

conversion of AR inhibitors into agonists. For example, F877L point mutation in the AR-LBD has been reported to be associated with enzalutamide resistance in both pre-clinical models and clinical studies. F877L mutation is also detected in a clinically-relevant number of enzalutamide-resistant patients.

5 There is thus a need for an improved therapy for prostate cancer and a method for identification of patients that are most likely to respond to the therapy.

Summary

10 It has been found that CYP11A1 inhibitors, such as 2-(isoindolin-2-ylmethyl)-5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-4H-pyran-4-one (1A) and 5-((1-(methylsulfonyl)piperidin-4-yl)methoxy)-2-((5-(trifluoromethyl)isoindolin-2-yl)methyl)-4H-pyran-4-one (1B), are particularly effective in the treatment of prostate cancer patients having an activating AR gene alteration, for example AR gene amplification or an activating AR-LBD mutation. A patient having such activating AR gene alteration was found to have a higher probability to be responsive to the treatment with a CYP11A1 inhibitors, such as compound (1A) or (1B), than a
15 patient who is not having an activating AR gene alteration. Such activating AR gene alteration is therefore also useful as a biomarker for selecting prostate cancer patients who have a higher probability to benefit from the treatment with CYP11A1 inhibitors.

20 The present disclosure provides a method for the treatment of prostate cancer in patients having an activating AR gene alteration comprising administration to said patients a therapeutically effective amount of a CYP11A1 inhibitor.

 The present disclosure provides a CYP11A1 inhibitor for use in a method for the treatment of prostate cancer in patients having an activating AR gene alteration.

25 In one aspect, the present disclosure provides use of a CYP11A1 inhibitor in the manufacture of a medicament for the treatment of prostate cancer in a patient having an activating androgen receptor (AR) gene alteration.

In another aspect, the present disclosure provides use of a pharmaceutical composition in the manufacture of a medicament for the treatment of prostate cancer in patients having an activating AR gene alteration, wherein the pharmaceutical composition comprises a CYP11A1 inhibitor as an active ingredient and a pharmaceutically acceptable carrier.

- 5 The present disclosure provides a method for treating prostate cancer comprising
- a) obtaining or having obtained a sample from the patient;
 - b) assaying or having assayed the sample to determine whether the patient has an activating AR gene alteration; and
 - c) if the patient has an activating AR gene alteration, treating the patient with a
- 10 therapeutically effective amount of a CYP11A1 inhibitor.

In another aspect, the present disclosure provides use of a CYP11A1 inhibitor in the manufacture of a medicament for treating prostate cancer in a patient, wherein the use comprises

- a) assaying or having assayed a sample from the patient to determine whether the patient
- 15 has an activating AR gene alteration; and
- b) if the patient has an activating AR gene alteration, using the CYP11A1 inhibitor for treating the patient.

According to one example, the activating AR gene alteration is an activating AR-LBD mutation. According to another example, the activating AR gene alteration is AR gene amplification.

- 5 The present disclosure provides a method of selecting a patient suffering from prostate cancer for the treatment with a CYP11A1 inhibitor comprising
- a) obtaining or having obtained a sample from the patient;
 - b) assaying or having assayed the sample to determine whether the patient has an activating AR gene alteration; and
 - 10 c) if the patient has an activating AR gene alteration, selecting the patient for the treatment with a CYP11A1 inhibitor.

 According to one example, the activating AR gene alteration is an activating AR-LBD mutation. According to another example, the activating AR gene alteration is AR gene amplification. In at least one example, the patient selected for treatment with a CYP11A1 inhibitor is administered a therapeutically effective amount of the CYP11A1 inhibitor.

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- In another aspect, the present disclosure provides a CYP11A1 inhibitor for use in selecting a patient suffering from prostate cancer for a treatment with the CYP11A1 inhibitor comprising
- a) assaying or having assayed a sample from the patient to determine whether the patient has an activating AR gene alteration; and
 - b) if the patient has an activating AR-LBD gene alteration, selecting the patient for the treatment with a CYP11A1 inhibitor.

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The present disclosure provides a method for identifying a patient suffering from prostate cancer who is more likely to respond to a treatment comprising a CYP11A1 inhibitor, the method comprising assaying or having assayed a sample obtained from the patient to determine whether the patient has an activating AR gene alteration, wherein such alteration identifies the patient as being more likely to respond to the treatment. In at least one example, the patient selected for treatment with a CYP11A1 inhibitor is administered a therapeutically effective amount of the CYP11A1 inhibitor.

