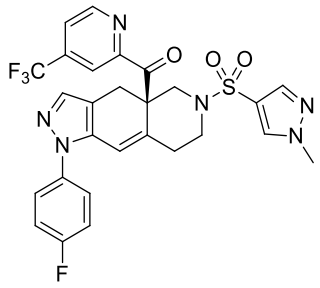
[0004] There is need in the art to provide more effective treatments for ACC, including need to enhance the effects of antibody checkpoint inhibitor treatments for patients suffering from ACC.

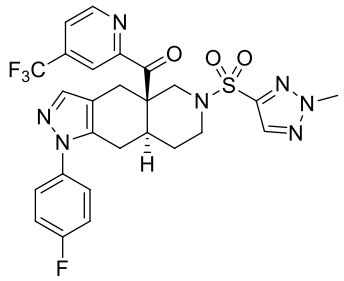
SUMMARY

[0004a] In one aspect of the present disclosure, there is provided a use of 1) a selective glucocorticoid receptor modulator (SGRM), and 2) an antibody checkpoint inhibitor in the manufacture of a medicament for use in combinatorial therapy for treating a subject suffering from adrenocortical carcinoma (ACC) tumor and having cortisol excess to a) restore T-cell and natural killer (NK) cell signaling pathways, b) increase T-cell and NK cell infiltration into said ACC tumor, and c) reduce neutrophil infiltration into the ACC tumor, wherein said SGRM is (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, also known as CORT125134 or relacorilant, which has the structure:



,

or is ((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, also known as CORT125281, which has the following structure:



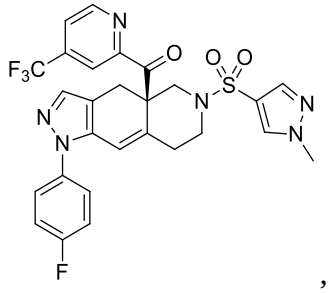
wherein said antibody checkpoint inhibitor is selected from an antibody effective against PD-1 selected from pembrolizumab, nivolumab, AMP-224, and pidilizumab; an antibody effective against CTLA-4 selected from ipilimumab and tremelimumab; and an antibody effective against PD-L1 selected from MEDI4736, atezolizumab (MPDL3280A), durvalumab, and BMS-936559; and wherein

a patient suffering from a) an adrenocortical tumor and b) suffering from glucocorticoid excess is identified;

and the antibody checkpoint inhibitor is to be administered to said identified patient;

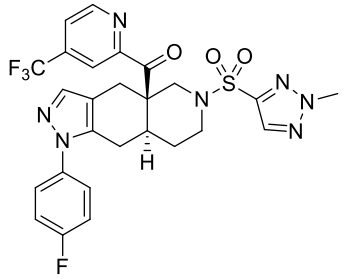
wherein a better treatment outcome from said identified patient is achieved than would be achieved by treatment with an antibody checkpoint inhibitor alone, wherein said treatment outcome is selected from a) restoration of T-cell and natural killer (NK) cell signaling pathways, b) increased T-cell and NK cell infiltration into the ACC tumor, and c) reduced neutrophil infiltration into the ACC tumor in the patient.

[0004b] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition comprising a selective glucocorticoid receptor modulator (SGRM) compound and an antibody checkpoint inhibitor effective against PD-1, CTLA-4 or PDL-1, in the manufacture of a medicament for treating adrenocortical carcinoma (ACC) tumor and having cortisol excess to a) restore T-cell and natural killer (NK) cell signaling pathways, b) increase T-cell and NK cell infiltration into said ACC tumor, and c) reduce neutrophil infiltration into the ACC tumor, wherein said SGRM is (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, also known as CORT125134 or relacorilant, which has the structure:



,

or is ((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, also known as CORT125281, which has the following structure:



wherein said antibody checkpoint inhibitor is selected from an antibody effective against PD-1 selected from pembrolizumab, nivolumab, AMP-224, and pidilizumab; an antibody effective against CTLA-4 selected from ipilimumab and tremelimumab; and an antibody effective against PD-L1 selected from MEDI4736, atezolizumab (MPDL3280A), durvalumab, and BMS-936559; and wherein

a patient suffering from a) an adrenocortical tumor and b) suffering from glucocorticoid excess is identified;

and the antibody checkpoint inhibitor is to be administered to said identified patient; wherein a better treatment outcome from said identified patient is achieved than would be achieved by treatment with an antibody checkpoint inhibitor alone, wherein said treatment outcome is selected from a) restoration of T-cell and natural killer (NK) cell signaling pathways, b) increased T-cell and NK cell infiltration into the ACC tumor, and c) reduced neutrophil infiltration into the ACC tumor in the patient.

