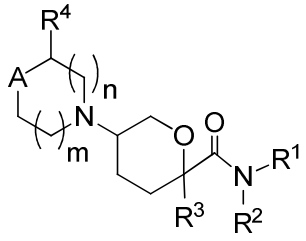
CLAIMS

1. Use of a CCR2 chemokine receptor antagonist and a PD-1 and/or PD-L1 inhibitor in the preparation of a medicament for treating cancer in a mammal.

2. Use of a CCR2 chemokine receptor antagonist and a PD-1 and/or PD-L1 inhibitor in the preparation of a medicament for treating cancer in mammal, wherein the CCR2 chemokine receptor antagonist is to be administered in combination, concomitantly or sequentially with the PD-1 and/or PD-L1 inibitor.

3. The use of claim 1 or claim 2, wherein said CCR2 antagonist has the formula:



(I);

or a pharmaceutically acceptable salt, hydrate, stereoisomer or rotamer thereof; wherein

A is $C(R^5)(R^6)$ or $N(R^5)$

the subscripts m and n are each independently integers of from 0 to 2, and m + n is ≤ 3;

R^1 is selected from the group consisting of aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein the heteroaryl portion has from 1-3 heteroatoms as ring members selected from N, O and S; and wherein said aryl and heteroaryl groups or portions are optionally substituted with from 1 to 5 R^x substituents;

R^2 is selected from the group consisting of H, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-C_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl-C_{1-4} alkyl, wherein the heteroaryl portion has from 1-3 heteroatoms as ring members selected from N, O and S; and wherein said aryl and heteroaryl groups or portions are optionally substituted with from 1 to 4 R^x substituents;

or optionally, R^1 and R^2 are combined with the nitrogen atom to which each is attached to form a 6- to 11-membered monocyclic or fused bicyclic- heterocyclic or heteroaryl ring, wherein the $-NR^1R^2$ is optionally further substituted with from 1 to 4 R^x substituents;

R^3 is selected from the group consisting of H, C_{1-8} alkyl, C_{3-8} cycloalkyl and C_{3-8} cycloalkyl-C_{1-4} alkyl, each of which is optionally substituted with from 1-3 R^y substituents;

R^4 is selected from the group consisting of H, C_{1-8} alkyl optionally substituted with 1 to 2 R^y, and $–CO_2H$:

R^5 is selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkyloxy, C_{3-8} cycloalkyl-C_{1-4} alkyl, C_{1-8} alkylamino, di-C_{1-8} alkylamino, aryl, aryloxy, arylamino, aryl-C_{1-4} alkyl, heteroaryl, heteroaryloxy, heteroarylamino and heteroaryl-C_{1-4} alkyl, each of which is optionally substituted with from 1 to 5 R^z substituents;

R^6 is selected from the group consisting of H, F, OH, C_{1-8} alkyl and C_{1-8} alkoxy, wherein the C_{1-8} alkyl and C_{1-8} alkoxy groups are optionally substituted with from 1 to 3 R^z substituents;

or optionally, R^5 and R^6 are joined to form a spirocyclic 5- or 6-membered cycloalkyl ring which is optionally unsaturated, and has a fused aryl group which is optionally substituted with from 1 to 4 R^z substituents;

