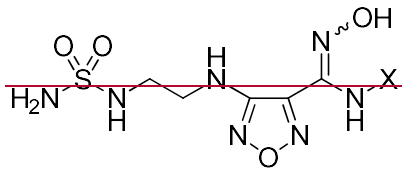
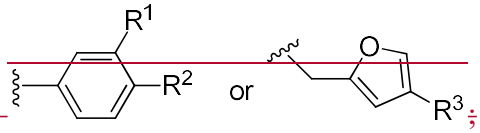
CLAIMS

~~1. A method for treating a cancer in an individual comprising administering to the individual a combination therapy which comprises an antagonist of a Programmed Death 1 protein (PD-1) and an inhibitor of indoleamine 2, 3-dioxygenase 1 (IDO1), wherein the IDO1 inhibitor is a compound of Formula I:~~



~~I~~

~~or a pharmaceutically acceptable salt thereof; wherein:~~

~~X is~~  ~~;~~

~~R^1 is Cl, Br, CF3, or CN;~~

~~R^2 is H or F; and~~

~~R^3 is Cl or Br.~~

~~2. The method according to claim 1, wherein the individual is a human and the PD-1 antagonist is~~

~~a) a monoclonal antibody, or an antigen binding fragment thereof, which specifically binds to human PD-1 and blocks the binding of human PD-L1 to human PD-1; or~~

~~b) a monoclonal antibody, or an antigen binding fragment thereof, which specifically binds to human PD-L1 and blocks the binding of human PD-L1 to human PD-1.~~

~~3. The method according to claim 2, wherein the PD-1 antagonist is an anti-PD-1 monoclonal antibody which comprises a heavy chain and a light chain, wherein the heavy and light chains comprise SEQ ID NO:21 and SEQ ID NO:22, respectively, or SEQ ID NO:23 and SEQ ID NO:24, respectively.~~

1. Use of an antagonist of a Programmed Death 1 protein (PD-1) in combination with an IDO1 inhibitor in the manufacture of a medicament for treating a cancer in an individual,

wherein the PD-1 antagonist is a monoclonal antibody with a heavy chain having the amino acid sequence of SEQ ID No: 21 and a light chain having the amino acid sequence of SEQ ID NO: 22; and the IDO1 inhibitor is 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide or a pharmaceutically acceptable salt thereof.

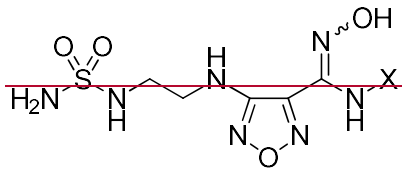
4.2. The ~~method~~ use according to ~~any one of~~ claim~~s~~ 1 ~~to 3~~, wherein the cancer is a solid tumor.

3. The use according to claim 1, wherein the cancer is bladder cancer, breast cancer, clear cell kidney cancer, head/neck squamous cell carcinoma, lung squamous cell carcinoma, malignant melanoma, non-small-cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, prostate cancer, renal cell cancer, small-cell lung cancer (SCLC), triple negative breast cancer, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, Hodgkin's lymphoma (HL), mantle cell lymphoma (MCL), multiple myeloma (MM), myeloid cell leukemia-1 protein (Mcl-1), myelodysplastic syndrome (MDS), non-Hodgkin's lymphoma (NHL), or small lymphocytic lymphoma (SLL).

5.4. The ~~method~~ use according to ~~any one of claims 1 to 4~~claim 1, wherein the cancer or tumor is selected from non-small-cell lung cancer (NSCLC), melanoma, transitional cell cancer of the bladder (TCC), renal cell cancer (RCC), triple negative breast cancer, adenocarcinoma of the endometrium, or squamous cell carcinoma of the head and neck.

