COMBINATION THERAPY FOR TREATMENT OF CANCER

CROSS-REFERENCE

[001] This application claims the benefit of U.S. Provisional Application No. 63/043,342, filed June 24, 2020; and U.S. Provisional Application No. 63/162,184, filed March 17, 2021, which are incorporated herein by reference.

BACKGROUND

[002] Cancer, an uncontrolled proliferation of cells, is a multifactorial disease characterized by tumor formation, growth, and in some instances, metastasis. Cells carrying an activated oncogene, damaged genome, or other cancer-promoting alterations can be prevented from replicating through an elaborate tumor suppression network. A central component of this tumor suppression network is p53, one of the most potent tumor suppressors in the cell. Both the wild type and mutant conformations of p53 are implicated in the progression of cancer.

INCORPORATION BY REFERENCE

[003] Each patent, publication, and non-patent literature cited in the application is hereby incorporated by reference in its entirety as if each was incorporated by reference individually.

SUMMARY

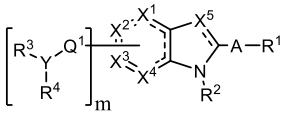
[004] Provided herein is a method of treating cancer in a subject in need thereof, the method comprising: (i) administering to the subject a therapeutically-effective amount of a compound, wherein the compound binds to a mutant p53 protein and reconforms the mutant p53 protein to a conformation of p53 that exhibits anti-cancer activity; and (ii) administering to the subject a therapeutically-effective amount of an anti-cancer agent that functions through a pathway other than p53-induced apoptosis.

[005] Also provided herein is a method of treating cancer in a subject in need thereof, the method comprising: (i) administering to the subject a therapeutically-effective amount of a compound that increases anti-cancer activity of a mutant p53 protein in the subject; and (ii) administering to the subject a therapeutically-effective amount of an anti-cancer agent that functions through a pathway other than p53-induced apoptosis.

[006] Further provided herein is a method of treating cancer, the method comprising: (i) administering to a subject in need thereof a therapeutically-effective amount of a compound that binds to a mutant p53 protein and reconforms the mutant p53 protein to a conformation of p53 that exhibits anti-cancer activity; and (ii) administering to the subject a therapeutically-effective amount of an additional anti-cancer agent that functions through a pathway other than p53-induced apoptosis, wherein if in a controlled study of treatment of the cancer in a first patient population and a second patient population: (a) a first median survival time of the first patient population is determined, wherein the first patient population is treated with the therapeutically-effective amount of the compound that binds to a mutant p53 protein and reconforms the mutant p53 protein to a conformation of p53 that exhibits anti-cancer activity; and (b) a second median survival time of the

second patient population is determined, wherein the second patient population is treated with the therapeutically-effective amount of the compound that binds to a mutant p53 protein and reconforms the mutant p53 protein to a conformation of p53 that exhibits anti-cancer activity and the therapeutically-effective amount of the additional therapeutic agent; then the second median survival time is at least about 50% greater than is the first median survival time.

[006a] In an aspect, there is provided the use of a compound in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein the compound is to be administered with a therapeutically-effective amount of an immune checkpoint inhibitor, wherein the compound is of the formula:



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wherein:

- each ------- is independently a single bond or a double bond;
- X^1 is CR^5, CR^5R^6, N, NR^5, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^2 is CR^7, CR^7R^8, N, NR^7, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^3 is CR^9, CR^9R^{10}, N, NR^9, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^4 is CR^{11}, $CR^{11}R^{12}$, N, NR^{11}, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^5 is CR^{13}, N, or NR^{13};

wherein at least one of X^1, X^2, X^3, and X^4 is a carbon atom connected to Q^1;

