(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 September 2017 (08.09.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/151613 A1

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61K 39/395* (2006.01)
A61K 31/569 (2006.01)

(21) International Application Number:
PCT/US2017/019948

(22) International Filing Date:
28 February 2017 (28.02.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/302,106 1 March 2016 (01.03.2016) US
62/320,276 8 April 2016 (08.04.2016) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) **Title**: THE USE OF GLUCOCORTICOID RECEPTOR MODULATORS TO POTENTIATE CHECKPOINT INHIBITORS

(57) **Abstract**: This invention provides a method that combines a checkpoint inhibitor and a glucocorticoid receptor modulator to treat cancer, e.g., a checkpoint inhibitor sensitive cancer.

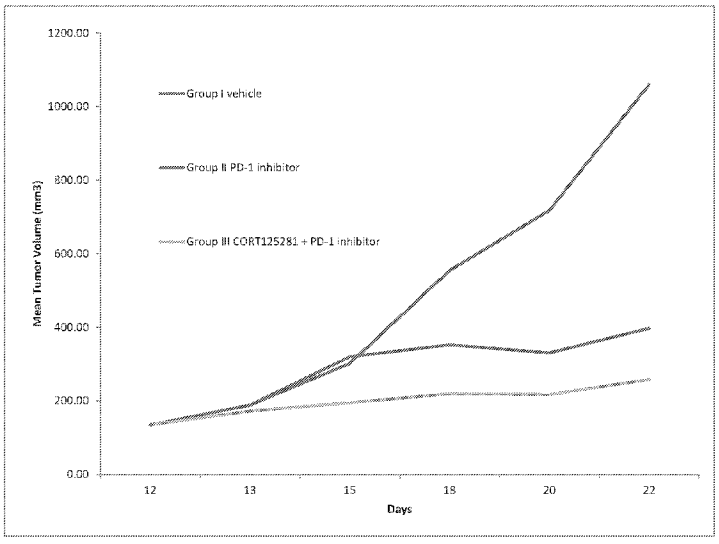

FIG. 2

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THE USE OF GLUCOCORTICOID RECEPTOR MODULATORS TO POTENTIATE CHECKPOINT INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of, and priority to, U.S. Provisional Patent Application Serial No. 62/302,106 filed March 1, 2016, and claims the benefit of, and priority to, U.S. Provisional Patent Application Serial No. 62/320,276 filed April 8, 2016, both of which applications are hereby incorporated herein by reference in their entireties.

BACKGROUND

[0002] Cancer is a group of varied diseases characterized by uncontrolled growth and spread of abnormal cells. The pathways regulating cell division and or cellular communication become altered in cancer cells such that the effects of these regulatory mechanisms in controlling and limiting cell growth fails or is bypassed. Through successive rounds of mutation and natural selection, a group of abnormal cells, generally originating from a single mutant cell, accumulates additional mutations that provide selective growth advantage over other cells, and thus evolves into a cell type that predominates in the cell mass. As the cancer cells further evolve, some become locally invasive and then metastasize to colonize tissues other than the cancer cell's tissue of origin. This property along with the heterogeneity of the tumor cell population makes cancer a particularly difficult disease to treat and eradicate.

[0003] Traditional cancer therapies take advantage of the higher proliferative capacity of cancer cells and their increased sensitivity to DNA damage: Ionizing radiation, including Y-rays and x-rays, and cytotoxic agents, such as bleomycin, cis-platin, vinblastine, cyclophosphamide, 5'- fluorouracil, and methotrexate rely upon a generalized damage to DNA and destabilization of chromosomal structure which eventually leads to destruction of cancer cells. These treatments are particularly effective for those types of cancers that have defects in cell cycle checkpoint, which limits the ability of these cells to repair damaged DNA before undergoing cell division. The non-selective nature of these treatments, however, often results in severe and debilitating

side effects. The systemic use of these drugs may result in damage to normally healthy organs and tissues, and compromise the long-term health of the patient.

[0004] Recently, immunotherapy targeting immune checkpoint signaling pathways has been shown to be effective in treating cancer. These pathways suppress immune response and are crucial for maintaining self-tolerance, modulating the duration and amplitude of physiological immune responses in peripheral tissues, and minimizing collateral tissue damage. It is believed that tumor cells can activate the immune checkpoint signaling pathways to decrease the effectiveness of the immune response against tumor tissues. Many of these immune checkpoint signaling pathways are initiated by interactions between checkpoint proteins present on the surface of the cells participating in the immune responses, e.g., T cells, and their ligands, thus they can be readily blocked by agents or modulated by recombinant forms of the checkpoint proteins or ligands or receptors. The agents blocking the immunosuppression pathway induced by checkpoint proteins are commonly referred to as checkpoint inhibitors and a few have been commercialized. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) antibodies, blocking the immunosuppression pathway by the checkpoint protein CTLA4, were the first of this class of immunotherapeutics to achieve US Food and Drug Administration (FDA) approval. Clinical findings with blockers of additional immune-checkpoint proteins, such as programmed cell death protein 1 (PD-1), indicate broad and diverse opportunities to enhance anti-tumor immunity with the potential to produce durable clinical responses.

