cancer. There is a large unmet need for effective, well-tolerated treatments for women with platinum-resistant ovarian cancer.

SUMMARY

[0008] Disclosed herein are novel methods for treating cancers, and novel uses of glucocorticoid receptor modulator (GRM) compounds, such as nonsteroidal GRMs, including heteroaryl-ketone fused azadecalin compounds, for treating cancers.

[0008a] In one aspect, there is provided the use of a glucocorticoid receptor modulator (GRM) in the manufacture of a medicament for treatment of cancer, wherein:

An effective amount of the GRM is to be intermittently administered to a patient hosting said cancer, wherein said patient is in need of, and is receiving, cancer chemotherapy treatment for said cancer, said treatment comprising a cancer chemotherapy agent to be administered according to a cancer chemotherapy dosing schedule, said dosing schedule requiring that there be at least one day without administration of said cancer chemotherapy agent between days on which the cancer chemotherapy agent is to be administered to the patient,

Wherein said intermittent administration comprises said GRM to be administered on the same day that said cancer chemotherapy agent is to be administered to the patient.

[0008b] In another aspect, there is provided the use of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a glucocorticoid-receptor modulator (GRM) in the manufacture of a medicament for treatment of cancer, wherein said cancer treatment comprises an effective amount of the GRM to be intermittently administered to a patient hosting said cancer, wherein said patient is in need of, and is receiving, cancer chemotherapy treatment for said cancer, said treatment comprising a cancer chemotherapy agent to be administered according to a cancer chemotherapy dosing schedule, said dosing schedule requiring that there be at least one day without administration of said cancer chemotherapy agent between days on which the cancer chemotherapy agent is to be administered to the patient,

Wherein said intermittent administration comprises said GRM to be administered on the same day that said cancer chemotherapy agent is to be administered to the patient.

[0009] Applicant discloses methods of treating cancer which comprise intermittently administering a GRM to a cancer patient who is receiving cancer chemotherapy. The GRM may be administered orally. The methods include intermittently administering an effective amount of

a GRM to a patient hosting a cancer, that patient being in need of, and receiving, cancer chemotherapy treatment for the cancer; the cancer chemotherapy treatment comprises administration of a cancer chemotherapy agent according to a cancer chemotherapy dosing schedule that includes at least one day without administration of the cancer chemotherapy agent between days of cancer chemotherapy agent administration. As disclosed herein, intermittent GRM administration comprises at least a first round of GRM administration and a second round of GRM administration, with at least one day without GRM administration separating the first round and the second round. The first round of GRM administration may be administration of a GRM on one day; or on two consecutive days; or on three consecutive days; or on more consecutive days. The second round of GRM administration may be administration of a GRM on one day; or on two consecutive days; or on three consecutive days; or on more consecutive days. The first round and the second round need not have the same number of days.

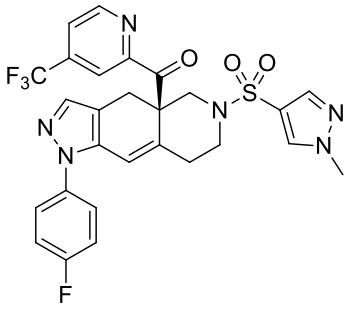
[0010] Intermittent GRM administration to a patient also receiving cancer chemotherapy may comprise administration of the GRM on days coordinated with the schedule of administration of the cancer chemotherapy. A round of GRM administration may be administered on a day related to, or may be administered on a day determined by, the cancer chemotherapy dosing schedule for the patient. For example, a round of GRM administration may be administered to the patient before, at the time of (e.g., on the same day as), or after the patient receives a dose of chemotherapy agent.

[0011] In examples, a round of GRM administration may be begun, or completed, one or more days before a day on which the patient is administered chemotherapy agent. In examples, a round of GRM administration may be begun, or completed, on a day on

which the patient is administered chemotherapy agent. In examples, a round of GRM administration may be begun, or completed, one or more days after the patient is administered chemotherapy agent.