- A is a linking group;
- Q^1 is C=O, C=S, $C=CR^{14}R^{15}$, $C=NR^{14}$, alkylene, alkenylene, or alkynylene, each of which is independently substituted or unsubstituted, or a bond;
- m is 1, 2, 3, or 4;
- Y is N, O, or absent;
- R^1 is alkyl, alkenyl, alkynyl, alkoxy, aryl, heteroaryl, heterocyclyl, or halogen, each of which is independently substituted or unsubstituted, or -$C(O)R^{16}$, -$C(O)OR^{16}$, -$C(O)NR^{16}R^{17}$, -OR^{16}, -SR^{16}, -$NR^{16}R^{17}$, -$NR^{16}C(O)R^{16}$, -$OC(O)R^{16}$, -$SiR^{16}R^{17}R^{18}$, or hydrogen;
- each R^3 and R^4 is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or -$C(O)R^{19}$, -$C(O)OR^{19}$, -$C(O)NR^{19}R^{20}$, -SOR^{19}, -SO_2R^{19}, or hydrogen, or R^3 and R^4 together with the nitrogen atom to which R^3 and R^4 are bound form a ring, wherein the ring is substituted or unsubstituted, or R^3 is absent;
- each R^2, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or -$C(O)R^{21}$, -$C(O)OR^{21}$, -$C(O)NR^{21}R^{22}$, -OR^{21}, -SR^{21}, -$NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$OC(O)R^{21}$, hydrogen, or halogen;

- each R^{19} and R^{20} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or -$C(O)R^{23}$, -$C(O)OR^{23}$, -$C(O)NR^{23}R^{24}$, -OR^{23}, -SR^{23}, -$NR^{23}R^{24}$, -$NR^{23}C(O)R^{24}$, -$OC(O)R^{23}$, hydrogen, or halogen;
- each R^{21} and R^{22} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or hydrogen; and
- each R^{23} and R^{24} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or hydrogen,

or a pharmaceutically-acceptable salt thereof.

BRIEF DESCRIPTION OF THE FIGURES

[007] **FIG. 1** shows changes in tumor volume (mm^3) in a mouse syngeneic model of sarcoma (MT373) over 27 days upon receiving treatment with vehicle (2Q7Dx4); anti-PD-1 200 μg (Q3Dx35); Compound 1, 75 mg/kg (2Q7Dx6); Compound 1, 150 mg/kg (2Q7Dx15); Compound 1, 75 mg/kg (2Q7Dx15) + anti-PD-1 (Q3Dx35); or Compound 1, 150 mg/kg (2Q7Dx15) + anti-PD-1 (Q3Dx35).

[008] **FIG. 2** shows changes in tumor volume (mm^3) in a mouse syngeneic model of sarcoma (MT373) over 185 days upon receiving treatment with vehicle (2Q7Dx4); anti-PD-1 200 μg (Q3Dx35); Compound 1, 75 mg/kg (2Q7Dx6); Compound 1, 150 mg/kg (2Q7Dx15); Compound 1, 75 mg/kg (2Q7Dx15) + anti-PD-1 (Q3Dx35); or Compound 1, 150 mg/kg (2Q7Dx15) + anti-PD-1 (Q3Dx35).

[009] **FIG. 3** shows changes in tumor volume (mm^3) in individual C57B1/6 mice implanted with MT373 mouse syngeneic sarcoma tumors upon receiving treatment with vehicle; anti-PD-1 200 μg; Compound 1, 75 mg/kg; Compound 1, 150 mg/kg; Compound 1, 75 mg/kg + anti-PD-1; or Compound 1, 150 mg/kg + anti-PD-1.

[010] **FIG. 4** shows changes in percentage survival of mice upon receiving treatment with vehicle; anti-PD-1; Compound 1, 75 mg/kg; Compound 1, 150 mg/kg; Compound 1, 75 mg/kg + anti-PD-1; or Compound 1, 150 mg/kg + anti-PD-1.

[011] **FIG. 5** shows the changes in percent body weight change in female C57B1/6 mice implanted with MT373 mouse syngeneic sarcoma tumors upon receiving treatment with vehicle (2Q7Dx4); anti-PD-1 200 μg (Q3Dx35); Compound 1, 75 mg/kg (2Q7Dx6); Compound 1, 150 mg/kg (2Q7Dx15); Compound 1, 75 mg/kg (2Q7Dx15) + anti-PD-1 (Q3Dx35); or Compound 1, 150 mg/kg (2Q7Dx15) + anti-PD-1 (Q3Dx35).