[0005] Adrenocortical carcinoma (ACC) multi-omics were analyzed to identify the molecular consequences of glucocorticoid (GC) activity and assess the rationale for combining relacorilant, a glucocorticoid receptor (GR) antagonist, with an immune

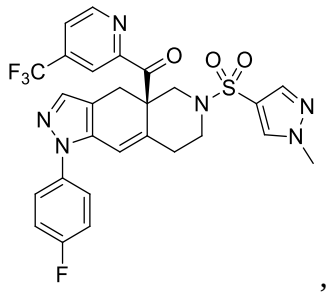
checkpoint inhibitor (ICI) in adrenocortical carcinoma with glucocorticoid excess (GC+ ACC). Applicant analyzed publicly-available data on ACC tumor gene transcription and GC excess (e.g., excess cortisol).

[0006] Treatment methods include administration of a selective glucocorticoid receptor modulator (SGRM) and an antibody checkpoint inhibitor to a patient suffering from an adrenocortical carcinoma (ACC) and having cortisol excess. A patient has cortisol excess where that patient's cortisol levels exceed the normal range, e.g., are above the upper limit of normal cortisol. In examples, cortisol excess is identified where the patient's cortisol levels are equal to or greater than about one and one half (1.5) times the normal cortisol level, or are equal to or greater than about twice (2) times the normal cortisol level. In examples, cortisol excess is identified where atypical elevations are observed in a patient's diurnal cortisol rhythm.

[0007] Effects of cortisol excess may include, for example, increased cortisol effects on immune responses in and to the tumor (e.g., immune suppression in the tumor, lymph nodes, and elsewhere). In examples, administration of a SGRM in combination with an antibody checkpoint inhibitor may be effective to reduce or reverse the effects of cortisol excess in an ACC patient with cortisol excess, and may be effective to reduce ACC tumor load in the patient. In examples, administration of a SGRM in combination with an antibody checkpoint inhibitor may be effective to reduce or reverse the effects of cortisol excess in an ACC patient with cortisol excess, and may be effective to restore T-cell and natural killer (NK) cell signaling pathways in the patient. In examples, administration of a SGRM in combination with an antibody checkpoint inhibitor may be effective to reduce or reverse the effects of cortisol excess in an ACC patient with cortisol excess, and may be effective to increase T-cell and natural killer (NK) cell infiltration into the ACC tumor in the patient. In examples, administration of a SGRM in combination with an antibody checkpoint

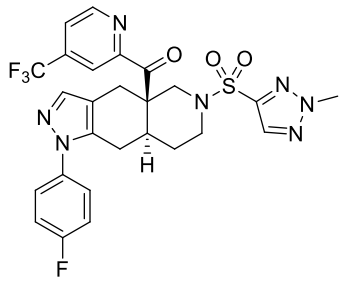
CLAIMS:

1. Use of 1) a selective glucocorticoid receptor modulator (SGRM), and 2) an antibody checkpoint inhibitor in the manufacture of a medicament for use in combinatorial therapy for treating a subject suffering from adrenocortical carcinoma (ACC) tumor and having cortisol excess to a) restore T-cell and natural killer (NK) cell signaling pathways, b) increase T-cell and NK cell infiltration into said ACC tumor, and c) reduce neutrophil infiltration into the ACC tumor, wherein said SGRM is (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, also known as CORT125134 or relacorilant, which has the structure:



,

or is ((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, also known as CORT125281, which has the following structure:



wherein said antibody checkpoint inhibitor is selected from an antibody effective against PD-1 selected from pembrolizumab, nivolumab, AMP-224, and pidilizumab; an antibody effective against CTLA-4 selected from ipilimumab and tremelimumab; and an antibody effective against PD-L1 selected from MEDI4736, atezolizumab (MPDL3280A), durvalumab, and BMS-936559; and wherein

a patient suffering from a) an adrenocortical tumor and b) suffering from glucocorticoid excess is identified;

and the antibody checkpoint inhibitor is to be administered to said identified patient;

wherein a better treatment outcome from said identified patient is achieved than would be achieved by treatment with an antibody checkpoint inhibitor alone, wherein said treatment outcome is selected from a) restoration of T-cell and natural killer (NK) cell signaling pathways, b) increased T-cell and NK cell infiltration into the ACC tumor, and c) reduced neutrophil infiltration into the ACC tumor in the patient.

2. The use of claim 1, wherein the antibody checkpoint inhibitor is selected from an antibody effective against PD-1, an antibody effective against CTLA-4 and an antibody effective against PD-L1.

