clinical trials in patients with Cushing's syndrome and in patients with various types of cancer including ovarian cancer and pancreatic cancer.

SUMMARY

[0005a] In one aspect of the present disclosure, there is provided a use of relacorilant in the manufacture of a medicament for treating cancer in a patient, wherein the patient is to be administered:

a) an effective dose of relacorilant; and

b) an effective dose of paclitaxel, wherein said paclitaxel has a single agent dose of about 100 mg/m^2 to about 125 mg/m^2 when administered without other pharmaceutical agents, wherein said effective dose of paclitaxel is reduced by about 20% to about 35% from said single agent dose of paclitaxel when co-administered with relacorilant;

wherein a) and b) are to be administered at times effective to provide the patient with an effective level of relacorilant and an effective level of paclitaxel at the same time,

whereby the cancer is treated.

[0005b] In another aspect of the present disclosure, there is provided a use of relacorilant in the manufacture of a medicament for treating cancer in a patient, wherein the patient is to be administered:

a) an effective dose of relacorilant; and

b) an effective dose of paclitaxel, wherein said paclitaxel has a single agent dose of about 100 mg/m^2 to about 125 mg/m^2 when administered without other pharmaceutical agents, wherein said effective dose of paclitaxel is between about 60 mg/m^2 to about 95 mg/m^2 when co-administered with relacorilant;

wherein a) and b) are to be administered at times effective to provide the patient with an effective level of relacorilant and an effective level of paclitaxel at the same time,

whereby the cancer is treated.

[0006] Many therapeutic drugs are substrates of CYP2C8 enzymes, CYP3A4 enzymes, or both; an otherwise safe dose of a first drug metabolized by these CYP enzymes may be a toxic dose when concomitantly administered with a second drug that is an inhibitor of the CYP enzyme. Where a therapeutic drug's primary route of elimination is through metabolism

by both CYP2C8 and CYP3A4 enzymes, administration of a concomitant drug that inhibits of both CYP2C8 and CYP3A4 would be expected to cause a substantial increase in the plasma levels of the therapeutic drug by blocking its only elimination pathways. Co-administration with a dual inhibitor of CYP2C8 and CYP3A4 would lead to a greater magnitude of drug-drug interactions (DDIs) versus co-administration with an inhibitor of only one of the enzymes. *In vitro* studies are used to indicate drug combinations expected to suffer from such negative DDIs.

[0007] Relacorilant is believed to be useful in treating many disorders, including cancer and hypercortisolism. Relacorilant is further believed to be useful in combination treatments for cancer and in treating hypercortisolism. *In vitro* tests demonstrated that relacorilant is a potent inhibitor of CYP2C8 (IC_{50} of 0.21 μM) and a potent inhibitor of CYP3A4 (IC_{50} of 1.32 μM). Such potent dual inhibition of both CYP2C8 and CYP3A4 would be expected to increase plasma exposure of dual CYP2C8 and CYP3A4 substrates by more than five-fold when co-administered with relacorilant. Thus, it was expected that significant reductions in doses of dual CYP2C8 and CYP3A4 substrates (e.g., paclitaxel) would be required when administered in combination with relacorilant.

[0008] Upon co-administration with relacorilant such potent inhibition of both CYP2C8 and CYP3A4 by relacorilant would be expected to increase plasma exposure of paclitaxel by blocking its primary pathway of elimination through CYP2C8- and CYP3A4-mediated metabolism. Thus, it was expected that significant reductions in paclitaxel dose would be required when administered in combination with relacorilant. On the basis of relacorilant's expected effect on paclitaxel metabolism, co-administration of paclitaxel and relacorilant would have been expected to require potential reductions in paclitaxel dose by 5-fold or more when paclitaxel is administered with relacorilant.

[0009] Surprisingly, Applicant has discovered that co-administration of paclitaxel and relacorilant does not require such significant reductions in paclitaxel dose. Applicant has discovered that the plasma levels of paclitaxel are not increased by 5-fold or more, but are surprisingly only increased by about 80% (compared to the plasma levels when the same dose of paclitaxel is administered alone) when co-administered with relacorilant.

