[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 tumor and having cortisol excess, wherein:

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

1) the selective glucocorticoid receptor modulator (SGRM), and 2) 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) reduction in ACC tumor load, b) restoration of T-cell and natural killer (NK) cell signaling pathways, c) increased T-cell and NK cell infiltration into the ACC tumor, and d) reduced neutrophil infiltration into the ACC tumor in the patient.

[0004b] In another aspect of the present disclosure, there is provided a pharmaceutical composition for treating adrenocortical carcinoma comprising a selective glucocorticoid receptor modulator (SGRM) compound and an antibody checkpoint inhibitor effective against PD-1, CTLA-4, PDL-1 or PDL-2.

[0004c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition for use in treating adrenocortical carcinoma comprising a selective glucocorticoid receptor modulator (SGRM) compound and an antibody checkpoint inhibitor effective against PD-1, CTLA-4, PDL-1 or PDL-2.

[0004d] 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, PDL-1 or PDL-2, in the manufacture of a medicament for treating adrenocortical carcinoma.

[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 tumor and having cortisol excess, wherein:

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

1) the selective glucocorticoid receptor modulator (SGRM), and 2) 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) reduction in ACC tumor load, b) restoration of T-cell and natural killer (NK) cell signaling pathways, c) increased T-cell and NK cell infiltration into the ACC tumor, and d) 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, an antibody effective against PD-L1, and an antibody effective against PD-L2.

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.

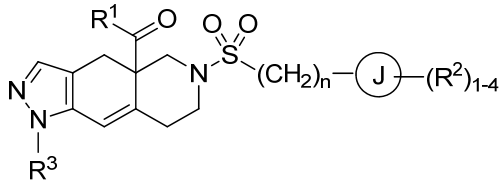
6. The use of claim 2, wherein the checkpoint inhibitor is an antibody effective against PD-L2.

7. The use of any of claims 1-6, 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.

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

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

10. The use of any of claims 1 - 9, wherein the SGRM is a heteroaryl-ketone fused azadecalin compound having the formula:



wherein

R1 is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from R1a;

each R1a is independently selected from the group consisting of hydrogen, C1-6 alkyl, halogen, C1-6 haloalkyl, C1-6 alkoxy, C1-6 haloalkoxy, CN, N-oxide, C3-8 cycloalkyl, and C3-8 heterocycloalkyl;

ring J is selected from the group consisting of a cycloalkyl ring, a heterocycloalkyl ring, an aryl ring and a heteroaryl ring, wherein the heterocycloalkyl and heteroaryl rings have from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S;

each R2 is independently selected from the group consisting of hydrogen, C1-6 alkyl, halogen, C1 6 haloalkyl, C1 6 alkoxy, C1-6 haloalkoxy, C1-6 alkyl-C1-6 alkoxy, CN, OH, NR2aR2b, C(O)R2a, C(O)OR2a, C(O)NR2aR2b, SR2a, S(O)R2a, S(O)2R2a, C3-8 cycloalkyl, and C3-8 heterocycloalkyl, wherein the heterocycloalkyl groups are optionally substituted with 1-4 R2c groups;

alternatively, two R2 groups linked to the same carbon are combined to form an oxo group (=O);

alternatively, two R2 groups are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S, wherein the heterocycloalkyl ring is optionally substituted with from 1 to 3 R2d groups;

R2a and R2b are each independently selected from the group consisting of hydrogen and C1-6 alkyl;

each R2c is independently selected from the group consisting of hydrogen, halogen, hydroxy, C1-6 alkoxy, C1-6 haloalkoxy, CN, and NR2aR2b;

each R2d is independently selected from the group consisting of hydrogen and C1-6 alkyl, or two R2d groups attached to the same ring atom are combined to form (=O);

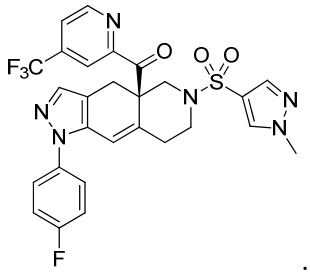
R3 is selected from the group consisting of phenyl and pyridyl, each optionally substituted with 1-4 R3a groups;

each R3a is independently selected from the group consisting of hydrogen, halogen, and C1-6 haloalkyl; and

subscript n is an integer from 0 to 3;

or salts and isomers thereof.

11. The use of claim 10, wherein the compound comprising a heteroaryl-ketone fused azadecalin is relacorilant, having the formula:



.