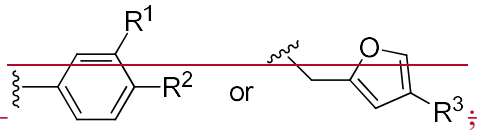
~~6. The method according to any one of claims 3 to 5, wherein the PD-1 antagonist is MK-3475.~~

~~7. A medicament comprising an antagonist of a Programmed Death 1 protein (PD-1) for use in combination with a IDO1 inhibitor for treating a cancer in an individual, wherein the wherein the IDO1 inhibitor is a compound of Formula I:~~



~~I~~

~~or a pharmaceutically acceptable salt thereof; wherein:~~

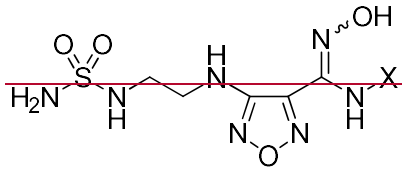
X is ;

R^1 is Cl, Br, CF_3, or CN;

R^2 is H or F; and

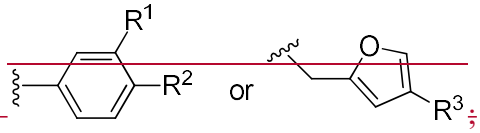
R^3 is Cl or Br.

8. A medicament comprising a IDO1 inhibitor for use in combination with an antagonist of a Programmed Death 1 protein (PD-1) for treating a cancer in an individual, wherein the IDO1 inhibitor is a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof; wherein:

X is ;

R^1 is Cl, Br, CF_3, or CN;

R^2 is H or F; and

R^3 is Cl or Br.

9. The medicament according to claim 7 or claim 8, wherein the individual is a human and the PD-1 antagonist is

a) a monoclonal antibody, or an antigen binding fragment thereof, which specifically binds to human PD-1 and blocks the binding of human PD-L1 to human PD-1; or

b) a monoclonal antibody, or an antigen binding fragment thereof, which specifically binds to human PD-L1 and blocks the binding of human PD-L1 to human PD-1.

~~10. The medicament according to any one of claims 7 to 9, wherein the PD-1 antagonist is an anti-PD-1 monoclonal antibody which comprises a heavy chain and a light chain, wherein the heavy and light chains comprise SEQ ID NO:21 and SEQ ID NO:22, respectively, or SEQ ID NO:23 and SEQ ID NO:24, respectively.~~

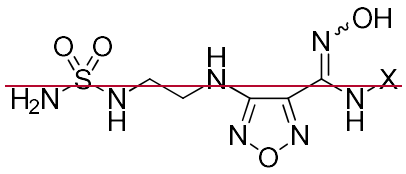
~~11. The medicament according to any one of claims 7 to 10, wherein the cancer is a solid tumor.~~

~~12.~~5. The ~~medicament~~ use according to ~~any one of claims 7 to 11~~claim 4, wherein the cancer is advanced renal cell carcinoma.

~~13. The medicament according to any one of claims 10 to 12, wherein the PD-1 antagonist is MK-3475 or nivolumab.~~

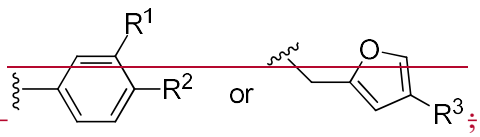
~~14.~~6. The ~~medicament~~ use according to any one of claims 1 to 4~~claim 13~~, wherein the PD-1 antagonist~~MK-3475~~ is formulated as a liquid medicament which comprises 25 mg/ml MK-3475, 7% (w/v) sucrose, 0.02% (w/v) polysorbate 80 in 10 mM histidine buffer pH 5.5.

