Methods of treating cancer using a combination of SERD Dosing Regimens

Cross Reference

This application incorporates by reference U.S. Provisional Application number 63/158,688, filed March 9, 2021, in its entirety, for all purposes.

Field

This disclosure is directed to the fields of cancer treatment.

Background

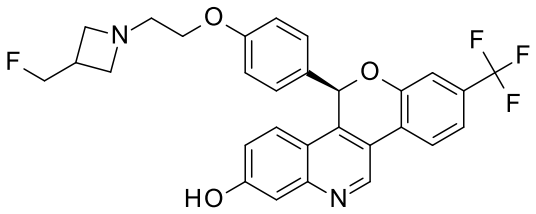
Selective estrogen receptor degraders (SERDs) bind to the estrogen receptor (ER) and downregulate ER-mediated transcriptional activity. This degradation and downregulation caused by SERDs can be useful in the treatment of cell proliferation disorders, such as cancer.

Drug development is unpredictable. It is common for new molecules to fail in preclinical and/or clinical stages, often for little understood reasons. Dosing is an added complexity that drives further unpredictability. Not all drug dosing regimens are equally active in all patient populations due to various factors, including but not limited to, body weight, performance status, number of prior systemic therapies, genetics, and histological tumor type. Toxicity issues introduce additional complexities. Efficacy and toxicity must be balanced. Additionally, it is not always possible to predict which patients will achieve therapeutic serum levels fast enough to receive benefit before disease progression. Administering a loading dose seeks to provide possible remediation of early progression in the previously non-responding subpopulation without resulting in toxicological barriers for that population or the previously responding population.

There remains a need to provide alternative treatment therapies for patients suffering from cancer. In addition, there remains a need to provide alternative treatment therapies that possess better tolerability profiles, or to provide alternative therapies that allow for maximum activity with limited adverse events and fewer dose interruptions or discontinuations. There remains a need for potent anti-estrogen treatments that antagonize and degrade ER with clinically relevant activity and bioavailability. (Shagufta, et al., Recent progress in selective estrogen receptor down regulators (SERDs) for the treatment of breast cancer, RSC Med. Chem., 2020,11, 438-454.)

Summary

In an aspect of the present disclosure, there is provided a use of a compound of Formula I:



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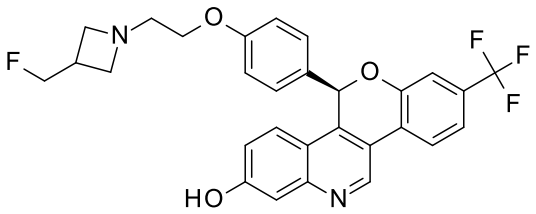
or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a patient in need of such treatment, wherein the compound or salt is to be administered to the patient at a dose between about 200 mg and about 400 mg, at least once a day for at least one week.

In another aspect of the present disclosure, there is provided a use of a compound of Formula I:



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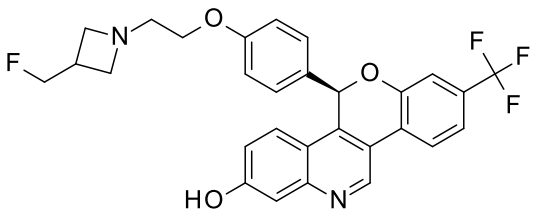
or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a patient, wherein the compound, or pharmaceutically acceptable salt thereof, is to be administered to the patient at a dose between about 200 mg and about 800 mg at least once a day for at least a week.

In a further aspect of the present disclosure, there is provided a use of a compound of Formula I:



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or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a patient, wherein the compound or salt is to be used in simultaneous, separate or sequential combination with a second therapeutic and a third therapeutic, wherein the second therapeutic and the third therapeutic are different and wherein the compound, or pharmaceutically acceptable salt thereof, is to be administered to the patient at a dose of between about 200 mg and about 400 mg at least once a day for at least one week.

In another aspect of the present disclosure, there is provided a use of a compound which is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-

chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1) in the manufacture of a medicament for treating ER+, HER2-negative breast cancer in a patient, wherein the compound is to be used in simultaneous, separate or sequential combination with pertuzumab and trastuzumab.