[0012] Applicant further discloses uses of a GRM for use in treating cancer according to the methods disclosed herein. For example, such uses comprise intermittently administering the GRM to a cancer patient who is being administered a cancer chemotherapy agent on multiple days, according to a dosing schedule that requires at least one day with no administration of the cancer chemotherapy agent to the patient, between days on which the cancer chemotherapy agent is administered to the patient. Intermittent GRM administration to a patient also receiving cancer chemotherapy may comprise administration of the GRM on days coordinated with the schedule of administration of the cancer chemotherapy. In examples, intermittent GRM administration includes administration of the GRM on the same day that the cancer chemotherapy agent is administered to the patient. Intermittent GRM administration may include administration of the GRM on one or more days when the cancer chemotherapy agent is not administered to the patient. Intermittent GRM administration may include administration of the GRM on the same day that the cancer chemotherapy agent is administered to the patient, and on one or more days when the cancer chemotherapy agent is not administered to the patient.

[0013] In examples, the GRM is a nonsteroidal GRM. In examples of the methods and uses disclosed herein, the nonsteroidal GRM is a compound comprising a heteroaryl ketone fused azadecalin structure; in examples, the GRM is a heteroaryl ketone fused azadecalin structure disclosed in U.S. Patent 8,859,774 (the contents of which is are hereby incorporated by reference in its entirety). The heteroaryl-ketone fused azadecalin GRM may be relacorilant, which 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 (“relacorilant”, having the following structure:



. Relacorilant is also known as CORT125134; it is disclosed as Example 18 of U.S. 8,859,774.

[0014] Cancer chemotherapy agents, as used herein, include all anti-neoplastic agents, such as chemotoxic compounds and formulations that are typically toxic to cancer cells (and often non-cancerous cells as well), antiproliferative agents, anti-metastatic agents, and, include antibodies, checkpoint inhibitors, and other agents and treatments that inhibit, stop, or reverse the growth or spread of cancer in a cancer patient, alone or in conjunction with other agents. The cancer chemotherapy agent may be a taxane, e.g., paclitaxel or nab-paclitaxel.

[0015] Cancers which may be treated by the novel methods disclosed herein include cancers of female reproductive organs and tissues, and peritoneal cancer. Such cancers include, for example, ovarian, fallopian tube, uterine, cervical, vaginal, vulvar, and peritoneal cancers. In examples, the novel methods are directed to ovarian cancer, including platinum-resistant ovarian cancer. In examples, the novel methods are directed to cervical cancer. In examples, the novel methods are directed to uterine cancer. In examples, the novel methods are directed to fallopian tube cancer. In examples, the novel methods for treating cancers are directed to peritoneal cancer.

[0016] The new and surprising treatment methods and uses disclosed herein are believed to provide improved and effective treatments for cancer patients suffering from peritoneal cancer or cancers of female reproductive organs and tissues, including, for example, ovarian, fallopian tube, uterine, cervical, vaginal, and vulvar cancers. Results from clinical studies disclosed herein (see, e.g., Study of Relacorilant in Combination With Nab-Paclitaxel for Patients With Recurrent Platinum-Resistant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer, NCT03776812) demonstrate that these methods (comprising combined administration of taxane chemotherapy and of the GR modulator relacorilant to patients suffering from female reproductive organ cancers and patients suffering from primary peritoneal cancer) provide greater benefit than taxane chemotherapy alone. For example, intermittent administration of relacorilant with nab-paclitaxel resulted in clinically meaningful benefit without increased side effect burden as compared to nab-paclitaxel monotherapy. Such benefits included improved progression free survival (PFS), with a hazard ratio (HR) of 0.66 (P=0.038; median PFS 5.6 vs 3.8 months); improved duration of response (DoR) with a HR of 0.36 (P=0.006; median DoR 5.6 vs 3.7 months); and improved overall survival (OS) with a HR of 0.67 (P=0.066; median OS 13.9 vs 12.2 months) as compared to nab-paclitaxel monotherapy alone.

