[0005] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR) (Greenwald *et al.*, Annu Rev Immunol. 2004; 23:515-48). Collectively, these signals govern the balance between T-cell activation and tolerance.

[0006] Immunotherapeutic approaches have recently demonstrated clinical efficacy in several cancer types, including melanoma and hormone-refractory prostate cancer. Tumors can modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. T cell checkpoint regulators, such as programmed death-1 (PD-1, CD279), are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades down-regulating T cell activation and proliferation.

[0007] PD-1 is a key immune checkpoint receptor expressed by activated T and B cells and mediates immunosuppression. PD-1 is a member of the CD28 family of receptors, which includes CD28, CTLA-4, ICOS, PD-1, and BTLA. Two cell surface glycoprotein ligands for PD-1 have been identified, Programmed Death Ligand- 1 (PD-L1) and Programmed Death Ligand-2 (PD-L2), that are expressed on antigen-presenting cells, as well as many human cancers and have been shown to downregulate T cell activation and cytokine secretion upon binding to PD-1. Inhibition of the PD- 1/PD-L1 interaction mediates potent antitumor activity in preclinical models (U.S. Patent Nos. 8,008,449 and 7,943,743), and the use of antibody inhibitors of the PD-1/PD-L1 interaction for treating cancer has entered clinical trials (Brahmer *et al.*, 2010; Topalian *et al.*, 20l2a; Topalian *et al.*, 2014; Hamid *et al.*, 2013; Brahmer *et al.*, 2012; Flies *et al.*, 2011; Pardoll, 2012; Hamid and Carvajal, 2013), and are currently approved for some cancer indications.

SUMMARY

[0008] It has been found that the combination of AHR inhibitor (R)-N-(2-(5-fluoropyridin-3-yl)-8-isopropylpyrazolo[1,5-a][1,3,5]triazin-4-yl)-2,3,4,9-tetrahydro-1H-carbazol-3-amine (Compound **A**) and a PDx inhibitor, such as nivolumab, has synergistic effects in treating cancer.

[0008a] In an aspect of the present disclosure, there is provided a use of Compound **A,** or a pharmaceutically acceptable salt thereof, and a PDx inhibitor, in the manufacture of a medicament for treating cancer in a patient in need thereof.

[0008b] In another aspect of the present disclosure, there is provided a use of a metabolite of Compound **A,** or a pharmaceutically acceptable salt thereof, or a prodrug thereof, and a PDx inhibitor, in the manufacture of a medicament for treating cancer in a patient in need thereof.

[0008c] In a further aspect of the present disclosure, there is provided a use of Compound **A,** or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of a metabolite of Compound **A,** or a pharmaceutically acceptable salt thereof, or a prodrug thereof, and doxorubicin, or a pharmaceutically acceptable salt or derivative thereof, in the manufacture of a medicament for treating cancer in a patient in need thereof.

[0009] Accordingly, in one example, the present disclosure provides a method for treating cancer in a patient comprising administering to the patient a therapeutically effective amount of Compound **A**, or a pharmaceutically acceptable salt thereof, and a PDx inhibitor. In some examples, a PDx inhibitor is selected from those as described herein. In some examples, a PDx inhibitor is a PD-1 inhibitor. In some examples, a PDx inhibitor is a PD-L1/L2 inhibitor. In some examples, the PDx inhibitor is an anti-PD-1 antibody. In some examples, the anti-PD-1 antibody is nivolumab. In some examples, the anti-PD-1 antibody is pembrolizumab.

[0010] In another example, the present disclosure provides a method for treating cancer in a patient comprising administering to the patient a therapeutically effective amount of a metabolite of Compound **A**, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, and a PDx inhibitor. In some examples, a metabolite of Compound **A** is selected from those as described herein. In some examples, a PDx inhibitor is selected from those as described herein. In some examples, a PDx inhibitor is a PD-1 inhibitor. In some examples, a PDx inhibitor is a PD-L1/L2 inhibitor. In some examples, the PDx inhibitor is an anti-PD-1 antibody. In some examples, the anti-PD-1 antibody is nivolumab. In some examples, the anti-PD-1 antibody is pembrolizumab.