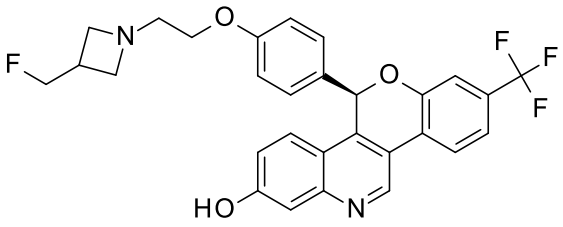
In a further aspect of the present disclosure, there is provided a use of a compound which is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1) in the manufacture of a medicament for treating ER+, HER2- negative breast cancer in a patient, wherein the compound is to be used in simultaneous, separate or sequential combination with abemaciclib, wherein the compound is to be administered to the patient at a dose of about 400 mg.

In another aspect of the present disclosure, there is provided a use of (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1), pertuzumab and trastuzumab in the manufacture of a medicament for treating ER+, HER2- cancer.

In a further aspect of the present disclosure, there is provided a use of (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1) and abemaciclib in the manufacture of a medicament for treating HR+ and ER+ cancer in a patient, wherein about 400 mg of the (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1) and abemaciclib are to be administered to the patient, wherein the cancer is selected from the group consisting of HER2- positive breast cancer, HER2-negative breast cancer and endometrioid endometrial cancer (EEC).

The present disclosure relates to new dosing protocols that use (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, hereafter known as Formula I, or a pharmaceutically acceptable salt thereof, as part of an adjuvant therapy, to treat cancer.

The compound of Formula I has the following structure:



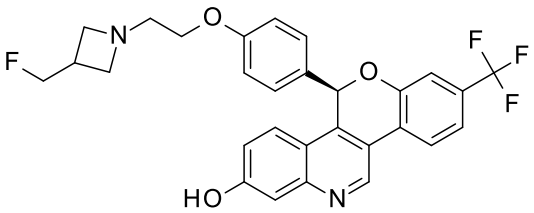
or pharmaceutically acceptable salt thereof.

This compound may be prepared as a free base or a pharmaceutically acceptable salt thereof , using the synthetic steps described in WO20/014435 or US10,654,866. This compound is known by the tradename "imlunestrant."

The compound of Formula I is an orally bioavailable, selective SERD. It is a potent degrader and selective antagonist of wild-type and mutant estrogen receptor α (ERα or ESR1). It would be useful to develop new treatment regimens and dosing protocols that use the compound of Formula I, in combination with one or more other therapeutic agents, in conjunction with surgery, or in combination with one or more other therapeutic agents and in conjunction with surgery, as part of an adjuvant therapy, to treat cancer.

Disclosed herein are dosing protocols that use the compound of Formula I to treat cancer. The protocols may be monotherapy or adjuvant therapy.

In an example, the dosing protocols comprise methods of treating a cancer comprising: administering a dose between about 200 mg and about 800 mg of a compound of Formula I:



or pharmaceutically acceptable salt thereof, to a patient in need of such treatment, at least once a day.

In another example, the dosing protocols comprise methods of treating a cancer comprising:

administering a dose between about 200 mg and about 400 mg of a compound of Formula I:

or pharmaceutically acceptable salt thereof, to a patient in need of such treatment, at least once a day for at least one week.

In an example, the dosing protocols comprise methods of treating a cancer comprising:

administering a dose of about 200 mg of the compound of Formula I or pharmaceutically acceptable salt thereof, at least once a day, to a patient in need of such treatment, for at least about one week and then increasing the dose to about 300 mg or about 400 mg at least once a day.

In an example, the dosing protocols comprise methods of treating a cancer comprising: administering a dose of about 200 mg of the compound of Formula I or pharmaceutically acceptable salt thereof,

at least once a day, to a patient in need of such treatment, for about two weeks to about six months, and then increasing the dose to about 300 mg at least once a day, for at least 21 days.

In an example, the dosing protocols comprise methods of treating a cancer comprising: administering a dose of about 200 mg of the compound of Formula I or pharmaceutically acceptable salt thereof, at least once a day, to a patient in need of such treatment, for about two weeks to about six months, and then increasing the dose to about 400 mg at least once a day, for at least 21 days.

In another example, the dosing protocols comprise methods of treating a cancer comprising administering a dose of about 400 mg of the compound of Formula I:
or pharmaceutically acceptable salt thereof, at least once a day, to a patient in need of such treatment.

In an example, the dosing protocols comprise methods of treating breast cancer, the methods comprising administering a dose of about 400 mg of the compound of Formula I or pharmaceutically acceptable salt thereof, at least once a day, to a patient in need of such treatment.