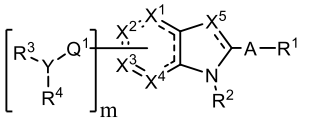
[012] **FIG. 6** shows changes in tumor volume (mm^3) in female C57B1/6 mice implanted with MT245 mouse syngeneic sarcoma tumors over 20 days upon receiving treatment with vehicle (Q7Dx3); anti-PD-1 200 μg (Q3Dx19); Compound 1, 150 mg/kg (Q7Dx5); Compound 1, 300 mg/kg (Q7Dx9); Compound 1, 600 mg/kg (Q7Dx9); Compound 1, 150 mg/kg (Q7Dx9) + anti-PD-1 200 μg (Q3Dx19); or Compound 1, 300 mg/kg (Q7Dx9) + anti-PD-1 200 μg (Q3Dx19).

[013] **FIG. 7** shows changes in tumor volume (mm^3) in female C57B1/6 mice implanted with MT245 mouse syngeneic sarcoma tumors over 157 days upon receiving treatment with vehicle (Q7Dx3); anti-PD-1 200 μg (Q3Dx19); Compound 1, 150 mg/kg (Q7Dx5); Compound 1, 300 mg/kg (Q7Dx9); Compound 1, 600 mg/kg (Q7Dx9); Compound 1, 150 mg/kg (Q7Dx9) + anti-PD-1 200 μg

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a compound in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein the compound is to be administered with a therapeutically-effective amount of an immune checkpoint inhibitor, wherein the compound is of the formula:



,

wherein:

- each ------- is independently a single bond or a double bond;
- X^1 is CR^5, CR^5R^6, N, NR^5, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^2 is CR^7, CR^7R^8, N, NR^7, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^3 is CR^9, CR^9R^{10}, N, NR^9, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^4 is CR^{11}, $CR^{11}R^{12}$, N, NR^{11}, O, S, C=O, C=S, or a carbon atom connected to Q^1;
- X^5 is CR^{13}, N, or NR^{13};

wherein at least one of X^1, X^2, X^3, and X^4 is a carbon atom connected to Q^1;

- A is a linking group;
- Q^1 is C=O, C=S, $C=CR^{14}R^{15}$, $C=NR^{14}$, alkylene, alkenylene, or alkynylene, each of which is independently substituted or unsubstituted, or a bond;
- m is 1, 2, 3, or 4;
- Y is N, O, or absent;
- R^1 is alkyl, alkenyl, alkynyl, alkoxy, aryl, heteroaryl, heterocyclyl, or halogen, each of which is independently substituted or unsubstituted, or -$C(O)R^{16}$, -$C(O)OR^{16}$, -$C(O)NR^{16}R^{17}$, -OR^{16}, -SR^{16}, -$NR^{16}R^{17}$, -$NR^{16}C(O)R^{16}$, -$OC(O)R^{16}$, -$SiR^{16}R^{17}R^{18}$, or hydrogen;
- each R^3 and R^4 is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or -$C(O)R^{19}$, -$C(O)OR^{19}$, -$C(O)NR^{19}R^{20}$, -SOR^{19}, -SO_2R^{19}, or hydrogen, or R^3 and R^4 together with the nitrogen atom to which R^3 and R^4 are bound form a ring, wherein the ring is substituted or unsubstituted, or R^3 is absent;
- each R^2, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or -$C(O)R^{21}$, -$C(O)OR^{21}$, -$C(O)NR^{21}R^{22}$, -OR^{21}, -SR^{21}, -$NR^{21}R^{22}$, -$NR^{21}C(O)R^{22}$, -$OC(O)R^{21}$, hydrogen, or halogen;
- each R^{19} and R^{20} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or -$C(O)R^{23}$, -$C(O)OR^{23}$, -$C(O)NR^{23}R^{24}$, -OR^{23}, -SR^{23}, -$NR^{23}R^{24}$, -$NR^{23}C(O)R^{24}$, -$OC(O)R^{23}$, hydrogen, or halogen;

- each R^{21} and R^{22} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or hydrogen; and
- each R^{23} and R^{24} is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted, or hydrogen,

or a pharmaceutically-acceptable salt thereof.

2. The use according to claim 1, wherein the cancer is ovarian cancer, breast cancer, or lung cancer.

3. The use according to claim 1 or claim 2, wherein a therapeutically-effective amount of the compound is to be administered, wherein the therapeutically effective amount of the compound is from about 100 mg to about 5000 mg.