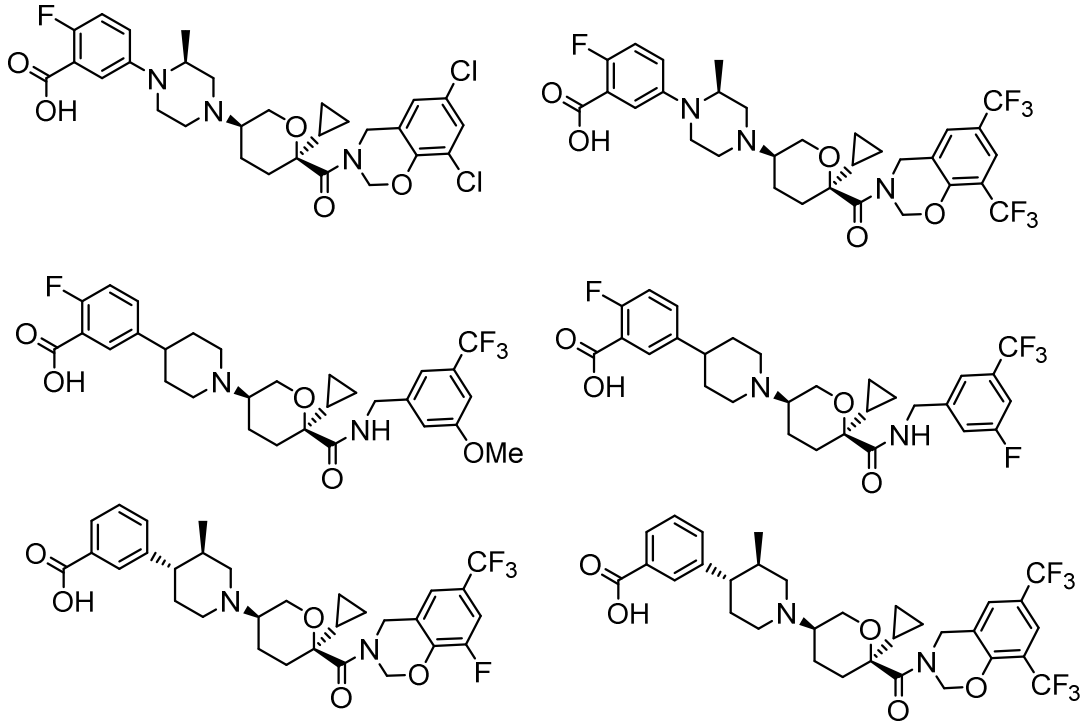
each R^x is independently selected from the group consisting of halogen, -CN, -R^c, -CO_2R^a, -$CONR^aR^b$, -$C(O)R^a$, -$OC(O)NR^aR^b$, -$NR^bC(O)R^a$, -$NR^bC(O)_2R^c$, -NR^a-$C(O)NR^aR^b$, -$NR^aC(O)NR^aR^b$, -NR^aR^b, -OR^a, -O-X^1-OR^a, -O-X^1-NR^aR^b, -O- X^1-CO_2R^a, -O-X^1-$CONR^aR^b$, -X^1-OR^a, -X^1-NR^aR^b, - X^1-CO_2R^a, -X^1-$CONR^aR^b$, -SF_5, -$S(O)_2NR^aR^b$, and 5- or 6-membered aryl or heteroaryl, wherein each X^1 is a C_{1-4} alkylene; each R^a and R^b is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and optionally substituted with oxo; each R^c is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl and C_{3-6} cycloalkyl; and optionally when two R^x substituents are on adjacent atoms, are combined to form a fused five or six-membered carbocyclic ring, and wherein the aryl or heteroaryl groups are optionally substituted with 1-3 members selected from halogen, hydroxyl, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

each R^y is independently selected from the group consisting of halogen, -CN, -R^f, -CO_2R^d, -$CONR^dR^e$, -$C(O)R^d$, -$OC(O)NR^dR^e$, -$NR^eC(O)R^d$, -$NR^eC(O)_2R^f$, -$NR^dC(O)NR^dR^e$, -$NR^dC(O)NR^dR^e$, -NR^dR^e, -OR^d, and -$S(O)_2NR^dR^e$; wherein each R^d and R^e is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as

ring members selected from N, O or S; each R^f is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl and C_{3-6} cycloalkyl;

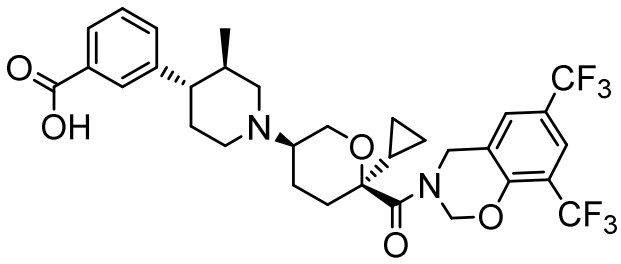
each R^z is independently selected from the group consisting of halogen, -CN, -R^i, -CO_2R^g, -$CONR^gR^h$, -$C(O)R^g$, -$OC(O)NR^gR^h$, -$NR^hC(O)R^g$, -$NR^hC(O)_2R^i$, -$NR^gC(O)NR^gR^h$, -NR^gR^h, -OR^g, -$S(O)_2NR^gR^h$, -X^1-R^j, -X^1-NR^gR^h, -X^1-$CONR^gR^h$, -X^1-$NR^hC(O)R^g$, -NHR^j, -$NHCH_2R^j$, and tetrazole; wherein each R^g and R^h is independently selected from hydrogen, C_{1-8} alkyl, C_{3-6} cycloalkyl and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S and is optionally substituted with one or two oxo; each R^i is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl and C_{3-6} cycloalkyl; and each R^j is selected from the group consisting of C_{3-6} cycloalkyl, pyrrolinyl, piperidinyl, morpholinyl, tetrahydrofuranyl, and tetrahydropyranyl.

