is a period of eight weeks or less.

~~5.~~ 6. The ~~combination for~~ use of Claim 1, wherein the combination ~~results~~ is to be administered to result in immunological memory to said cancer.

~~6.~~ 7. The ~~combination for~~ use of Claim 1, wherein the anticancer agents, ~~a~~ and the CK2 inhibitor ~~and optionally an immune checkpoint inhibitor~~ are in synergistically effective amounts.

~~7.~~ 8. The ~~combination for~~ use of Claim ~~4~~5, wherein the cycle is a period of four weeks.

~~8.~~ 9. The ~~combination for~~ use of Claim ~~4~~5, wherein the administration cycle comprises administering to the subject one or more first treatments (e.g. induction therapy, such as a combination of chemotherapeutic agent and CK2 inhibitor) in an amount and regimen sufficient to achieve a response (partial or complete response), and then administering an amount of an immune checkpoint inhibitor to the subject.

~~9.~~ 10. The ~~combination for~~ use of Claim ~~4~~5, wherein the administration cycle comprises administering CK2 inhibitor in every day and a chemotherapeutic agent once a week.

~~10.~~ 11. The ~~combination for~~ use of Claim ~~9~~10, wherein the administration cycle further comprises administrating an immune checkpoint inhibitor twice a week.

~~11.~~ 12. The ~~combination for~~ use of Claim ~~4~~5, wherein the CK2 inhibitor is to be administered in a daily dose in the range from ~~about~~ 25 mg per kg of subject weight (~~about~~ 25 mg/kg) to ~~about~~ 2000 mg/kg.

~~12.~~ 13. The ~~combination for~~ use of Claim ~~4~~12, wherein the daily dose is in the range of ~~about~~ 50 mg/kg to ~~about~~ 200 mg/kg. ~~In some embodiments, the CK2 inhibitor is administered twice a day.~~

~~13.~~ 14. The ~~combination for~~ use of Claim ~~4~~5, wherein the anti-cancer agents ~~is~~ are each to be administered in a dose in the range from ~~about~~ 1 mg per kg of subject weight (~~about~~ 1 mg/kg) to ~~about~~ 20 mg/kg.

~~14.~~ 15. The ~~combination for~~ use of Claim ~~4~~5, wherein the dose of the anti-cancer agents ~~is~~ are each in the range of ~~about~~ 5 mg/kg to ~~about~~ 10 mg/kg.

~~15.~~ 16. The ~~combination for~~ use of Claim ~~4~~5, wherein the immune checkpoint inhibitor is to be administered in a dose in the range from ~~about~~ 1 mg per kg of subject weight (~~about~~ 1 mg/kg) to ~~about~~ 20 mg/kg.

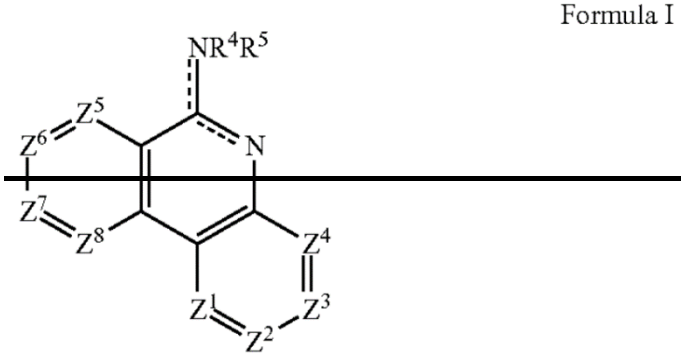
~~16.~~ 17. The ~~combination for~~ use of Claim ~~4~~5, wherein the dose of the immune checkpoint inhibitor is in the range of ~~about~~ 8 mg/kg to ~~about~~ 15 mg/kg.

~~17.~~ 18. The ~~combination for~~ use of Claim 1, wherein the cancer is glioblastoma, skin cancer (such as melanoma and basal cell carcinoma), liver cancer (such as hepatocellular carcinoma), colorectal carcinoma, glioblastoma, gastric cancer, colorectal cancer, esophageal cancer, lung cancer (such as non-small cell lung cancer (NSCLC) and small cell lung cancer), pancreatic cancer, renal cell carcinoma, benign prostate hyperplasia, prostate cancer, ovarian cancer, melanoma, breast cancer, chronic lymphocytic leukemia (CLL), Merkel cell carcinoma, Non-Hodgkin lymphoma, acute myeloid leukemia (AML), gallbladder cancer, cholangiocarcinoma, urinary bladder cancer, or uterine cancer.