[0010] Thus, based on *in vitro* potent, dual inhibition of both CYP2C8 and CYP3A4, a significant increase of 5-fold or more in paclitaxel exposure is expected when paclitaxel is administered concomitantly with relacorilant. Surprisingly, Applicant discloses herein that relacorilant and paclitaxel may be concomitantly administered with only a small reduction in the dose of paclitaxel. Accordingly, in contrast to the expected requirement of reductions in paclitaxel dose by 5-fold or more, Applicant discloses herein that relacorilant may be safely administered along with paclitaxel, where the dose of paclitaxel is reduced by about 20% to about 35% (e.g., by about 20%, or by about 25%, or by about 30%, or by about 35%) as compared to the paclitaxel dose that is administered in the absence of relacorilant (typically about 100-125 mg/m^2). Applicant discloses herein that relacorilant may be safely administered along with paclitaxel, where the dose of paclitaxel is reduced to about 80 mg/m^2 (e.g., to about 65 mg mg/m^2, or about 70 mg/m^2, or about 75 mg/m^2, or about 80 mg/m^2, or about 85 mg/m^2, or about 90 mg/m^2, or about 95 mg/m^2) from the paclitaxel dose that is administered in the absence of relacorilant (typically about 100-125 mg/m^2). In examples, paclitaxel is administered in the form of nab-paclitaxel. Such concomitant administration of paclitaxel and relacorilant is believed to be safe for the subject and to provide the therapeutic benefits of both drugs to the subject.

[0011] The methods disclosed herein surprisingly provide safe methods for administering drug combinations and dosages that were previously expected to be unsafe, allowing safe and effective concomitant administration of paclitaxel with relacorilant. Such drug combinations are believed to provide more effective treatments than treatment with only one of the drugs in the absence of the other. The surprising ability to safely administer these drug combinations provides advantages including more effective treatments, absence of previously expected side effects, and other advantages.

CLAIMS

1. Use of relacorilant in the manufacture of a medicament for treating cancer in a patient, wherein the patient is to be administered:

a) an effective dose of relacorilant; and

b) an effective dose of paclitaxel, wherein said paclitaxel has a single agent dose of about 100 mg/m^2 to about 125 mg/m^2 when administered without other pharmaceutical agents, wherein said effective dose of paclitaxel is reduced by about 20% to about 35% from said single agent dose of paclitaxel when co-administered with relacorilant;

wherein a) and b) are to be administered at times effective to provide the patient with an effective level of relacorilant and an effective level of paclitaxel at the same time,

whereby the cancer is treated.

2. The use of claim 1, wherein said effective dose of paclitaxel is reduced from said single agent dose of paclitaxel by an amount selected from about 20%, about 25%, about 30%, and about 35%, when co-administered with relacorilant.

3. The use of claim 1, wherein said effective dose of paclitaxel is reduced from said single agent dose of paclitaxel to an effective dose of paclitaxel selected from about 72 mg/m^2, about 75 mg/m^2, about 80 mg/m^2, about 83 mg/m^2, about 88 mg/m^2, about 94 mg/m^2, and about 96 mg/m^2 of paclitaxel.

4. The use of claim 1, wherein paclitaxel is in the form of nab-paclitaxel.

5. The use of claim 1, wherein said effective dose of relacorilant is between 75 milligrams per day (mg/day) and 200 mg/day of relacorilant.

6. The use of claim 5, wherein said effective dose of relacorilant is selected from 75 mg/day, 100 mg/day, 125 mg/day, 150 mg/day, 175 mg/day, and 200 mg/day of relacorilant.

7. The use of claim 1, wherein said cancer comprises a solid tumor.

8. The use of claim 1, wherein said cancer is selected from ovarian cancer, pancreatic cancer, prostate cancer, esophageal cancer, and melanoma.