4. The use of claim 1 or claim 2, wherein said CCR2 inhibitor has the formula



or a pharmaceutically acceptable salt thereof.

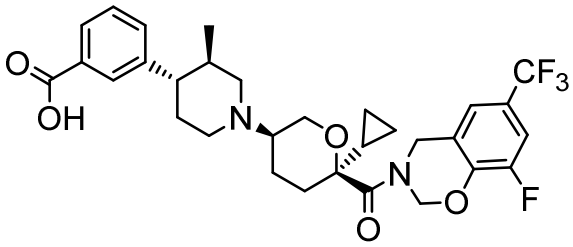
5. The use of claim 1 or claim 2, wherein said CCR2 inhibitor has the formula



(Compound 1)

or a pharmaceutically acceptable salt thereof.

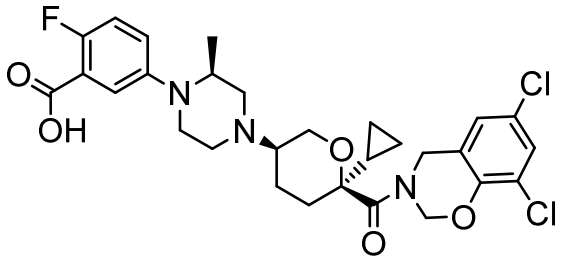
6. The use of claim 1 or claim 2, wherein said CCR2 inhibitor has the formula



(Compound 2)

or a pharmaceutically acceptable salt thereof.

7. The use of claim 1 or claim 2, wherein said CCR2 inhibitor has the formula



(Compound 3)

or a pharmaceutically acceptable salt thereof.

8. The use of any one of claims 1 to 7, wherein said PD-1 and/or PD-L1 inhibitor is a PD-1 inhibitor.

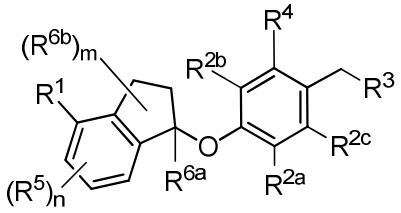
9. The use of claim 8, wherein the PD-1 inhibitor is selected from the group consisting of pembrolizumab, nivolumab, IBI-308, mDX-400, BGB-108, MEDI-0680, SHR-1210, PF-06801591, PDR-001, GB-226, STI-1110, biosimilars thereof, biobetters thereof, and bioequivalents thereof.

10. The use of claim 8, wherein said anti-PD-1 antibody is selected from the group consisting of Nivolumab, Pembrolizumab, and Pidilizumab,

11. The use of any one of claims 1 to 7, wherein said PD-1 and/or PD-L1 inhibitor is a PD-L1 inhibitor.

12. The use of claim11, wherein the PD-L1 inhibitor is selected from the group consisting of durvalumab, atezolizumab, avelumab, BMS-936559, ALN-PDL, TSR-042, KD-033, CA-170, CA-327, STI-1014, KY-1003, biosimilars thereof, biobetters thereof, and bioequivalents thereof.

13. The use of any one of claims 1 to 7, wherein said PD-1 and/or PD-L1 inhibitor is a compound of formula (II)



(II)

or a pharmaceutically acceptable salt thereof; wherein:

R^1 is selected from the group consisting of halogen, C_{5-8} cycloalkyl, C_{6-10} aryl and thienyl, wherein the C_{6-10} aryl and thienyl are optionally substituted with 1 to 5 R^x substituents;

each R^x is independently selected from the group consisting of halogen, -CN, $-R^c$, $-CO_2R^a$, $-CONR^aR^b$, $-C(O)R^a$, $-OC(O)NR^aR^b$, $-NR^bC(O)R^a$, $-NR^bC(O)_2R^c$, $-NR^a$-$C(O)NR^aR^b$, $-NR^aR^b$, $-OR^a$, $-O$-X^1-OR^a, $-O$- X^1-CO_2R^a, $-O$-X^1-$CONR^aR^b$, $-X^1$-OR^a, $-X^1$-NR^aR^b, - X^1-CO_2R^a, $-X^1$-$CONR^aR^b$, $-SF_5$, and $-S(O)_2NR^aR^b$, wherein each X^1 is a C_{1-4} alkylene; each R^a and R^b is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, wherein the five or six-membered ring is optionally substituted with oxo; each R^c is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl and C_{1-8} haloalkyl; and optionally when two R^x substituents are on adjacent atoms, they are combined to form a fused five, six or seven-membered carbocyclic or heterocyclic ring optionally substituted with from 1 to 3 substituents independently selected from halo, oxo, C_{1-8} haloalkyl and C_{1-8} alkyl;

each R^{2a}, R^{2b} and R^{2c} is independently selected from the group consisting of H, halogen, -CN, -R^d, -CO_2R^e, -$CONR^eR^f$, -$C(O)R^e$, -$OC(O)NR^eR^f$, -$NR^fC(O)R^e$, -$NR^fC(O)_2R^d$, -NR^e-$C(O)NR^eR^f$, -NR^eR^f, -OR^e, -O-X^2-OR^e , -O-X^2-NR^eR^f, -O- X^2-CO_2R^e, -O-X^2-$CONR^eR^f$, -X^2-OR^e, -X^2-NR^eR^f, -X^2-CO_2R^e, -X^2-$CONR^eR^f$, -SF_5, -$S(O)_2NR^eR^f$, C_{6-10} aryl and C_{5-10} heteroaryl, wherein each X^2 is a C_{1-4} alkylene; each R^e and R^f is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O and S, and optionally substituted with oxo; each R^d is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, and C_{1-8} haloalkyl;

R^3 is selected from the group consisting of -NR^gR^h and C_{4-12} heterocyclyl, wherein the C_{4-12} heterocyclyl is optionally substituted with 1 to 6 R^y;

each R^y is independently selected from the group consisting of halogen, -CN, -R^i, -CO_2R^j, -$CONR^jR^k$, -$CONHC_{1-6}$ alkyl-OH, -$C(O)R^j$, -$OC(O)NR^jR^k$, -$NR^jC(O)R^k$, -$NR^jC(O)_2R^k$, CONOH, PO_3H_2, -NR^j-C_{1-6} alkyl-$C(O)_2R^k$, -$NR^jC(O)NR^jR^k$, -NR^jR^k, -OR^j, -$S(O)_2NR^jR^k$, -O-C_{1-6}alkyl-OR^j, -O-C_{1-6} alkyl-NR^jR^k, -O-C_{1-6} alkyl-CO_2R^j, -O-C_{1-6} alkyl-$CONR^jR^k$, -C_{1-6} alkyl-OR^j, - C_{1-6} alkyl-NR^jR^k, -C_{1-6} alkyl-CO_2R^j, -C_{1-6} alkyl-$CONR^jR^k$, and SF_5,

wherein the C_{1-6} alkyl portion of R^y is optionally further substituted with OH, SO_2NH_2, $CONH_2$, CONOH, PO_3H_2, COO-C_{1-8}alkyl or CO_2H, wherein each R^j and R^k is independently selected from hydrogen, C_{1-8} alkyl optionally substituted with 1 to 2 substituents selected from OH, SO_2NH_2, $CONH_2$, CONOH, PO_3H_2, COO-C_{1-8}alkyl or CO_2H, and C_{1-8} haloalkyl optionally substituted with 1 to 2 substituents selected from OH, SO_2NH_2, $CONH_2$, CONOH, PO_3H_2, COO-C_{1-8}alkyl or CO_2H, or when attached to the same nitrogen atom R^j and R^k can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and optionally substituted with oxo; each R^i is independently selected from the group consisting of –OH, C_{1-8} alkyl, C_{2-8} alkenyl, and C_{1-8} haloalkyl each of which may be optionally substituted with OH, SO_2NH_2, $CONH_2$, CONOH, PO_3H_2, COO-C_{1-8}alkyl or CO_2H;

R^g is selected from the group consisting of H, C_{1-8} haloalkyl and C_{1-8} alkyl;