[0017] As noted above, there is a large, previously unmet need for effective, well-tolerated treatments for cancers, including platinum-resistant cancers, such as ovarian cancer, cervical

WE CLAIM:

1. Use of a glucocorticoid receptor modulator (GRM) in the manufacture of a medicament for treatment of cancer, wherein:

An effective amount of the GRM is to be intermittently administered to a patient hosting said cancer, wherein said patient is in need of, and is receiving, cancer chemotherapy treatment for said cancer, said treatment comprising of a cancer chemotherapy agent to be administered according to a cancer chemotherapy dosing schedule, said dosing schedule requiring that there be at least one day without administration of said cancer chemotherapy agent between days on which the cancer chemotherapy agent is to be administered to the patient,

Wherein said intermittent administration comprises said GRM to be administered on the same day that said cancer chemotherapy agent is to be administered to the patient.

2. The use of claim 1, wherein said cancer is a cancer selected from the group consisting of ovarian, fallopian tube, uterine, cervical, vaginal, vulvar, and peritoneal cancer.

3. The use of claim 1, wherein said cancer is ovarian cancer.

4. The use of claim 1, wherein the cancer chemotherapy agent is a taxane.

5. The use of claim 4, wherein the cancer chemotherapy agent is a taxane selected from the group of taxanes consisting of paclitaxel, nab-paclitaxel, docetaxel, larotaxel, tesetaxel, cabazitaxel, and ortataxel.

6. The use of claim 5, wherein the cancer chemotherapy agent is a taxane containing paclitaxel.

7. The use of claim 5, wherein the cancer chemotherapy agent is nab-paclitaxel.

8. The use of any of claims 1 to 7, wherein the GRM is also to be administered on the day after the cancer chemotherapy agent is to be administered to the patient.

9. The use of any of claims 1 to 7, wherein the GRM is also to be administered on the day before the cancer chemotherapy agent is to be administered to the patient.

10. The use of any of claims 1 to 9, wherein the GRM is to be administered on the day before, the day of, and the day after the cancer chemotherapy agent is to be administered to the patient.

11. The use of any of claims 1 to 10, wherein there are at least 4 days without administration of the GRM between days on which the GRM is to be administered to the patient.

12. The use of any of claims 1 to 11, wherein said cancer chemotherapy dosing schedule comprises said cancer chemotherapy agent to be administered on a first day, and again on a day seven days after said first day, without administration of said cancer chemotherapy agent on days between the first and said day seven days after said first day.

13. The use of any of claims 1 to 12, wherein said cancer chemotherapy agent is to be administered to the patient according to the cancer chemotherapy dosing schedule for three consecutive weeks.

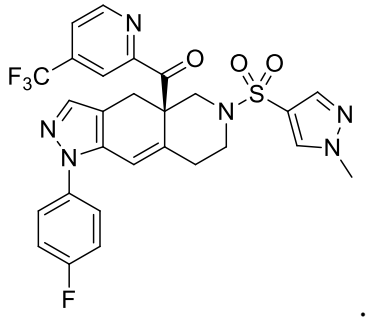
14. The use of claim 13, wherein said cancer chemotherapy agent is to be administered to the patient according to the cancer chemotherapy dosing schedule for three consecutive weeks, and then not to be administered the week following the last of said three consecutive weeks.

15. The use of claim 13 or claim 14, wherein said cancer chemotherapy agent is to be administered to the patient according to the cancer chemotherapy dosing schedule for three consecutive weeks, and then not to be administered the week following the last of said three consecutive weeks, and then said weekly dosing regimen is repeated for three further consecutive weeks.

16. The use of any of claims 1 to 15, wherein said glucocorticoid receptor modulator (GRM) is a non-steroidal GRM.

17. The use of any of claims 1 to 16, wherein said glucocorticoid receptor modulator (GRM) is a heteroaryl-ketone fused azadecalin GRM.

18. The use of any of claims 1 to 17, wherein said glucocorticoid receptor modulator (GRM) is the heteroaryl ketone fused azadecalin compound (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 ("relacorilant"), which has the following structure:



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19. The use of any of claims 1 to 18, wherein the patient has been administered bevacizumab before receiving administration of said GRM.