~~15. A kit which comprises a first container, a second container and a package insert, wherein the first container comprises at least one dose of a medicament comprising an antagonist of a Programmed Death 1 protein (PD-1), the second container comprises at least one dose of a medicament comprising a IDO1 inhibitor, and the package insert comprises instructions for treating an individual for cancer using the medicaments, wherein the cancer is melanoma, bladder cancer, renal cell cancer, triple negative breast cancer, endometrial cancer or squamous cell carcinoma of the head and neck and wherein the IDO1 inhibitor is a compound of Formula I:~~



~~I~~

~~or a pharmaceutically acceptable salt thereof; wherein:~~

~~X is~~  ~~;~~

~~R^1 is Cl, Br, CF_3, or CN;~~

R^2 is H or F; and

R^3 is Cl or Br.

16. The kit according to claim 16, wherein the instructions state that the medicaments are intended for use in treating an individual having a cancer that tests positive for PD-L1 expression by an immunohistochemical (IHC) assay.

17. The kit according to claim 16 or claim 17, wherein the individual is a human and the PD-1 antagonist is

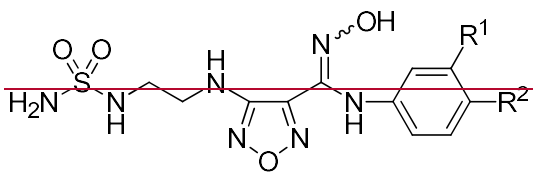
a) a monoclonal antibody, or an antigen binding fragment thereof, which specifically binds to human PD-1 and blocks the binding of human PD-L1 to human PD-1; or

b) a monoclonal antibody, or an antigen binding fragment thereof, which specifically binds to human PD-L1 and blocks the binding of human PD-L1 to human PD-1.

18. The kit according to any one of claims 16-18, wherein the PD-1 antagonist is MK-3475.

19. The method, use or kit according to any one of claims 1 to 19, wherein the cancer is bladder cancer, breast cancer, clear cell kidney cancer, head/neck squamous cell carcinoma, lung squamous cell carcinoma, malignant melanoma, non-small cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, prostate cancer, renal cell cancer, small cell lung cancer (SCLC), triple negative breast cancer, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, Hodgkin's lymphoma (HL), mantle cell lymphoma (MCL), multiple myeloma (MM), myeloid cell leukemia-1 protein (Mcl-1), myelodysplastic syndrome (MDS), non-Hodgkin's lymphoma (NHL), or small lymphocytic lymphoma (SLL).

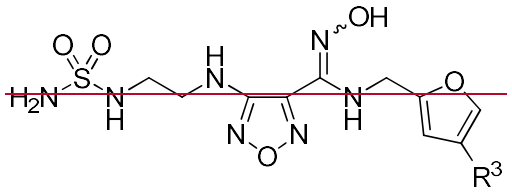
20. The method, medicament, or kit according to any one of claims 1 to 20, wherein the IDO inhibitor is a compound of Formula Ia:



Ia

or a pharmaceutically acceptable salt thereof.

21. The method, medicament, or kit of any one of claims 1 to 20, wherein the IDO inhibitor is a compound of Formula Ib:



Ib

or a pharmaceutically acceptable salt thereof.

22. The method, medicament, or kit according to any one of claims 1 to 20, wherein the IDO inhibitor is 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-bromo-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, or a pharmaceutically acceptable salt thereof.

23. The method, medicament, or kit according to any one of claims 1 to 20, wherein the IDO inhibitor is 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-chloro-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, or a pharmaceutically acceptable salt thereof.

24. The method, medicament, or kit according to any one of claims 1 to 20, wherein the IDO inhibitor is 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-[4-fluoro-3-(trifluoromethyl)phenyl]-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, or a pharmaceutically acceptable salt thereof.

25. The method, medicament, or kit according to any one of claims 1 to 20, wherein the IDO inhibitor is 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N'-hydroxy-N-[3-(trifluoromethyl)phenyl]-1,2,5-oxadiazole-3-carboximidamide, or a pharmaceutically acceptable salt thereof.

26. The method, medicament, or kit according to any one of claims 1 to 20, wherein the IDO inhibitor is 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-(3-cyano-4-fluorophenyl)-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, or a pharmaceutically acceptable salt thereof.