R^h is selected from -C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkyl-COOH, C_{1-8} alkyl-OH, C_{1-8} alkyl-$CONH_2$, C_{1-8} alkyl-SO_2NH_2, C_{1-8} alkyl-PO_3H_2, C_{1-8} alkyl-CONOH, C_{1-8} alkyl-

$NR^{h1}R^{h2}$, -C(O)-C_{1-8}alkyl, -C(O)-C_{1-8}alkyl-OH, -C(O)-C_{1-8}alkyl-COOH, C_{3-10} cycloalkyl,-C_{3-10} cycloalkyl-COOH, -C_{3-10} cycloalkyl-OH, C_{4-8} heterocyclyl, -C_{4-8} heterocyclyl-COOH, -C_{4-8} heterocyclyl-OH, -C_{1-8} alkyl-C_{4-8} heterocyclyl, -C_{1-8} alkyl-C_{3-10} cycloalkyl, C_{5-10} heteroaryl, -C_{1-8}alkyl-C_{5-10} heteroaryl, C_{10} carbocyclyl, -C_{1-8} alkyl-C_{6-10} aryl, -C_{1-8} alkyl-(C=O)-C_{6-10} aryl, -C_{1-8} alkyl-NH(C=O)-C_{1-8} alkenyl , -C_{1-8} alkyl-NH(C=O)-C_{1-8} alkyl, -C_{1-8} alkyl-NH(C=O)-C_{1-8} alkynyl, -C_{1-8} alkyl-(C=O)-NH-C_{1-8} alkyl-COOH, and -C_{1-8} alkyl-(C=O)-NH-C_{1-8} alkyl-OH optionally substituted with CO_2H; or

R^h combined with the N to which it is attached is a mono-, di- or tri-peptide comprising 1-3 natural amino acids and 0-2 non-natural amino acids, wherein

the non-natural aminoacids have an alpha carbon substituent selected from the group consisting of C_{2-4} hydroxyalkyl, C_{1-3} alkyl-guanidinyl, and C_{1-4} alkyl-heteroaryl,

the alpha carbon of each natural or non-natural amino acids are optionally further substituted with a methyl group, and

the terminal moiety of the mono-, di-, or tri-peptide is selected from the group consisting of C(O)OH, C(O)O-C_{1-6} alkyl, and PO_3H_2, wherein

R^{h1} and R^{h2} are each independently selected from the group consisting of H, C_{1-6} alkyl, and C_{1-4} hydroxyalkyl;

the C_{1-8} alkyl portions of R^h are optionally further substituted with from 1 to 3 substituents independently selected from OH, COOH, SO_2NH_2, $CONH_2$, CONOH, COO-C_{1-8} alkyl, PO_3H_2 and C_{5-6} heteroaryl optionally substituted with 1 to 2 C_{1-3} alkyl substituents,

the C_{10} carbocyclyl, C_{5-10} heteroaryl and the C_{6-10} aryl portions of R^h are optionally substituted with 1 to 3 substituents independently selected from OH, $B(OH)_2$, COOH, SO_2NH_2, $CONH_2$, CONOH, PO_3H_2, COO-C_{1-8}alkyl, C_{1-4}alkyl, C_{1-4}alkyl-OH, C_{1-4}alkyl-SO_2NH_2, C_{1-4}alkyl $CONH_2$, C_{1-4}alkyl-CONOH, C_{1-4}alkyl-PO_3H_2, C_{1-4}alkyl-COOH, and phenyl and

the C_{4-8} heterocyclyl and C_{3-10} cycloalkyl portions of R^h are optionally substituted with 1 to 4 R^w substituents;

each R^w substituent is independently selected from C_{1-4} alkyl, C_{1-4} alkyl-OH, C_{1-4} alkyl-COOH, C_{1-4} alkyl-SO_2NH_2, C_{1-4} alkyl $CONH_2$, C_{1-4} alkyl- CONOH, C_{1-4} alkyl-PO_3H, OH, COO-C_{1-8} alkyl, COOH, SO_2NH_2, $CONH_2$, CONOH, PO_3H_2 and oxo;