In another aspect, the present disclosure provides a CYP11A1 inhibitor for use in identifying a patient suffering from prostate cancer who is more likely to respond to a treatment comprising a CYP11A1 inhibitor, the use comprising assaying or having assayed a sample obtained from the patient to determine whether the patient has an activating AR gene alteration, wherein such alteration identifies the patient as being more likely to respond to the treatment.

Brief description of the drawings

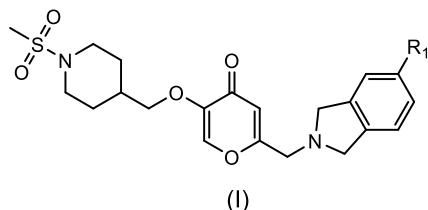
FIG. 1 shows the prostate-specific antigen (PSA) change from baseline (%) with or without identified activating AR gene alteration(s) in 37 prostate cancer patients with prior ARSi treatment.

FIG. 2 shows the PSA change from baseline (%) in 16 patients with activating AR-LBD mutation with the identity of mutation(s) in each patient shown.

Claims

1. Use of a CYP11A1 inhibitor in the manufacture of a medicament for the treatment of prostate cancer in a patient having an activating androgen receptor (AR) gene alteration.

2. The use according to claim 1, wherein the CYP11A1 inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt thereof



wherein R₁ is hydrogen or -CF₃.

3. The use according to claim 2, wherein R₁ is hydrogen.

4. The use according to claim 2, wherein R₁ is -CF₃.

5. The use according to any one of claims 1 to 4, wherein the patient having an activating AR gene alteration has a higher probability to be responsive to the treatment than the patient who does not have an activating AR gene alteration.

6. The use according to any one of claims 1 to 5, wherein the activating AR gene alteration is an AR gene amplification, optionally

the activating AR gene alteration is an activating AR-LBD mutation, optionally

the activating AR-LBD mutation is an activating AR-LBD point mutation, optionally

the activating AR-LBD point mutation is selected from the group consisting of Q671R,

I673T, L702H, V716M, V716L, K718E, R727L, V731M, W742L, W742C, A749T, A749V, M750I, G751S, V758A, S783N, Q799E, R847G, E873Q, H875Y, H875Q, F877L, T878A, T878S, D880E, L882I, S889G, D891N, D891H, D891Y, E894K, M896T, M896V, A897T, E898G, K911R, T919S and Q920R.

7. The use according to claim 6, wherein the patient has one or more of the activating AR-LBD point mutations selected from the group consisting of L702H, V716M, V716L, W742L, W742C, H875Y, F877L, T878A, T878S, D891Y, M896T and M896V, optionally

the patient has one or more of the activating AR-LBD point mutations selected from the group consisting of L702H, V716M, V716L, W742C, H875Y, F877L, T878A, D891Y and M896T.

8. The use according to any one of claims 1 to 7 wherein the patient has previously received therapy with an androgen receptor antagonist or a CYP17A1 inhibitor, optionally the patient has previously received therapy with enzalutamide or abiraterone acetate or a pharmaceutically acceptable salt thereof.

9. The use according to any one of claims 1 to 8 wherein the patient is resistant to androgen receptor antagonist therapy or a CYP17A1 inhibitor therapy, optionally the patient is resistant to treatment with enzalutamide or abiraterone acetate or a pharmaceutically acceptable salt thereof.

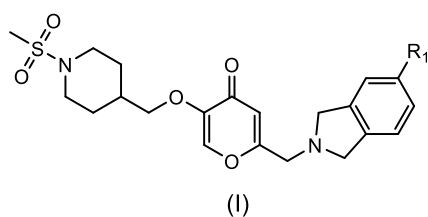
10. The use according to any one of claims 1 to 9 wherein the prostate cancer to be treated is castration resistant prostate cancer (CRPC), optionally the prostate cancer to be treated is metastatic castration resistant prostate cancer (mCRPC).

11. Use of a CYP11A1 inhibitor in the manufacture of a medicament for treating prostate cancer in a patient, wherein the use comprises

a) assaying or having assayed a sample from the patient to determine whether the patient has an activating AR gene alteration; and

b) if the patient has an activating AR gene alteration, using the CYP11A1 inhibitor for treating the patient.

12. The use according to claim 11, wherein the CYP11A1 inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt thereof



wherein R₁ is hydrogen or -CF₃.

13. The use according to claim 12, wherein R₁ is hydrogen.

14. The use according to claim 12, wherein R₁ is -CF₃.

15. The use according to any of claims 11 to 14, wherein the patient having an activating AR gene alteration has a higher probability to be responsive to the treatment than a patient who does not have an activating AR gene alteration.

16. The use according to any one of claims 11 to 15, wherein the activating AR gene alteration is an AR gene amplification, optionally
the activating AR gene alteration is an activating AR-LBD mutation, optionally,
the sample comprises AR or a portion thereof from the patient.