In an example, the dosing protocols comprise methods of treating breast cancer, the methods comprising administering a dose of about 400 mg of the compound of Formula I or pharmaceutically acceptable salt thereof,

at least once a day, to a patient in need of such treatment, for at least about one week to about six months, and then decreasing the dose to about 200 mg at least once a day.

In an example, the dosing protocols comprise methods of treating a cancer comprising administering a dose of about 400 mg of the compound of Formula I or pharmaceutically acceptable salt thereof, at least once a day, to a patient in need of such treatment, for about two weeks to about six months, and then decreasing the dose to about 200 mg at least once a day for at least 21 days.

In an example, the dosing protocols comprise methods of treating a cancer comprising administering the compound of Formula I or pharmaceutically acceptable salt thereof, in combination with a second therapeutic agent for the treatment of a cancer in a patient, the cancer selected from the group consisting of: breast cancer including metastatic breast cancer (mBC), advanced breast cancer, ovarian cancer, endometrial cancer, including endometrioid endometrial cancer (EEC), prostate cancer, uterine cancer, gastric cancer, and lung cancer, wherein the compound of Formula I or a pharmaceutically acceptable salt thereof is administered at a dose between about 200 mg and about 400 mg.

In an example, the dosing protocols comprise methods of treating a cancer comprising administering a dose of about 400 mg of the compound of Formula I or pharmaceutically acceptable salt thereof, at least once a day, to a patient in need of such treatment.

In an example, disclosed herein is a method of treating a cancer comprising: administering a dose between about 200 mg and about 400 mg of a compound of Formula I or pharmaceutically acceptable salt thereof, a second therapeutic, and a third therapeutic, wherein the second therapeutic and the third therapeutic are different, to a patient in need of such treatment, at least once a day for at least one week.

In an example, disclosed herein is a method of treating breast cancer, the method comprising administering a dose of about 400 mg of the compound of Formula I or pharmaceutically acceptable salt thereof, at least once a day, to a patient in need of such treatment.

In an example, the dosing protocols comprise methods of treating ER+, HER2-negative breast cancer, the method comprising administering (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1), pertuzumab and trastuzumab.

In another example, the dosing protocols comprise methods of treating ER+, HER2-positive breast cancer, the method comprising administering (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1), pertuzumab and trastuzumab.

In an example, the dosing protocols comprise methods of treating ER+, HER2-negative breast cancer, the method comprising administering 400 mg of (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1), 6 mg/kg of pertuzumab (Q21D) and 420 mg trastuzumab (Q21D), where Q21D means every 21 days.

In another example, the dosing protocols comprise methods of treating ER+, HER2-positive breast cancer, the method comprising administering (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1), 6 mg/kg of pertuzumab (Q21D) and 420 mg trastuzumab (Q21D).

In an example, the dosing protocols comprise methods of treating ER+, HER2-negative breast cancer, the method comprising administering about 400 mg at least once a day of (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1), and abemaciclib.

In an example, the dosing protocols comprise a compound of Formula I or pharmaceutically acceptable salt thereof, for use in treating cancer, wherein the compound, or pharmaceutically acceptable salt thereof, is administered to a patient at a dose between about 200 mg and about 800 mg at least once a day for at least a week.

In another example, the dosing protocols comprise a compound of Formula I or pharmaceutically acceptable salt thereof for use in treating cancer, wherein the compound, or pharmaceutically acceptable salt thereof, is administered to a patient at a dose of about 200 mg at least once a day for about two weeks to about six months, and then the dose is increased to about 300 mg at least once a day for at least 21 days.

In an example, the dosing protocols comprising a compound of Formula I or pharmaceutically acceptable salt thereof, for use in treating cancer, wherein the compound, or pharmaceutically acceptable salt thereof, is administered to a patient at a dose of about 200 mg at least once a day for about two weeks to about six months, and then the dose is increased to about 400 mg at least once a day for at least 21 days. In an example, the dosing protocols comprisea compound of Formula I or pharmaceutically acceptable salt thereof, for use in treating cancer, wherein the compound, or pharmaceutically acceptable compound, is administered to a patient at a dose of about 200 mg at least once a day for about two weeks to about six months, and then the dose is increased to about 400 mg at least once a day for at least 21 days.