R^4 is selected from the group consisting of O-C_{1-8} alkyl, O-C_{1-8} haloalkyl, O-C_{1-8} alkyl-R^z, C_{6-10} aryl, C_{5-10} heteroaryl , -O-C_{1-4} alkyl-C_{6-10}aryl and -O-C_{1-4} alkyl-C_{5-10} heteroaryl, wherein the C_{6-10} aryl and the C_{5-10} heteroaryl are optionally substituted with 1 to 5 R^z;

each R^z is independently selected from the group consisting of halogen, -CN, -R^m, -CO_2R^n, -$CONR^nR^p$, -$C(O)R^n$, -$OC(O)NR^nR^p$, -$NR^nC(O)R^p$, -$NR^nC(O)_2R^m$, -NR^n-$C(O)NR^nR^p$, -NR^nR^p, -OR^n, -O-X^3-OR^n , -O-X^3-NR^nR^p, -O- X^3-CO_2R^n, -O-X^3-$CONR^nR^p$, -X^3-OR^n, -X^3-NR^nR^p, - X^3-CO_2R^n, -X^3-$CONR^nR^p$, -SF_5, -$S(O)_2R^nR^p$, -$S(O)_2NR^nR^p$, and three to seven-membered carbocyclic or four to seven-membered heterocyclic ring wherein the three to seven-membered carbocyclic or four to seven-membered heterocyclic ring is optionally substituted with 1 to 5 R^t, wherein each R^t is independently selected from the group consisting of C_{1-8} alkyl, C_{1-8}haloalkyl, -CO_2R^n, -$CONR^nR^p$, -$C(O)R^n$, -$OC(O)NR^nR^p$, -$NR^nC(O)R^p$, -$NR^nC(O)_2R^m$, -NR^n-$C(O)NR^nR^p$, -NR^nR^p, -OR^n, -O-X^3-OR^n , -O-X^3-NR^nR^p, -O- X^3-CO_2R^n, -O-X^3-$CONR^nR^p$, -X^3-OR^n, -X^3-NR^nR^p, - X^3-CO_2R^n, -X^3-$CONR^nR^p$, -SF_5, and -$S(O)_2NR^nR^p$;

wherein each X^3 is a C_{1-4} alkylene; each R^n and R^p is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and optionally substituted with oxo; each R^m is independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, and C_{1-8} haloalkyl; and optionally when two R^z substituents are on adjacent atoms, they are combined to form a fused five or six-membered carbocyclic or heterocyclic ring optionally substituted with oxo;

n is 0, 1, 2 or 3;

each R^5 is independently selected from the group consisting of halogen, -CN, -R^q, -CO_2R^r, -$CONR^rR^s$, -$C(O)R^r$, -$OC(O)NR^rR^s$, -$NR^rC(O)R^s$, -$NR^rC(O)_2R^q$, -NR^r-$C(O)NR^rR^s$, -NR^rR^s, -OR^r, -O-X^4-OR^r , -O-X^4-NR^rR^s, -O- X^4-CO_2R^r, -O-X^4-$CONR^rR^s$, -X^4-OR^r, -X^4-NR^rR^s, -X^4-CO_2R^r, -X^4-$CONR^rR^s$, -SF_5, -$S(O)_2NR^rR^s$, wherein each X^4 is a C_{1-4} alkylene; each R^r and R^s is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and optionally substituted with

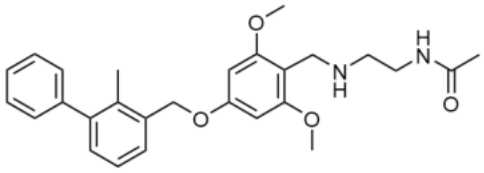
oxo; each R^q is independently selected from the group consisting of C_{1-8} alkyl, and C_{1-8} haloalkyl;

R^{6a} is selected from the group consisting of H, C_{1-4} alkyl and C_{1-4} haloalkyl;

each R^{6b} is independently selected from the group consisting of F, C_{1-4} alkyl, O-R^u, C_{1-4} haloalkyl, NR^uR^v, wherein each R^u and R^v is independently selected from hydrogen, C_{1-8} alkyl, and C_{1-8} haloalkyl, or when attached to the same nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional heteroatoms as ring members selected from N, O or S, and optionally substituted with oxo; and

m is 0, 1, 2, 3 or 4.