~~18. The combination for use of Claim 1, wherein the anticancer agent is cisplatin, gemcitabine, carboplatin, methotrexate, vincristine, adriamycin, bleomycin, hydroxyurea, salinosporamide A, bortezomib, PS-519, omuralide, cyclophosphamide, ifosfamide, docetaxel, doxorubicin, , 5-fluorouracil, vinblastine, or paclitaxel.~~

~~19. The combination for use of claim 1, wherein the CK2 inhibitor is a compound having a structure of Formula I, or a pharmaceutically acceptable salt or ester thereof, wherein:~~

Formula I



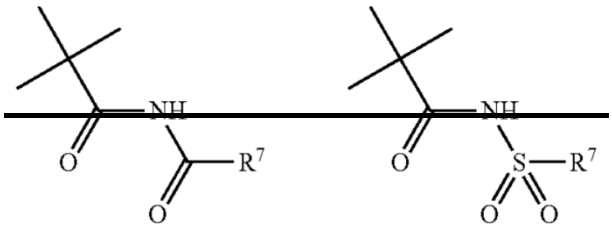
~~each Z^1, Z^2, Z^3, and Z^4 is N or CR^3;~~

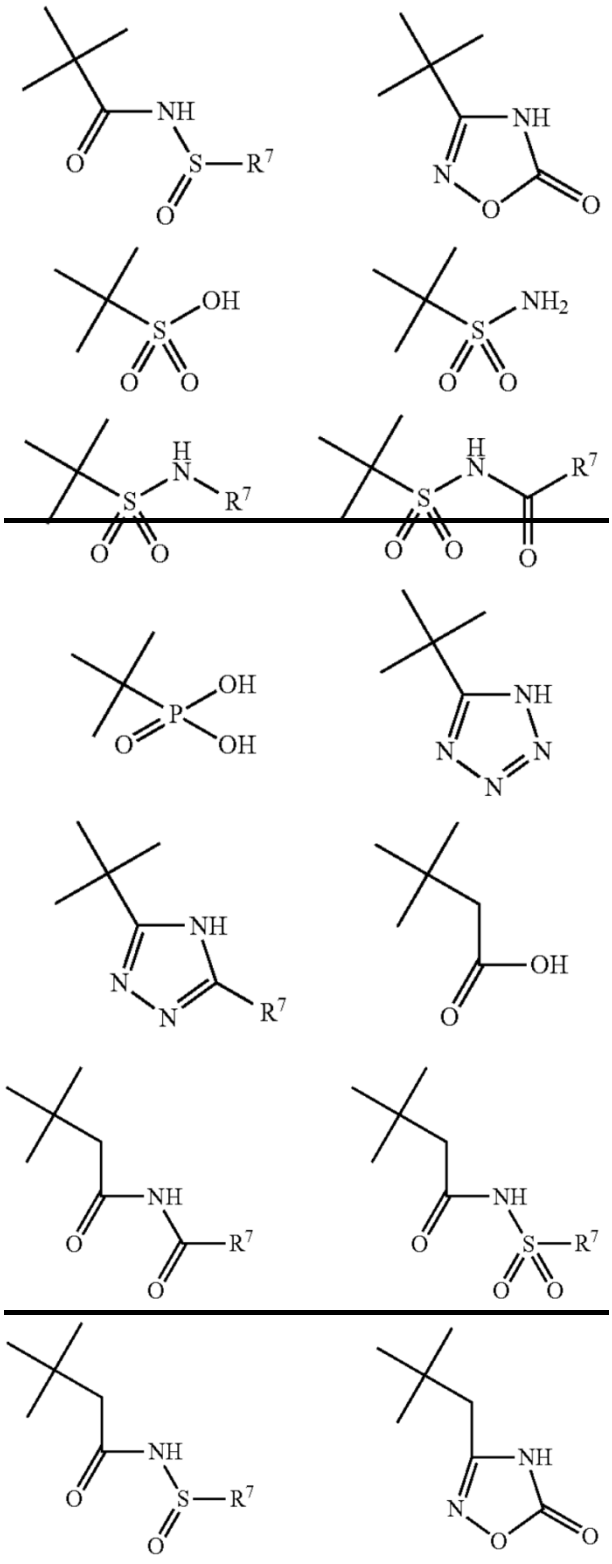
~~each of Z^5, Z^6, Z^7 and Z^8 is N or CR^6;~~