3. The use of claim 2, wherein the checkpoint inhibitor is an antibody effective against PD-1.

4. The use of claim 2, wherein the checkpoint inhibitor is an antibody effective against CTLA-4.

5. The use of claim 2, wherein the checkpoint inhibitor is an antibody effective against PD-L1.

6. The use of any of claims 1-5, wherein a chemotherapeutic agent selected from the group consisting of taxanes, alkylating agents, topoisomerase inhibitors, endoplasmic reticulum stress inducing agents, antimetabolites, mitotic inhibitors and combinations thereof, is to be further administered.

7. The use of claim 6, wherein the chemotherapeutic agent is a taxane.

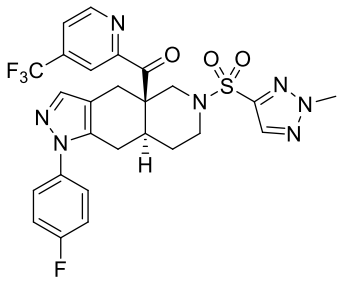
8. The use of claim 7, wherein the chemotherapeutic agent is selected from the group consisting of nab-paclitaxel, 5-fluorouracil (5-FU), gemcitabine, cisplatin and capecitabine.

9. The use of any of claims 1 to 8, wherein the SGRM is relacorilant and the checkpoint inhibitor is an antibody effective against PD-1.

10. The use of any of claims 1 to 8 wherein the SGRM is relacorilant and the checkpoint inhibitor is an antibody effective against CTLA-4.

11. The use of any of claims 1 to 8 wherein the SGRM is relacorilant and the checkpoint inhibitor is an antibody effective against PD-L1.

12. The use of claim 1, wherein the octahydro fused azadecalin SGRM is ((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, also known as CORT125281, which has the following structure:



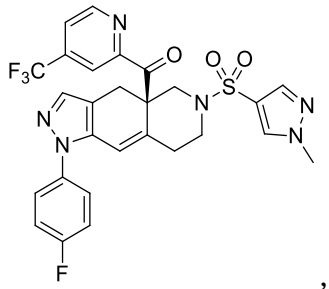
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13. The use of any of claims 1 to 8, wherein the SGRM is CORT125281 and the checkpoint inhibitor is an antibody effective against PD-1.

14. The use of any of claims 1 to 8 wherein the SGRM is CORT125281 and the checkpoint inhibitor is an antibody effective against CTLA-4.

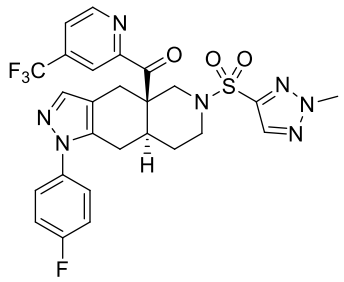
15. The use of any of claims 1 to 8 wherein the SGRM is CORT125281 and the checkpoint inhibitor is an antibody effective against PD-L1.

16. Use of a pharmaceutical composition comprising a selective glucocorticoid receptor modulator (SGRM) compound and an antibody checkpoint inhibitor effective against PD-1, CTLA-4 or PDL-1, in the manufacture of a medicament for treating adrenocortical carcinoma (ACC) tumor and having cortisol excess to a) restore T-cell and natural killer (NK) cell signaling pathways, b) increase T-cell and NK cell infiltration into said ACC tumor, and c) reduce neutrophil infiltration into the ACC tumor, wherein said SGRM is (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, also known as CORT125134 or relacorilant, which has the structure:



,

or is ((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, also known as CORT125281, which has the following structure:



wherein said antibody checkpoint inhibitor is selected from an antibody effective against PD-1 selected from pembrolizumab, nivolumab, AMP-224, and pidilizumab; an antibody effective against CTLA-4 selected from ipilimumab and tremelimumab; and an antibody effective against PD-L1 selected from MEDI4736, atezolizumab (MPDL3280A), durvalumab, and BMS-936559; and wherein

a patient suffering from a) an adrenocortical tumor and b) suffering from glucocorticoid excess is identified;

and the antibody checkpoint inhibitor is to be administered to said identified patient;

wherein a better treatment outcome from said identified patient is achieved than would be achieved by treatment with an antibody checkpoint inhibitor alone, wherein said treatment outcome is selected from a) restoration of T-cell and natural killer (NK) cell signaling pathways, b) increased T-cell and NK cell infiltration into the ACC tumor, and c) reduced neutrophil infiltration into the ACC tumor in the patient.

17. The pharmaceutical composition, pharmaceutical composition for use, or use of claim16, wherein the SGRM is relacorilant and the checkpoint inhibitor is an antibody effective against PD-L1.