14. The use any one of claims 1 to 7, wherein said PD-1/PD-L1 inhibitor is



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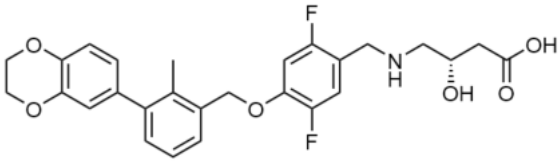

or a pharmaceutically acceptable salt thereof.

15. The use of any one of claims 1 to14, wherein the CCR2 chemokine receptor antagonist and the PD-1 inhibitor and/or the PD-L1 inhibitor are to be administered concomitantly.

16. The use of claim 15, wherein the CCR2 chemokine receptor antagonist, and the PD-1 inhibitor and/or the PD-L1 inhibitor are to be administered in a combination formulation.

17. The use of any one of claims 1 to14, wherein the CCR2 chemokine receptor antagonist, and the PD-1 inhibitor and/or the PD-L1 inhibitor are to be administered sequentially.

18. The use of claim 17, wherein the CCR2 chemokine receptor antagonist is to be administered prior to administration of the PD-1 inhibitor and/or the PD-L1 inhibitor.

19. The use of claim 17, wherein the CCR2 chemokine receptor antagonist is to be administered after the administration of the PD-1 inhibitor and/or the PD-L1 inhibitor.

20. The use of any one of claims 1 to19, wherein the CCR2 chemokine receptor antagonist is to be administered orally and the PD-1 inhibitor and/or the PD-L1 inhibitor is to be administered intravenously.

21. The use of any one of claims 1 to 20, wherein the subject is a human subject.

22. The use of any one of claims 1 to 21, wherein said cancer is a solid cancer.

23. The use of any one of claims 1 to 21, wherein the cancer is selected from the group consisting of brain cancer, breast cancer, triple negative breast cancer, bladder cancer, bone cancer, colorectal cancer, lung cancer, kidney cancer, liver cancer, stomach cancer, prostate cancer, sarcoma, melanoma, carcinoma, and lymphoma.

24. The use of any one of claims 22, wherein said cancer is selected from the group consisting of colorectal cancer, glioblastoma, and pancreatic cancer.

25. The use of any one of claims 22, wherein said cancer is colorectal cancer.

26. The use of any one of claims 22, wherein said cancer is glioblastoma.

27. The use of any one of claims 22, wherein said cancer is pancreatic cancer.

28. A composition for use in treating a subject having cancer, comprising a therapeutically effective amount of a CCR2 chemokine receptor antagonist, a therapeutically effective amount of a PD-1 inhibitor and/or a PD-L1 inhibitor, and a pharmaceutically acceptable carrier or excipient.

29. The composition of claim 28, wherein the CCR2 chemokine receptor is selected from any one of claims 3 to5.

30. The composition of claim 28 or claim 29, wherein the PD-1 inhibitor and/or the PD-L1 inhibitor is selected from any one of claims 8 to14.

31. A kit for use in treating a subject having a solid tumor cancer, said kit comprising a CCR2 chemokine receptor antagonist and a PD-1 inhibitor and/or a PD-L1 inhibitor, with instruction for effective administration.

32. Use of a CCR2 chemokine receptor antagonist and a PD-1 inhibitor and/or a PD-L1 Inhibitor in the manufacture of a kit for treating a subject having a tumor cancer.

33. The kit of claim 31 or the use of claim 32, wherein the CCR2 chemokine receptor is selected from any one of claims 3 to 5.

34. The kit of claim 31 or claim 33 or the use of claim 32 or claim 33, wherein the PD-1 inhibitor and/or the PD-L1 inhibitor is selected from any one of claims 7 to 13.

35. The kit of any one of claims 31 and 33 or 34 or the use of any one of claims 32-34, wherein the CCR2 chemokine receptor antagonist and the PD-1 inhibitor and/or the PD-L1 inhibitor are formulated for concomitant administration.

36. The kit of any one of claims 31 and 33 to 35 or the use of any one of claims 32 to 35, wherein the CCR2 chemokine receptor antagonist and the PD-1 inhibitor and/or the PD-L1 inhibitor are formulated for sequential administration.

37. A kit for use in treating a subject having a solid tumor cancer, said kit comprising a CCR2 chemokine receptor antagonist and a PD-1 inhibitor and/or a PD-L1 inhibitor as a combined preparation for simultaneous, concomitant; separate or sequential use in the subject.