[0005] Glucocorticoid receptor (GR) mediated signaling pathways have dynamic biologic effects involving different components of the immune system and their in vivo effects are unpredictable. For example, glucocorticoids have been reported to have both immunosuppressive effects -- such as, suppression of proinflammatory cytokines, promotion of anti-inflammatory cytokines, inhibition of dendritic cells, suppression of natural killer cells, promotion of T-regulatory cells, and induction of T cell apoptosis, -- and immune-enhancing effects. See Hinrichs J. Immunother. 2005: 28 (6): 517-524. The effects of GR mediated signaling pathway on cancer cells is likewise elusive. On one hand, it is believed that activating the GR signaling pathways induce apoptosis in certain types of cancer cells, for example, malignant lymphoid cancers. See Schlossmacher, *J. Endocrino.* (2011). On the other hand, it has also been reported that agents blocking the GR signaling pathway can potentiate

chemotherapy in killing cancer cells. See U.S. Pat. No. 9149485. This current invention uses a novel combination therapy that targets both the checkpoint signaling pathway and GR signaling pathway to treat patients suffering from a tumor load.

SUMMARY

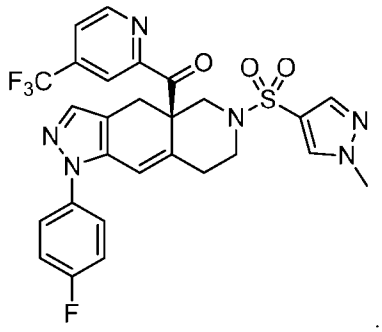
[0006] The cancer treatment method disclosed herein includes administering to a patient suffering from a tumor load a therapeutic amount of a checkpoint inhibitor and a selective glucocorticoid receptor modulator (SGRM) in an amount effective to potentiate the activity of the checkpoint inhibitor. The combination therapy of the checkpoint inhibitor and SGRM provides superior tumor load reduction compared to treatment with a checkpoint inhibitor alone.

[0007] In some cases, the checkpoint inhibitor is an antibody against at least one checkpoint protein, e.g., PD-1, CTLA-4, PD-L1 or PD-L2. In some cases, the checkpoint inhibitor is an antibody that is effective against two or more of the checkpoint proteins selected from the group of PD-1, CTLA-4, PD-L1 and PD-L2.

[0008] In some cases, the checkpoint inhibitor is a small molecule, non-protein compound that inhibits at least one checkpoint protein. In one embodiment, the checkpoint inhibitor is a small molecule, non-protein compound that inhibits a checkpoint protein selected from the group consisting of PD-1, CTLA-4, PD-L1 and PD-L2.

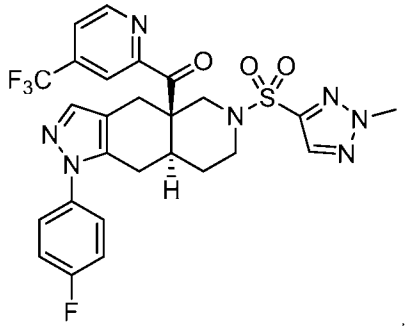
[0009] In one embodiment, the SGRM is mifepristone. In some cases, the SGRM is a compound having a non-steroidal backbone. In some cases, the SGRM is a fused azadecalin.

[0010] In some cases, the SGRM is CORT 125134, i.e., (R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone, which has the following structure:



[0011] In some cases, the SGRM is mifepristone.

[0012] In some cases, the SGRM is CORT125281, i.e., ((4aR,8aS)-1-(4-fluorophenyl)-6-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone, which has the following structure:



[0013] In one embodiment, the cancer expresses the glucocorticoid receptor (GR^+).

[0014] In some cases, the cancer is a GR^+ cancer and the cancer is selected from the group consisting of breast cancer, prostate cancer, melanoma, sarcoma, renal cell cancer, head and neck cancer, hepatocellular cancer, glioblastoma, cervical cancer, neuroendocrine cancer, bladder cancer, prostate cancer, esophageal cancer, mesothelioma, lung cancer, ovarian cancer, pancreatic cancer, gall bladder cancer, gastric cancer, endometrial cancer, and colon cancer.

[0015] In one embodiment, the checkpoint inhibitor and SGRM are co-administered. In a preferred embodiment, the SGRM is CORT125134 and the checkpoint inhibitor is an antibody against PD-1.

[0016] In some embodiments, provided herein is a SGRM for use in combination with a checkpoint inhibitor in a method of treating a patient hosting a tumor load, the method comprising administering to a patient suffering from a tumor load a therapeutic amount of a checkpoint inhibitor and a selective glucocorticoid receptor modulator (SGRM) in an amount effective to potentiate the activity of the checkpoint inhibitor. In addition, all the related embodiments described above are also included in these embodiments of the disclosure.

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