In an example, the dosing protocols comprise a compound of Formula I or pharmaceutically acceptable salt thereof, for use in treating cancer, wherein the compound, or pharmaceutically acceptable compound, is administered to a patient at a dose of about 400 mg at least once a day.

In an example, the dosing protocols comprise a compound of Formula I or pharmaceutically acceptable salt thereof, for use in treating cancer, wherein the compound, or

pharmaceutically acceptable compound, is administered to a patient at a dose of about 400 mg at least once a day for about two weeks to about six months, and then the dose is decreased to about 200 mg at least once a day for at least 21 days.

In an example, the dosing protocols comprise a compound of Formula I or pharmaceutically acceptable salt thereof, for use in simultaneous, separate or sequential combination with a second therapeutic in treating cancer in a patient, wherein the compound, or pharmaceutically acceptable salt thereof, is administered at a dose of between about 200 mg and about 400 mg at least once a day for at least one week.

In an example, the dosing protocols comprise a compound of Formula I or pharmaceutically acceptable salt thereof, for use in simultaneous, separate or sequential combination with a second therapeutic and a third therapeutic in treating cancer in a patient, wherein the second therapeutic and the third therapeutic are different and wherein the compound, or pharmaceutically acceptable salt thereof, is administered at a dose of between about 200 mg and about 400 mg at least once a day for at least one week.

In an example, the dosing protocols comprise a compound of Formula I or pharmaceutically acceptable salt thereof, for use in simultaneous, separate or sequential combination with a second therapeutic in treating cancer in a patient, wherein the cancer is selected from the group consisting of: breast cancer including metastatic breast cancer (mBC) and advanced breast cancer, ovarian cancer, endometrial cancer, including endometrioid endometrial cancer (EEC), prostate cancer, uterine cancer, gastric cancer, and lung cancer, the compound or pharmaceutically acceptable salt thereof is administered at a dose between about 200 mg and about 400 mg.

In an example, disclosed herein is a compound of Formula I or pharmaceutically acceptable salt thereof, for use in treating cancer in a patient, wherein the compound, or pharmaceutically acceptable salt thereof, is administered at a dose of about 400 mg at least once a day. In an example, the breast cancer is ER+, HER2-, metastatic breast cancer. In another example, the breast cancer is ER+, HER2-, advanced breast cancer.

In an example, the dosing protocols comprise a compound which is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1) for use in simultaneous, separate or sequential combination with pertuzumab and trastuzumab for treating ER+, HER2- negative breast cancer.

In an example, the dosing protocols comprise a compound which is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-

c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1) for use in simultaneous, separate or sequential combination with pertuzumab and trastuzumab for treating ER+, HER2- positive breast cancer.

In an example, the dosing protocols comprise a compound which is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1) for use in simultaneous, separate or sequential combination with abemaciclib for treating ER+, HER2- negative breast cancer, wherein the compound is administered at a dose of about 400 mg. In an example, the compound is administered at a dose of about 200 mg. In another example, the compound is administered at a dose of about 300 mg.

The protocols use the compound of Formula I or a pharmaceutically acceptable salt thereof in combination with one or more other therapeutic agents, in conjunction with surgery, or in combination with both one or more other therapeutic agents and in conjunction with surgery, in adjuvant therapy. In an example, the compound of Formula I or a pharmaceutically acceptable salt thereof is administered for at least a week, prior to surgery. In an alternate example, the compound of Formula I or a pharmaceutically acceptable salt thereof is administered for at least a week, after surgery. In another example, the compound of Formula I or a pharmaceutically acceptable salt thereof is administered for at least a week, prior to surgery and for at least a week, after surgery. Preferably, the compound is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1).

In one example, disclosed herein is a method of treating a cancer comprising: administering a dose between about 200 mg and about 400 mg of a compound of Formula I or a pharmaceutically acceptable salt thereof to a patient in need of such treatment, at least once a day for at least one week.

Preferably, the pharmaceutically acceptable salt of the compound of Formula I is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1).

In another example, disclosed herein is a method of treating cancer, the method comprising: administering a dose of about 200 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof at least once a day, to a patient in need of such treatment, for about two weeks to about six months, and then increasing the dose to about 300 mg at least once a day, for at least 14 days or at least 21 days or at least 28 days. Preferably,

the compound is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1).

In still another example, disclosed herein is a method of treating cancer, the method comprising: administering a dose of about 200 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof at least once a day, to a patient in need of such treatment, for about two weeks to about six months, and then increasing the dose to about 400 mg at least once a day, for at least 14 days, or at least 21 days, or at least 28 days. Preferably, the compound is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1).

