suppression of effector T-cell function and augmented differentiation of regulatory T cells (19-23). The anti-tumor efficacy of immunotherapeutic antibodies like anti-CTLA-4, anti-PD1/anti-PD-L1, and agonistic anti-GITR were significantly higher in IDO-deficient mice compared to wild type mice (24). This suggests that T-cell based immunotherapies were hampered due to IDO activity and blocking this pathway could boost the therapeutic potential of these antibodies.

[0006] INCB024360 is a selective inhibitor of IDO1 enzyme activity, which is currently in clinical development by Inctye Corporation as a single agent and in combination with other modalities for multiple cancers (25, 26).

[0007] MK-3475 is a selective humanized anti-human PD-1 monoclonal antibody of the IgG4/kappa isotype which is currently in clinical development by Merck as a single agent and in combination with other modalities for multiple cancers.

SUMMARY ~~OF THE INVENTION~~

[0008] In one ~~embodiment~~example, the ~~invention~~disclosure provides a method for treating a cancer in an individual comprising administering to the individual a combination therapy which comprises a PD-1 antagonist and an IDO1 inhibitor.

[0008a] In one aspect, the present disclosure refers to 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.

[0009] In another ~~embodiment~~example, the ~~invention~~disclosure provides a medicament comprising a PD-1 antagonist for use in combination with an IDO1 inhibitor for treating a cancer.

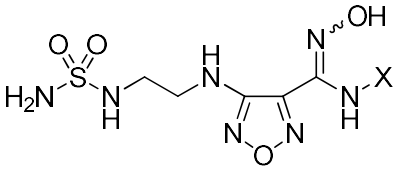
[0010] In yet another ~~embodiment~~example, the ~~invention~~disclosure provides a medicament comprising a IDO1 inhibitor for use in combination with a PD-1 antagonist for treating a cancer.

[0011] Other ~~embodiment~~examples provide use of a PD-1 antagonist in the manufacture of medicament for treating a cancer in an individual when administered in combination with an IDO1 inhibitor and use of an IDO1 inhibitor in the manufacture of a medicament for treating a cancer in an individual when administered in combination with a PD-1 antagonist.

[0012] In a still further ~~embodiment~~example, the ~~invention~~disclosure provides use of a PD-1 antagonist and an IDO1 inhibitor in the manufacture of medicaments for treating a cancer in an individual. In some preferred ~~embodiment~~examples, the medicaments comprise a kit, and the kit also comprises a package insert comprising instructions for using the PD-1 antagonist in combination with an IDO1 inhibitor to treat a cancer in an individual.

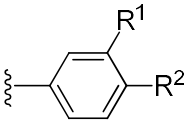
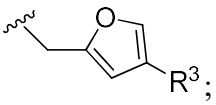
[0013] In all of the above treatment method, medicaments and uses, the PD-1 antagonist inhibits the binding of PD-L1 to PD-1, and preferably also inhibits the binding of PD-L2 to PD-1. In some preferred ~~embodiment~~examples of the above treatment method, medicaments and uses, the PD-1 antagonist is a monoclonal antibody, or an antigen binding fragment thereof, which specifically binds to PD-1 or to PD-L1 and blocks the binding of PD-L1 to PD-1. In one particularly preferred ~~embodiment~~example, the PD-1 antagonist is an anti-PD-1 antibody which comprises a heavy chain and a light chain, and wherein the heavy and light chains comprise the amino acid sequences shown in Figure 6 (SEQ ID NO:21 and SEQ ID NO:22).

[0014] In all of the above ~~embodiment~~examples of the treatment method, medicaments and uses, the IDO1 inhibitor is a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof; wherein:

X is  or ;

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

R^2 is H or F; and

R^3 is Cl or Br.

[0015] In some ~~embodiment~~examples of the above treatment method, medicaments and uses of the ~~invention~~disclosure, the individual is a human and the cancer is a solid tumor and in some preferred ~~embodiment~~examples, the solid tumor is transitional cell cancer of the urinary bladder, adenocarcinoma of the endometrium, bladder cancer, breast cancer, clear cell kidney cancer, head/neck squamous cell carcinoma, lung squamous cell carcinoma, melanoma, non-small-cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, prostate cancer, renal cell cancer (RCC), small-cell lung cancer (SCLC) or triple negative breast cancer. In other preferred ~~embodiment~~examples, the cancer is

advanced or metastatic NSCLC, melanoma, bladder cancer, renal cell cancer, triple negative breast cancer, endometrial cancer or squamous cell carcinoma of the head and neck, and in more preferred ~~embodiment~~examples, the cancer is stage IIIb, stage IV or recurrent NSCLC in an individual previously treated with a platinum-based chemotherapy regimen.

[0016] In other ~~embodiment~~examples of the above treatment method, medicaments and uses of the ~~invention~~disclosure, the individual is a human and the cancer is a Heme malignancy and in some preferred ~~embodiment~~examples, the Heme malignancy is acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), diffuse large B-cell lymphoma (DLBCL), EBV-positive DLBCL, primary mediastinal large B-cell lymphoma, T-cell/histiocyte-rich large B-cell lymphoma, 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).

[0017] Also, in preferred ~~embodiment~~examples of any of the above treatment method, medicaments and uses, the cancer tests positive for the expression of one or both of PD-L1 and PD-L2. In particularly preferred ~~embodiment~~examples, the cancer has elevated PD-L1 expression.

[0018] In one particularly preferred ~~embodiment~~example of the above treatment method, medicaments and uses, the individual is a human and the cancer is advanced or metastatic NSCLC that tests positive for human PD-L1.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] FIGURE 1 shows amino acid sequences of the light chain and heavy chain CDRs for an exemplary anti-PD-1 monoclonal antibody useful in the present invention (SEQ ID NOs:1-6).

[0020] FIGURE 2 shows amino acid sequences of the light chain and heavy chain CDRs for another exemplary anti-PD-1 monoclonal antibody useful in the present invention (SEQ ID NOs:7-12).

[0021] FIGURE 3 shows amino acid sequences of the heavy chain variable region and full length heavy chain for an exemplary anti-PD-1 monoclonal antibody useful in the present invention (SEQ ID NO:13 and SEQ ID NO:14).