[0011] In some examples, a cancer is selected from those as described herein.

[0012] It has also been found that the combination of Compound **A** and a topoisomerase inhibitor, such as doxorubicin, or a pharmaceutically acceptable salt or derivative thereof, has synergistic effects in treating cancer. In another example, the present disclosure provides a method for treating cancer in a patient comprising administering to the patient a therapeutically effective amount of Compound **A**, or a pharmaceutically acceptable salt thereof, and doxorubicin, or a pharmaceutically acceptable salt or derivative thereof. In another example, the present disclosure provides a method for treating cancer in a patient comprising administering to the patient a therapeutically effective amount of a metabolite of Compound **A**, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, and doxorubicin, or a pharmaceutically acceptable salt or derivative thereof. In some examples, a metabolite of Compound **A** is selected from those as described herein.

[0013] In some examples, a cancer is selected from those as described herein.

CLAIMS

1. Use of Compound **A,** or a pharmaceutically acceptable salt thereof, and a PDx inhibitor, in the manufacture of a medicament for treating cancer in a patient in need thereof.

2. Use of a metabolite of Compound **A,** or a pharmaceutically acceptable salt thereof, or a prodrug thereof, and a PDx inhibitor, in the manufacture of a medicament for treating cancer in a patient in need thereof.

3. The use of claims 1 or 2, wherein about 200 – 1600 mg of Compound A, or a pharmaceutically acceptable salt thereof, or about 200 – 1600 mg of a metabolite of Compound A, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be administered daily to the patient; optionally wherein:

about 200 mg of Compound A, or a pharmaceutically acceptable salt thereof, or about 200 mg of a metabolite of Compound A, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be administered daily;

about 400 mg of Compound A, or a pharmaceutically acceptable salt thereof, or about 400 mg of a metabolite of Compound A, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be administered daily;

about 600 mg of Compound A, or a pharmaceutically acceptable salt thereof, or about 600 mg of a metabolite of Compound **A**, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be administered daily;

about 800 mg of Compound A, or a pharmaceutically acceptable salt thereof, or about 800 mg of a metabolite of Compound A, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be administered daily;

about 1200 mg of Compound A, or a pharmaceutically acceptable salt thereof, or about 1200 mg of a metabolite of Compound A, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be administered daily; or

about 1600 mg of Compound A, or a pharmaceutically acceptable salt thereof, or about 1600 mg of a metabolite of Compound A, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be administered daily;

further optionally:

wherein the about 1200 mg of Compound A, or a pharmaceutically acceptable salt thereof, or the about 1200 mg of a metabolite of Compound A**,** or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be dosed twice daily as two separate doses of about 600 mg; and

wherein the about 1600 mg of Compound A, or a pharmaceutically acceptable salt thereof, or the about 1600 mg of a metabolite of Compound A**,** or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be dosed twice daily as two separate doses of about 800 mg.

4. The use of any one of claims 1-3, wherein the PDx inhibitor is an anti-PD-1 antibody or an anti-PD-L1/L2 antibody; optionally thereto,

wherein the anti-PD-1 antibody cross-competes with nivolumab for binding to human PD-1; and/or

wherein the anti-PD-1 antibody binds to the same epitope as nivolumab.

5. The use of claim 4, wherein the anti-PD-1 antibody is a chimeric antibody, a humanized antibody, a human monoclonal antibody, or an antigen-binding portion thereof; optionally thereto:

wherein the anti-PD-1 antibody comprises a heavy chain constant region of a human IgGl isotype or a human IgG4 isotype;

further optionally:

wherein the anti-PD-1 antibody is nivolumab or pembrolizumab.

6. The use of claims 4 or 5, wherein the anti-PD-1 antibody is to be administered at a dose ranging from 0.1 mg/kg to 10.0 mg/kg body weight once every 2, 3, or 4 weeks; optionally thereto,

wherein the anti-PD-1 antibody is to be administered at a dose of 3 mg/kg, 5 mg/kg, or 10 mg/kg body weight once every 3 weeks.