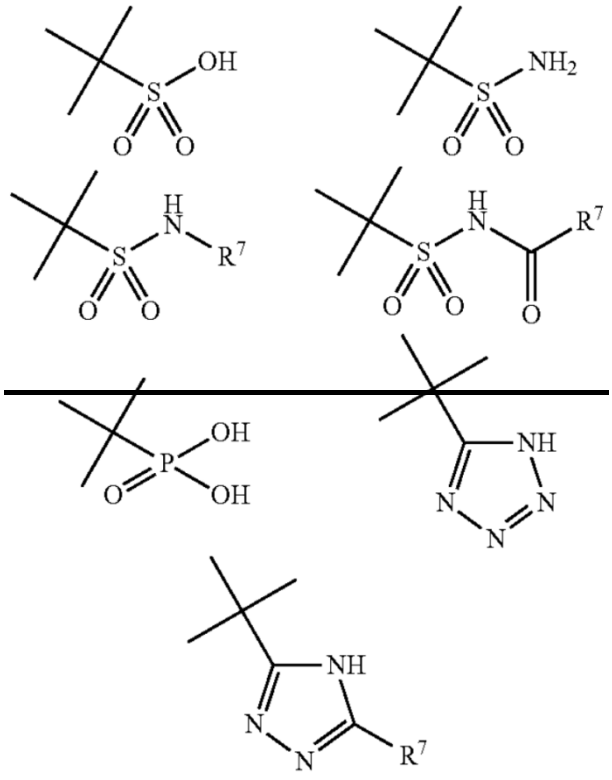
none, one or two of Z^1—Z^4 are N and none, one or two of Z^5—Z^8 are N, and at least one of Z^1—Z^4 and Z^5—Z^8 is a nitrogen atom;

each R^3 and each R^6 is independently H or an optionally substituted C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C12 heteroaryl, C7-C12 arylalkyl, or C6-C12 heteroarylalkyl group, or

each R^6 is independently halo, OR, NR_2, NROR, $NRNR_2$, SR, SOR, SO_2R, SO_2NR_2, $NRSO_2R$, $NRCONR_2$, NRCOOR, NRCOR, CN, OC(O)R, COR, NO_2, or a polar substituent selected from a carboxylic acid, a carboxylate salt, an ester, a carboxamide, a tetrazole, or a carboxy bioisostere selected the group consisting of







and each R^3 is independently halo, OR, NR_2, NROR, $NRNR_2$, SR, SOR, SO_2R, SO_2NR_2, $NRSO_2R$, $NRCONR_2$, NRCOOR, NRCOR, CN, OC(O)R, COR, polar substituent as defined above, or NO_2, and

at least one R^3 is a polar substituent;

wherein each R is independently H or C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-C12 arylalkyl, or C6-C12 heteroarylalkyl,

and wherein two R on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S;

and each R group, and each ring formed by linking two R groups together, is optionally substituted with one or more substituents selected from halo, =O, =N—CN, =N—OR′, =NR′, OR′, NR'_2, SR′, SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, NR′COOR', NR′COR′, CN, COOR′, $CONR'_2$, OC(O)R′, COR', and NO_2,

wherein each R′ is independently H, C1-C6 alkyl, C2-C6 heteroalkyl, C1-C6 acyl, C2-C6 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-12 arylalkyl, or C6-12 heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C1-C4 alkyl, C1-C4 heteroalkyl, C1-C6 acyl, C1-C6 heteroacyl, hydroxy, amino, and =O;

and wherein two R′ can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

R^4 is H or an optionally substituted member selected from the group consisting of C1-C6 alkyl, C2-C6 heteroalkyl, and C1-C6 acyl;

each R^5 is an optionally substituted member selected from the group consisting of C1-10 alkyl, C2-10 alkenyl, C2-10 heteroalkyl, C3-8 carbocyclic ring, and C3-8 heterocyclic ring optionally fused to an additional optionally substituted carbocyclic or heterocyclic ring; or R^5 is a C1-10 alkyl, C2-10 alkenyl, or C2-10 heteroalkyl substituted with an optionally substituted C3-8 carbocyclic ring or C3-8 heterocyclic ring; and

in each $-NR^4R^5$, R^4 and R^5 together with N may form an optionally substituted 3-8 membered ring, which may optionally contain an additional heteroatom selected from N, O and S as a ring member;

provided that when $-NR^4R^5$ in Formula (I) is —NH Φ, where Φ is optionally substituted phenyl:

if all of Z^5—Z^8 are CH or one of Z^5—Z^8 is N, at least one of Z^1—Z^4 is CR^3 and at least one R^3 must be a non-hydrogen substituent; or

if each R^3 is H, then Φ must be substituted;

wherein each R^7 is independently H or an optionally substituted member selected from the group consisting of C1-10 alkyl, C2-10 alkenyl, C2-10 heteroalkyl, C3-8 carbocyclic ring, and C3-8 heterocyclic ring optionally fused to an additional optionally substituted

~~carbocyclic or heterocyclic ring; or R^7 is a C1-10 alkyl, C2-10 alkenyl, or C2-10 heteroalkyl substituted with an optionally substituted C3-8 carbocyclic ring or C3-8 heterocyclic ring.~~

~~20. The combination for use of Claim 1, wherein the CK2 inhibitor is CX-4945.~~

~~21.~~ 19. The ~~combination for~~ use of Claim ~~1~~2, wherein the immune check point inhibitor is a PD-1, or CTLA-4 inhibitor.

~~22.~~ 20. The ~~combination for~~ use of Claim ~~21~~19, wherein the immune check point inhibitor is lambrolizumab, pidilizumab, nivolumab, ticilimumab or ipilimumab.