9. The use of claim 1, wherein said cancer is ovarian cancer or pancreatic cancer.

10. The use of claim 1, wherein said relacorilant is to be administered orally.

11. The use of claim 1, wherein relacorilant is to be administered every day.

12. The use of claim 1, wherein relacorilant is to be administered intermittently.

13. The use of claim 12, wherein relacorilant is to be administered the day before, the day of and the day after the paclitaxel administration.

14. The use of claim 12, wherein the doses of relacorilant and of paclitaxel are to be administered according to a 28-day schedule, wherein paclitaxel is in the form of nab-paclitaxel, and wherein the dose of nab-paclitaxel is selected from about 60 mg/m^2, about 72 mg/m^2, about 75 mg/m^2, about 80 mg/m^2, and about 83 mg/m^2 of nab-paclitaxel to be administered by intravenous infusion on days 1, 8 and 15 of each 28-day cycle.

15. The use of claim 14, wherein relacorilant is to be administered the day before, the day of and the day after nab-paclitaxel administration.

16. The use of claim 15, wherein relacorilant is to be administered the day before, the day of and the day after nab-paclitaxel administration at a dose selected from 75, mg, 100 mg, 150 mg, 175 mg, 200 mg, and 200 mg of relacorilant.

17. Use of relacorilant in the manufacture of a medicament for treating cancer in a patient, wherein the patient is to be administered:

a) an effective dose of relacorilant; and

b) an effective dose of paclitaxel, wherein said paclitaxel has a single agent dose of about 100 mg/m^2 to about 125 mg/m^2 when administered without other pharmaceutical agents, wherein said effective dose of paclitaxel is between about 60 mg/m^2 to about 95 mg/m^2 when co-administered with relacorilant;

wherein a) and b) are to be administered at times effective to provide the patient with an effective level of relacorilant and an effective level of paclitaxel at the same time,

whereby the cancer is treated.

18. The use of claim 17, wherein said paclitaxel is in the form of nab-paclitaxel.

19. The use of claim 17, wherein said effective dose of paclitaxel is selected from about 60 mg/m^2, about 65 mg/m^2, about 70 mg/m^2, about 75 mg/m^2, about 80 mg/m^2, about 85 mg/m^2, about 90 mg/m^2, and about 95 mg/m^2 of paclitaxel.

20. The use of claim 17, wherein said effective dose of relacorilant is between 75 milligrams per day (mg/day) and 200 mg/day of relacorilant.

21. The use of claim 17, wherein said effective dose of relacorilant is selected from 75 mg/day, 100 mg/day, 125 mg/day, 150 mg/day, 175 mg/day, and 200 mg/day of relacorilant.

22. The use of claim 17, wherein said cancer comprises a solid tumor.

23. The use of claim 17, wherein said cancer is selected from ovarian cancer, pancreatic cancer, prostate cancer, esophageal cancer, and melanoma.

24. The use of claim 17, wherein said cancer is ovarian cancer or pancreatic cancer.

25. The use of claim 17, wherein said relacorilant is to be administered orally.

26. The use of claim 17, wherein relacorilant is to be administered every day.

27. The use of claim 1, wherein relacorilant is to be administered intermittently.

28. The use of claim 26, wherein relacorilant is to be administered the day before, the day of and the day after the paclitaxel administration.

29. The use of claim 17, wherein paclitaxel is in the form of nab-paclitaxel, and wherein relacorilant is to be administered intermittently the day before, the day of and the day after the nab-paclitaxel administration, at a dose selected from 75, mg, 100 mg, 150 mg, 175 mg, 200 mg, and 200 mg of relacorilant.

30. The use of claim 28, wherein the doses of relacorilant and of paclitaxel are to be administered according to a 28-day schedule, wherein paclitaxel is in the form of nab-paclitaxel, wherein the dose of nab-paclitaxel is selected from about 60 mg/m^2, about 72 mg/m^2, about 75 mg/m^2, about 80 mg/m^2, and about 83 mg/m^2 of nab-paclitaxel to be administered by intravenous infusion on days 1, 8 and 15 of each 28-day cycle.