7. The use of claims 4 or 5, wherein the anti-PD-1 antibody is to be administered at a flat dose; optionally thereto:

wherein the anti-PD-1 antibody is to be administered at a flat dose of at least about 200 mg, at least about 220 mg, at least about 240 mg, at least about 260 mg, at least about 280 mg, at least about 300 mg, at least about 320 mg, at least about 340 mg, at least about 360 mg, at least about 380 mg, at least about 400 mg, at least about 420 mg, at least about 440 mg, at least about 460 mg, at least about 480 mg, at least about 500 mg, or at least about 550 mg; and/or

wherein the anti-PD-1 antibody is to be administered at a flat dose once about every 1, 2, 3, or 4 weeks;

further optionally:

wherein the anti-PD-1 antibody is to be administered at a flat dose of about 360 mg once about every 3 weeks;

wherein the anti-PD-1 antibody is to be administered at a flat dose of about 240 mg once about every 2 weeks; or

wherein the anti-PD-1 antibody is to be administered at a flat dose of about 480 mg once about every 4 weeks.

8. The use of claim 4, wherein the anti-PD-L1/L2 antibody is a chimeric antibody, a humanized antibody, a human monoclonal antibody, or an antigen-binding portion thereof; optionally thereto:

wherein the anti-PD-L1/L2 antibody comprises a heavy chain constant region of a human IgGl isotype;

wherein the anti-PD-L1/L2 antibody cross-competes for binding to human PD-L1 with an antibody selected from atezolizumab, durvalumab, and avelumab; and/or

wherein the anti-PD-L1/L2 antibody binds the same epitope on human PD-L1 as an antibody selected from atezolizumab, durvalumab, and avelumab; further optionally:

wherein the anti-PD-L1/L2 antibody is atezolizumab, durvalumab, or avelumab.

9. The use of claim 4 or 8, wherein the anti-PD-L1/L2 antibody is to be administered at a dose ranging from 0.1 mg/kg to 15.0 mg/kg body weight once every 2, 3, or 4 weeks; optionally thereto:

wherein the anti-PD-L1/L2 antibody is to be administered at a dose of 3 mg/kg or 5 mg/kg body weight once every 2 weeks; or

wherein the anti-PD-L1/L2 antibody is to be administered at a dose of 10 mg/kg body weight once every 3 weeks.

10. The use of claim 4, 8, or 9 wherein the anti-PD-L1/L2 antibody is to be administered at a flat dose; optionally thereto:

wherein the anti-PD-L1/L2 antibody is to be administered at a flat dose of at least about 240 mg, at least about 300 mg, at least about 320 mg, at least about 400 mg, at least about 480 mg, at least about 500 mg, at least about 560 mg, at least about 600 mg, at least about 640 mg, at least about 700 mg, at least 720 mg, at least about 800 mg, at least about 880 mg, at least about 900 mg, at least 960 mg, at least about 1000 mg, at least about 1040 mg, at least about 1100 mg, at least about 1120 mg, at least about 1200 mg, at least about 1280 mg, at least about 1300 mg, at least about 1360 mg, at least about 1400 mg, or at least about 1500 mg; and/or

wherein the anti-PD-L1/L2 antibody is to be administered at a flat dose once about every 1, 2, 3, or 4 weeks,

further optionally:

wherein the anti-PD-Ll/L2 antibody is to be administered at a flat dose of about 1200 mg once about every 3 weeks.

11. The use of claim 3, wherein:

a. Compound **A**, or a pharmaceutically acceptable salt thereof, or a metabolite of Compound **A,** or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be administered daily at a dose of 800 mg; and

b. the anti-PD-1 antibody is to be administered at a flat dose of about 480 mg once about every 4 weeks.

12. The use of claim 3, wherein:

a. Compound **A**, or a pharmaceutically acceptable salt thereof, or a metabolite of Compound **A,** or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be administered daily at a dose of 1200 mg; and

b. the anti-PD-1 antibody is to be administered at a flat dose of about 480 mg once about every 4 weeks.

13. The use of any one of claims 1-12, wherein compound **A,** or a pharmaceutically acceptable salt thereof, and a PDx inhibitor, are to be administered to the patient, and wherein the patient exhibits progression-free survival of at least about one month after the administration; optionally thereto,

wherein the patient exhibits an overall survival of at least about one month after the administration; optionally thereto, wherein the patient exhibits an objective response rate of at least about 15%.