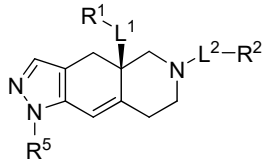
12. The use of any of claims 1 to 9, wherein the SGRM is relacorilant and the checkpoint inhibitor is an antibody effective against PD-1.

13. The use of any of claims 1 to 9 wherein the SGRM is relacorilant and the checkpoint inhibitor is an antibody effective against CTLA-4.

14. The use of any of claims 1 to 9 wherein the SGRM is relacorilant and the checkpoint inhibitor is an antibody effective against PD-L1.

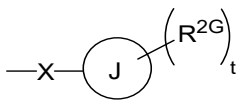
15. The use of any of claims 1 to 9 wherein the SGRM is relacorilant and the checkpoint inhibitor is an antibody effective against PDL-2.

16. The use of any of claims 1-9, wherein the SGRM is a fused azadecalin compound having the formula:



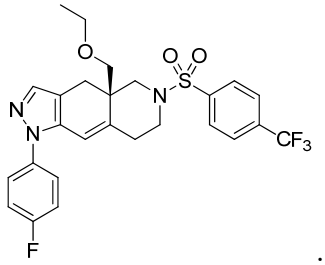
wherein L^1 and L^2 are members independently selected from a bond and unsubstituted alkylene; R^1 is a member selected from unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted heterocycloalkyl, $-OR^{1A}$, $NR^{1C}R^{1D}$, $-C(O)NR^{1C}R^{1D}$, and $-C(O)OR^{1A}$, wherein R^{1A} is a member selected from hydrogen, unsubstituted alkyl, and unsubstituted heteroalkyl; R^{1C} and R^{1D} are members independently selected from unsubstituted alkyl and unsubstituted heteroalkyl, and are optionally joined to form an unsubstituted ring with the nitrogen to

which they are attached, wherein said ring optionally comprises an additional ring nitrogen. R^2 has the formula:



wherein R2G is a member selected from hydrogen, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, -CN, and -CF3; J is phenyl; t is an integer from 0 to 5; X is -S(O2)-; and R5 is phenyl optionally substituted with 1-5 R5A groups, wherein R5A is a member selected from hydrogen, halogen, -OR5A1, S(O2)NR5A2R5A3, -CN, and unsubstituted alkyl, and R5A1 is a member selected from hydrogen and unsubstituted alkyl, and R5A2 and R5A3 are members independently selected from hydrogen and unsubstituted alkyl, or salts and isomers thereof.

17. The use of claim 16, wherein the fused azadecalin compound is (R)-(4a-ethoxymethyl-1-(4-fluorophenyl)-6-(4-trifluoromethyl-benzenesulfonyl)-4,4a,5,6,7,8-hexahydro-1H,1,2,6-triaza-cyclopenta[b]naphthalene, also known as CORT108297, which has the formula:



.

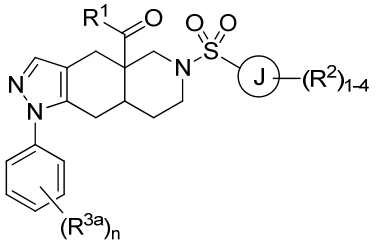
18. The use of any of claims 1 to 9, wherein the SGRM is CORT108297 and the checkpoint inhibitor is an antibody effective against PD-1.

19. The use of any of claims 1 to 9 wherein the SGRM is CORT108297 and the checkpoint inhibitor is an antibody effective against CTLA-4.

20. The use of any of claims 1 to 9 wherein the SGRM is CORT108297 and the checkpoint inhibitor is an antibody effective against PD-L1.

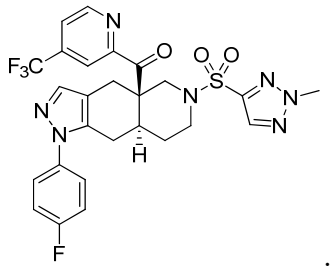
21. The use of any of claims 1 to 9 wherein the SGRM is CORT108297 and the checkpoint inhibitor is an antibody effective against PDL-2.