4. The use according to any one of claims 1-3, wherein the immune checkpoint inhibitor is an anti-PD-1 agent.

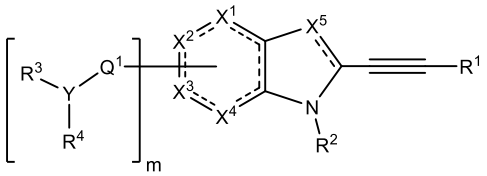
5. The use according to claim 4, wherein the anti-PD-1 agent is nivolumab.

6. The use according to claim 4, wherein the anti-PD-1 agent is pembrolizumab,

7. The use according to claim 4, wherein the anti-PD-1 agent is cemiplimab.

8. The use according to any one of claims 1-7, wherein the therapeutically effective amount of the immune checkpoint inhibitor is from about 1 mg/kg to about 5 mg/kg.

9. The use according to any one of claims 1-8, wherein the compound is of the formula:



wherein:

Q^1 is a bond;

Y is N;

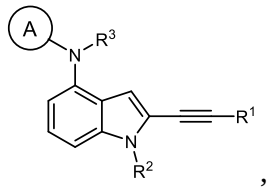
m is 1; and

each R^3 and R^4 is independently alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted; or hydrogen,

or a pharmaceutically-acceptable salt thereof.

10. The use according to claim 9, wherein R^3 is H; and R^4 is aryl, heteroaryl, or heterocyclyl, each of which is independently substituted or unsubstituted.

11. The use according to claim 9, wherein the compound is of the formula:



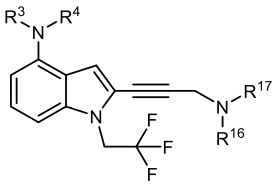
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wherein ring A is aryl, heteroaryl or heterocyclyl, each of which is substituted or unsubstituted.

12. The use according to any one of claims 9-11, wherein R^1 is alkyl or alkenyl, each of which is unsubstituted or substituted, or -C(O)R^{16}, -C(O)OR^{16}, or -C(O)N$R^{16}R^{17}$.

13. The use according to any one of claims 9-11, wherein R^1 is alkyl substituted with N$R^{16}R^{17}$.

14. The use according to claim 9 or claim 10, wherein the compound is of the formula:

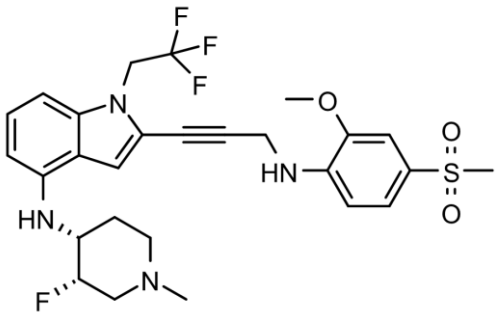


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15. The use according to any one of claims 9-14, wherein each R^{16} and R^{17} is independently alkyl, alkenyl, aryl, heteroaryl, heterocyclyl, each of which is independently substituted or unsubstituted; or hydrogen.

16. The use according to any one of claims 9-14, wherein R^{16} is hydrogen or alkyl; and R^{17} is phenyl substituted with a sulfoxide group, carboxyl group, amide group, amino group, alkyl, alkoxy, hydroxy, halo, cyano, or heterocyclyl.

17. The use according to any one of claims 1-8, wherein the compound is



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or a pharmaceutically-acceptable salt thereof.

18. The use according to any one of claims 1-8, wherein the compound is 4-((3-(4-(((3S,4R)-3-fluoro-1-methylpiperidin-4-yl)amino)-1-(2,2,2-trifluoroethyl)-1H-indol-2-yl)prop-2-yn-1-yl)amino)-3-methoxy-N-methylbenzamide, or a pharmaceutically-acceptable salt thereof.

19. The use according to any one of claims 1-8, wherein the compound is N-(2,3-dihydroxypropyl)-4-{[3-(4-{[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]amino}-1-(2,2,2-trifluoroethyl)-1H-indol-2-yl)prop-2-yn-1-yl]amino}-3-methoxybenzamide, or a pharmaceutically-acceptable salt thereof.