## Claims

**What is claimed is:**

1. A combination of an anti-cancer agent, a CK2 inhibitor and optionally an immune checkpoint inhibitor for use in the treatment of 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.
2. The combination for use of Claim 1, wherein the administration increases tumor-specific T cells in the tumor microenvironment in a subject.
3. The combination for use of Claim 1, wherein the combination of the anticancer agent and a CK2 inhibitor can be administered concurrently, sequentially, intermittently or periodically.
4. The combination for use of Claim 1, wherein the method comprises at least one administration cycle, wherein the cycle is a period of eight weeks or less.
5. The combination for use of Claim 1, wherein the combination results in immunological memory to said cancer.
6. The combination for use of Claim 1, wherein the anticancer agent, a CK2 inhibitor and optionally an immune checkpoint inhibitor are in synergistically effective amounts.
7. The combination for use of Claim 4, wherein the cycle is a period of four weeks.

8. The combination for use of Claim 4, 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. The combination for use of Claim 4, wherein the administration cycle comprises administering CK2 inhibitor in every day and a chemotherapeutic agent once a week.
10. The combination for use of Claim 9, wherein the administration cycle further comprises administrating an immune checkpoint inhibitor twice a week.
11. The combination for use of Claim 4, wherein the CK2 inhibitor is 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. The combination for use of Claim 4, 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. The combination for use of Claim 4, wherein the anti-cancer agent is 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. The combination for use of Claim 4, wherein the dose of the anti-cancer agent is in the range of about 5 mg/kg to about 10 mg/kg.

15. The combination for use of Claim 4, wherein the immune checkpoint inhibitor is 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.

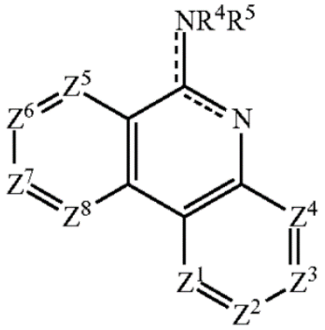
16. The combination for use of Claim 4, wherein the dose of immune checkpoint inhibitor is in the range of about 8 mg/kg to about 15 mg/kg.

17. 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



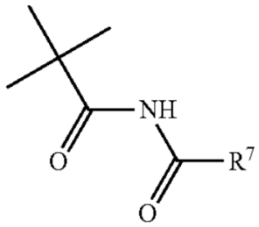
each $Z^1$, $Z^2$, $Z^3$, and $Z^4$ is N or $CR^3$;

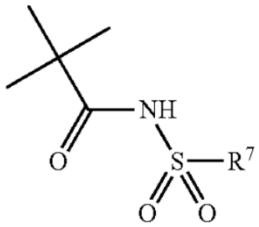
each of $Z^5$, $Z^6$, $Z^7$ and $Z^8$ is N or $CR^6$;

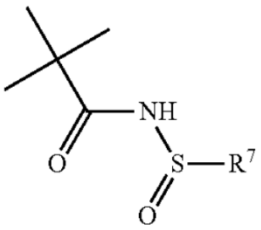
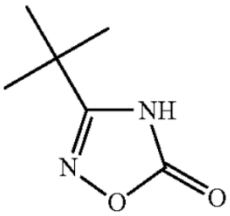
none, one or two of $Z^1$—$Z^4$ are N and none, one or two of $Z^5$—$Z^8$ are N, and at least one of $Z^1$—$Z^4$ and $Z^5$—$Z^8$ is a nitrogen atom;

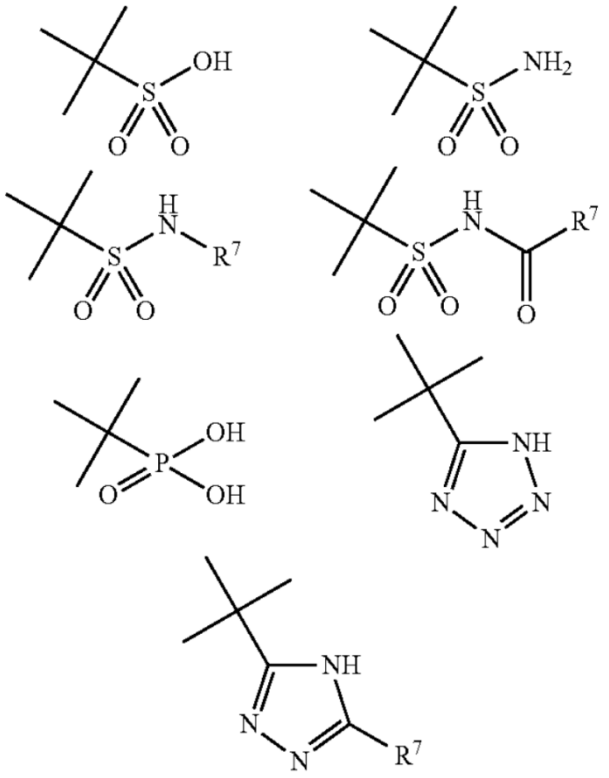
each $R^3$ and each $R^6$ is independently H or an optionally substituted C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C12 heteroaryl, C7-C12 arylalkyl, or C6-C12 heteroarylalkyl group, or

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

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