17. The use according to any one of claims 11 to 16, wherein the sample comprises a polynucleotide encoding AR or a portion thereof from the patient, optionally
the use comprises determining the sequence of the AR-LBD polynucleotide or a portion thereof from the patient.

18. The use according to claim 17, comprising subjecting the sample to a gene panel assay targeting the AR-LBD region designed to hybrid-capture known AR-LBD alterations.

19. The use according to any one of claims 11 to 18, wherein the prostate cancer to be treated is castration resistant prostate cancer (CRPC), optionally

the prostate cancer to be treated is metastatic castration resistant prostate cancer (mCRPC), optionally

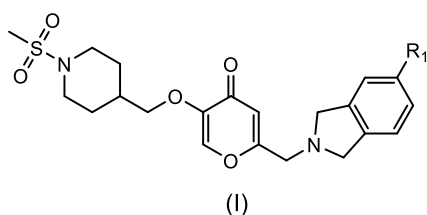
the prostate cancer to be treated is castration sensitive prostate cancer (CSPC), optionally
the prostate cancer to be treated is metastatic castration sensitive prostate cancer (mCSPC).

20. A CYP11A1 inhibitor for use in selecting a patient suffering from prostate cancer for a treatment with the CYP11A1 inhibitor comprising

a) assaying or having assayed a sample from the patient to determine whether the patient has an activating AR gene alteration; and

b) if the patient has an activating AR-LBD gene alteration, selecting the patient for the treatment with a CYP11A1 inhibitor.

21. The CYP11A1 inhibitor for use according to claim 20, wherein the CYP11A1 inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt thereof



wherein R_1 is hydrogen or $-CF_3$.

22. The CYP11A1 inhibitor for use according to claim 21, wherein R_1 is hydrogen.

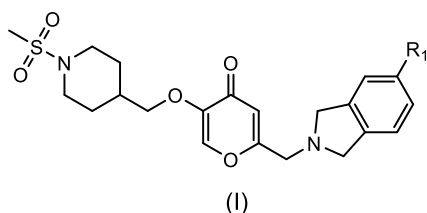
23. The CYP11A1 inhibitor for use according to claim 21, wherein R_1 is $-CF_3$.

24. The CYP11A1 inhibitor for use according to any one of claim 20 to 23, wherein the patient having an activating AR gene alteration has a higher probability to be responsive to the treatment than a patient who does not have an activating AR gene alteration.

25. The CYP11A1 inhibitor for use according to any one of claims 20 to 24, wherein the patient suffers from castration resistant prostate cancer (CRPC), optionally the patient suffers from metastatic castration resistant prostate cancer (mCRPC), optionally the patient suffers from castration sensitive prostate cancer (CSPC), optionally the patient suffers from metastatic castration sensitive prostate cancer (mCSPC).

26. A CYP11A1 inhibitor for use in identifying a patient suffering from prostate cancer who is more likely to respond to a treatment comprising a CYP11A1 inhibitor, the use comprising assaying or having assayed a sample obtained from the patient to determine whether the patient has an activating AR gene alteration, wherein such alteration identifies the patient as being more likely to respond to the treatment.

27. The CYP11A1 inhibitor for use according to claim 26, wherein the CYP11A1 inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt thereof



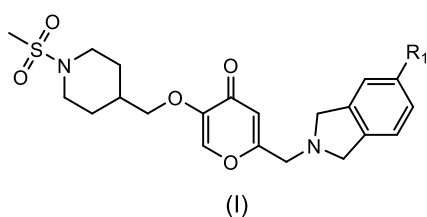
wherein R_1 is hydrogen or $-CF_3$.

28. The CYP11A1 inhibitor for use according to claim 27, wherein R_1 is hydrogen.

29. The CYP11A1 inhibitor for use according to claim 27, wherein R_1 is $-CF_3$.

30. Use of a pharmaceutical composition in the manufacture of a medicament for the treatment of prostate cancer in patients having an activating AR gene alteration, wherein the pharmaceutical composition comprises a CYP11A1 inhibitor as an active ingredient and a pharmaceutically acceptable carrier.

31. The use according to claim 30, wherein the CYP11A1 inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt thereof



wherein R_1 is hydrogen or $-CF_3$.

32. The use according to claim 31, wherein R_1 is hydrogen.

33. The use according to claim 31, wherein R_1 is $-CF_3$.

34. The use according to any one of claims 31 to 33, wherein the patient having an activating AR gene alteration has a higher probability to be responsive to the treatment with a CYP11A1 inhibitor than a patient who does not have an activating AR gene alteration.