14. The use of any one of claims 1-13, wherein the cancer is selected from a hematological cancer, a lymphoma, a myeloma, a leukemia, a neurological cancer, skin cancer, breast cancer, a prostate cancer, a colorectal cancer, lung cancer, head and neck cancer, a gastrointestinal cancer, a liver cancer, a pancreatic cancer, a genitourinary cancer, a bone cancer, renal cancer, a vascular cancer, urothelial carcinoma; head and neck squamous cell carcinoma; melanoma; ovarian cancer; renal cell carcinoma; cervical cancer, gastrointestinal/stomach (GIST) cancer; non-small cell lung cancer (NSCLC); acute myeloid leukemia (AML); and esophageal cancer; optionally thereto,

wherein the urothelial carcinoma is bladder cancer or a transitional cell carcinoma;

wherein the melanoma is a uveal melanoma;

wherein the ovarian cancer is a serous subtype of ovarian cancer;

wherein the renal cell carcinoma is a clear cell renal cell carcinoma subtype; and

wherein the NSCLC is advanced and/or metastatic NSCLC.

15. Use of Compound **A,** or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of a metabolite of Compound **A,** or a pharmaceutically acceptable salt thereof, or a prodrug thereof, and doxorubicin, or a pharmaceutically acceptable salt or derivative thereof, in the manufacture of a medicament for treating cancer in a patient in need thereof.

16. The use of claim 15, about 200 – 1600 mg of Compound A, or a pharmaceutically acceptable salt thereof, or about 200 – 1600 mg of a metabolite of Compound A, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be administered to the patient daily; optionally thereto:

about 200 mg of Compound A, or a pharmaceutically acceptable salt thereof, or about 200 mg of a metabolite of Compound A, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be administered to the patient daily;

about 400 mg of Compound A, or a pharmaceutically acceptable salt thereof, or about 400 mg of a metabolite of Compound A, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be administered to the patient daily;

about 600 mg of Compound A, or a pharmaceutically acceptable salt thereof, or about 600 mg of a metabolite of Compound **A**, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be administered to the patient daily;

about 800 mg of Compound A, or a pharmaceutically acceptable salt thereof, or about 800 mg of a metabolite of Compound A, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be administered to the patient daily;

about 1200 mg of Compound A, or a pharmaceutically acceptable salt thereof, or about 1200 mg of a metabolite of Compound A, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be administered to the patient daily, or

about 1600 mg of Compound A, or a pharmaceutically acceptable salt thereof, or about 1600 mg of a metabolite of Compound A, or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be administered to the patient daily,

further optionally:

wherein the about 1200 mg of Compound A, or a pharmaceutically acceptable salt thereof, or the about 1200 mg of a metabolite of Compound A**,** or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be dosed twice daily as two separate doses of about 600 mg; and

wherein the about 1600 mg of Compound A, or a pharmaceutically acceptable salt thereof, or the about 1600 mg of a metabolite of Compound A**,** or a pharmaceutically acceptable salt thereof, or a prodrug thereof, is to be dosed twice daily as two separate doses of about 800 mg.

17. The use of claim 15 or 16, wherein compound **A,** or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of a metabolite of Compound **A,** or a pharmaceutically acceptable salt thereof, or a prodrug thereof, and doxorubicin, or a

pharmaceutically acceptable salt or derivative thereof, are to be administered to the patient, and wherein the patient exhibits progression-free survival of at least about one month after the administration, optionally thereto:

wherein the patient exhibits an overall survival of at least about one month after the administration; and/or

wherein the patient exhibits an objective response rate of at least about 15%.

18. The use of any one of claims 15-17, wherein the cancer is selected from a hematological cancer, a lymphoma, a myeloma, a leukemia, a neurological cancer, skin cancer, breast cancer, a prostate cancer, a colorectal cancer, lung cancer, head and neck cancer, a gastrointestinal cancer, a liver cancer, a pancreatic cancer, a genitourinary cancer, a bone cancer, renal cancer, and a vascular cancer, optionally thereto, wherein the cancer is ovarian cancer.