22. The use of any of claims 1-9, wherein the SGRM is an octahydro fused azadecalin compound having the formula:



wherein R1 is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O, and S, optionally substituted with 1-4 groups each independently selected from R1a; each R1a is independently selected from the group consisting of hydrogen, C1-6 alkyl, halogen, C1-6 haloalkyl, C1-6 alkoxy, C1-6 haloalkoxy, N-oxide, and C3-8 cycloalkyl; ring J is selected from the group consisting of an aryl ring and a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O, and S; each R2 is independently selected from the group consisting of hydrogen, C1-6 alkyl, halogen, C1-6 haloalkyl, C1-6 alkoxy, C1-6 haloalkoxy, C1-6 alkyl-C1-6 alkoxy, CN, OH, NR2aR2b, C(O)R2a, C(O)OR2a, C(O)NR2aR2b, SR2a, S(O)R2a, S(O)2R2a, C3-8 cycloalkyl, and C3-8 heterocycloalkyl having from 1 to 3 heteroatoms each independently selected from the group consisting of N, O, and S; alternatively, the two R2 groups on adjacent ring atoms are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O, and S, wherein the heterocycloalkyl ring is optionally substituted with 1-3 R2c groups; R2a, R2b, and R2c are each independently selected from the group consisting of hydrogen and C1-6 alkyl; each R3a is independently halogen; and subscript n is an integer from 0 to 3, or salts and isomers thereof.

23. The use of claim 22, 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:



.

24. The use of any of claims 1 to 9, wherein the SGRM is CORT125281 and the checkpoint inhibitor is an antibody effective against PD-1.

25. The use of any of claims 1 to 9 wherein the SGRM is CORT125281 and the checkpoint inhibitor is an antibody effective against CTLA-4.

26. The use of any of claims 1 to 9 wherein the SGRM is CORT125281 and the checkpoint inhibitor is an antibody effective against PD-L1.

27. The use of any of claims 1 to 9 wherein the SGRM is CORT125281 and the checkpoint inhibitor is an antibody effective against PDL-2.

28. A pharmaceutical composition for treating adrenocortical carcinoma comprising a selective glucocorticoid receptor modulator (SGRM) compound and an antibody checkpoint inhibitor effective against PD-1, CTLA-4, PDL-1 or PDL-2.

29. A pharmaceutical composition for use in treating adrenocortical carcinoma comprising a selective glucocorticoid receptor modulator (SGRM) compound and an antibody checkpoint inhibitor effective against PD-1, CTLA-4, PDL-1 or PDL-2.

30. Use of a pharmaceutical composition comprising a selective glucocorticoid receptor modulator (SGRM) compound and an antibody checkpoint inhibitor effective against PD-1, CTLA-4, PDL-1 or PDL-2, in the manufacture of a medicament for treating adrenocortical carcinoma.

31. The pharmaceutical composition of claim 28, pharmaceutical composition for use of claim 29, or use of claim 30, wherein the SGRM is a compound selected from a heteroaryl ketone fused azadecalin SGRM, a fused azadecalin SGRM, and an octahydro fused azadecalin SGRM.

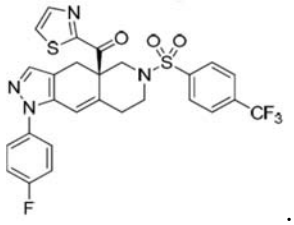
32. The pharmaceutical composition, pharmaceutical composition for use, or use of any one of claims 28 to 31, wherein the SGRM is relacorilant and the checkpoint inhibitor is an antibody effective against PD-1.

33. The pharmaceutical composition, pharmaceutical composition for use, or use of any one of claims 28 to 31, wherein the SGRM is relacorilant and the checkpoint inhibitor is an antibody effective against CTLA-4.

34. The pharmaceutical composition, pharmaceutical composition for use, or use of any one of claims 28 to 31, wherein the SGRM is relacorilant and the checkpoint inhibitor is an antibody effective against PD-L1.

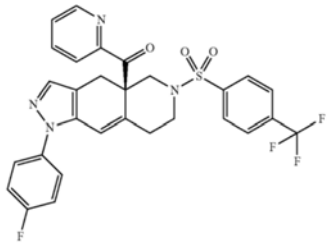
35. The pharmaceutical composition, pharmaceutical composition for use, or use of any one of claims 28 to 31, wherein the SGRM is relacorilant and the checkpoint inhibitor is an antibody effective against PDL-2.

36. The use of any of claims 1, 2 to 9, or the pharmaceutical composition, pharmaceutical composition for use, or use of any one of claims 28 to 31, wherein the SGRM is the heteroaryl-ketone fused azadecalin compound (R)-(1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(thiazol-2-yl)methanone (termed "CORT122928"), which has the following structure:



.

37. The use of any of claims 1, 2 to 9, or the pharmaceutical composition, pharmaceutical composition for use, or use of any one of claims 28 to 31, wherein the SGRM is the compound (R)-(1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl) sulfonyl)-4, 4a, 5,6,7,8-hexahydro-1-H-pyrazolo P,4-g]isoquinolin-4a-yl) (pyridin-2-yl)methanone (termed "CORT113176"), which has the following structure:



.