20. Use of a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a glucocorticoid-receptor modulator (GRM) in the manufacture of a medicament for treatment of cancer, wherein said cancer treatment comprises an effective amount of the GRM to be intermittently administered to a patient hosting said cancer, wherein said patient is in need of, and is receiving, cancer chemotherapy treatment for said cancer, said treatment comprising a cancer chemotherapy agent to be administered according to a cancer chemotherapy dosing schedule, said dosing schedule requiring that there be at least one day without administration of said cancer chemotherapy agent between days on which the cancer chemotherapy agent is to be administered to the patient,

Wherein said intermittent administration comprises said GRM to be administered on the same day that said cancer chemotherapy agent is to be administered to the patient.

21. The use of claim 20, wherein said cancer is a cancer selected from the group consisting of ovarian, fallopian tube, uterine, cervical, vaginal, vulvar, and peritoneal cancer.

22. The use of claim 20, wherein said cancer is ovarian cancer.

23. The use of claim 20, wherein the cancer chemotherapy agent is a taxane.

24. The use of claim 23, wherein the cancer chemotherapy agent is a taxane selected from the group of taxanes consisting of paclitaxel, nab-paclitaxel, docetaxel, larotaxel, tesetaxel, cabazitaxel, and ortataxel.

25. The use of claim 24, wherein the cancer chemotherapy agent is a taxane containing paclitaxel.

26. The use of claim 24, wherein the cancer chemotherapy agent is nab-paclitaxel.

27. The use of any of claims 20 to 26, wherein the GRM is also to be administered on the day after the cancer chemotherapy agent is to be administered to the patient.

28. The use of any of claims 20 to 27, wherein the GRM is also to be administered on the day before the cancer chemotherapy agent is to be administered to the patient.

29. The use of any of claims 20 to 28, wherein the GRM is to be administered on the day before, the day of, and the day after the cancer chemotherapy agent is to be administered to the patient.

30. The use of any of claims 20 to 29, wherein there are at least 4 days without administration of the GRM between days on which the GRM is to be administered to the patient.

31. The use of any of claims 20 to 30, wherein said cancer chemotherapy dosing schedule comprises said cancer chemotherapy agent to be administered on a first day, and

again on a day seven days after said first day, without administration of said cancer chemotherapy agent on days between the first and said day seven days after said first day.

32. The use of any of claims 20 to 31, wherein said cancer chemotherapy agent is to be administered to the patient according to the cancer chemotherapy dosing schedule for three consecutive weeks.

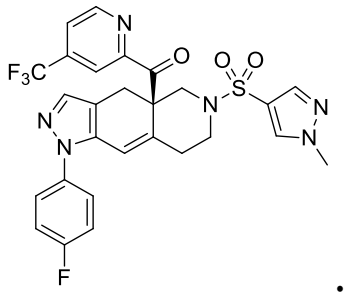
33. The use of claim 32, wherein said cancer chemotherapy agent is to be administered to the patient according to the cancer chemotherapy dosing schedule for three consecutive weeks, and then not to be administered the week following the last of said three consecutive weeks.

34. The use of claim 32 or claim 33, wherein said cancer chemotherapy agent is to be administered to the patient according to the cancer chemotherapy dosing schedule for three consecutive weeks, and then not to be administered the week following the last of said three consecutive weeks, and then said weekly dosing regimen is repeated for three further consecutive weeks.

35. The use of any of claims 20 to 34, wherein said a glucocorticoid receptor modulator (GRM) is a non-steroidal GRM.

36. The use of any of claims 20 to 35, wherein said a GRM is a heteroaryl-ketone fused azadecalin GRM.

37. The use of any of claims 20 to 36, wherein said GRM is the heteroaryl ketone fused azadecalin compound (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 ("relacorilant"), which has the following structure:



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38. The use of any of claims 20 to 37, wherein the patient has received bevacizumab.