27. The method, medicament, or kit according to any one of claims 1 to 20, wherein the IDO inhibitor is 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-[(4-bromo-2-furyl)methyl]-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, or a pharmaceutically acceptable salt thereof.

~~28. The method, medicament, or kit according to any one of claims 1 to 20, wherein the IDO inhibitor is 4-({2-[(aminosulfonyl)amino]ethyl}amino)-N-[(4-chloro-2-furyl)methyl]-N'-hydroxy-1,2,5-oxadiazole-3-carboximidamide, or a pharmaceutically acceptable salt thereof.~~

~~29. The method, medicament, or kit according to any one of claims 1 to 20, wherein the PD-1 antagonist is MK-3475 and the IDO inhibitor is INCB024360.~~

~~30.~~7. The ~~method, medicament, or kit~~use according to any one of claims 1 to 5~~claim 29~~, wherein the PD-1 antagonist is to be administered to a subject in need in an amount of 2 mg/kg and the IDO inhibitor is to be administered to the subject at a dose of 25 mg or 50 mg.

~~31.~~8. The ~~method, medicament, or kit~~ use according to any one of claims 1 to 5~~claim 29~~, wherein the PD-1 antagonist is to be administered to a subject in need in an amount of 200 mg and the IDO inhibitor is to be administered to the subject at a dose of 25 mg or 50 mg.

~~32.~~9. The ~~method, medicament, or kit~~use according to any one of claims 1 to 5~~claim 30~~, wherein the PD-1 antagonist is to be administered to a subject in need in an amount of 2 mg/kg and the IDO inhibitor is to be administered to the subject at a dose of 25 mg.

~~33.~~10. The ~~method, medicament, or kit~~use according to any one of claims 1 to 5~~claim 30~~, wherein the PD-1 antagonist is to be administered to a subject in need in an amount of 2 mg/kg and the IDO inhibitor is to be administered to the subject at a dose of 50 mg.

~~34.~~11. The ~~method, medicament, or kit~~use according to any one of claims 1 to 5~~claim 31~~, wherein the PD-1 antagonist is to be administered to a subject in need in an amount of 200 mg and the IDO inhibitor is to be administered to the subject at a dose of 25 mg.

~~35.~~12. The ~~method, medicament, or kit~~ use according to any one of claims 1 to 5~~claim 31~~, wherein the PD-1 antagonist is to be administered to a subject in need in an amount of 200 mg and the IDO inhibitor is to be administered to the subject at a dose of 50 mg.

~~36.~~13. The ~~method, medicament, or kit~~use according to any one of claims ~~30~~ 1 to ~~35~~8, wherein the IDO inhibitor is to be administered to the subject at a dose of 25 mg BID.

~~37.~~14. The ~~method, medicament, or kit~~use according to any one of claims 1~~30~~ to ~~35~~, wherein the IDO inhibitor is to be administered to the subject at a dose of 50 mg BID.

~~38.~~15. The ~~method, medicament, or kit~~use according to any one of claims 1~~30~~ to ~~37~~, wherein the PD-1 antagonist is to be administered every three weeks and one dose of the IDO inhibitor is to be administered two times per day.

~~39. The method, medicament, or kit according to claim 38, wherein the IDO inhibitor is administered at twelve hour intervals.~~

~~40. The method, medicament, or kit according to any one of claims 30 to 39, wherein the PD-1 antagonist and the IDO inhibitor are dosed over a 21-day dosing period.~~

~~41. The method, medicament, or kit according to any one of claims 30 to 40, wherein the cancer is selected from one or more of non-small-cell lung cancer (NSCLC), melanoma, transitional cell cancer of the bladder (TCC), renal cell cancer (RCC), triple negative breast cancer, adenocarcinoma of the endometrium, or squamous cell carcinoma of the head and neck.~~