In yet another example, disclosed herein is a method of treating cancer, the method comprising: administering a dose of about 400 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof at least once a day, to a patient in need of such treatment, for about two weeks to about six months, and then decreasing the dose to about 200 mg at least once a day for at least 14 days, or at least 21 days, or at least 28 days. Preferably, the compound is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1).

In a further example, disclosed herein is the use of a compound of Formula I or a pharmaceutically acceptable salt thereof to treat cancer, the use comprising administering about 200 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof at least once a day, to a patient in need of such treatment, for about two weeks to about six months, and then increasing the dose to about 400 mg at least once a day, for at least 14 days or at least 21 days or at least 28 days. Preferably, the compound is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1).

In a still further example, disclosed herein is the use of a compound of Formula I or a pharmaceutically acceptable salt thereof to treat cancer, the use comprising administering about 400 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof at least once a day, to a patient in need of such treatment, for about two weeks to about six months, and then decreasing the dose to about 200 mg at least once a day for at least 14 days or at least 21 days or at least 28 days. Preferably, the compound is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1).

In a yet still further example, disclosed herein is the use of the compound of Formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating

cancer, wherein the medicament comprises about 200 mg to about 400 mg of the compound or salt thereof, and the medicament is administered at least once a day for at least one week. Preferably, the compound is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1).

In an example, the dosing protocols comprise a compound which is 400 mg of (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1), for use in simultaneous, separate or sequential combination with 6 mg/kg of pertuzumab (Q21D) and 420 mg trastuzumab (Q21D), for treating ER+, HER2-negative breast cancer, where Q21D means every 21 days.

In an example, the dosing protocols comprise a compound which is 400 mg of (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1), for use in simultaneous, separate or sequential combination with 6 mg/kg of pertuzumab (Q21D) and 420 mg trastuzumab (Q21D), for treating ER+, HER2-positive breast cancer, where Q21D means every 21 days.

In an example, the compound of Formula I or pharmaceutically acceptable salt thereof is administered for about two weeks, to a patient having ER-positive, human epidermal growth factor receptor 2 negative (HER2-negative) early stage (stage I-III) breast cancer. Preferably, the compound is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1).

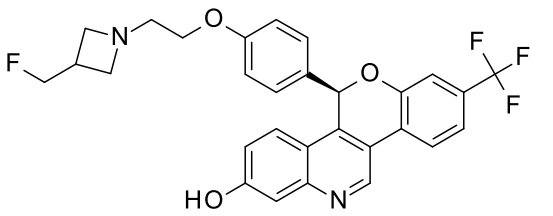
In an example, disclosed herein are methods of treating a cancer comprising: administering a dose between about 200 mg and about 400 mg of a compound of Formula I or pharmaceutically acceptable salt thereof, a second therapeutic, and a third therapeutic, wherein the second therapeutic and the third therapeutic are different, to a patient in need of such treatment, at least once a day for at least one week. In all examples, a preferred pharmaceutically acceptable salt of the compound of Formula I is the tosylate salt, i.e., the 4-methylbenezenesulfonic acid salt.

Brief Description of the Figures

Figure 1 is a chart showing mean (+Standard Deviation) total plasma concentration time profiles on Day 15 of a clinical trial dose escalation study following multiple oral doses of (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1) within the range of 200 mg to 1200 mg QD.

Claims

1. Use of a compound of Formula I:



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or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a patient in need of such treatment, wherein the compound or salt is to be administered to the patient at a dose between about 200 mg and about 400 mg, at least once a day for at least one week.

2. The use of claim 1, wherein the pharmaceutically acceptable salt is the tosylate salt.

3. The use of claim 1 or 2, wherein the dose is about 200 mg, about 300 mg, or about 400 mg.

4. The use of claim 1, wherein the dose is about 400 mg.

5. The use of any one of claims 1-4, wherein the patient has been identified or diagnosed as having a cancer selected from the group consisting of: breast cancer, ovarian cancer, endometrial cancer, prostate cancer, uterine cancer, gastric cancer, and lung cancer.

6. The use of any one of claims 1-5, wherein the cancer is HR-positive.

7. The use of claim 6, wherein the HR-positive cancer is ER-positive and HER2-negative.

8. The use of claim 6, wherein the HR-positive cancer is ER-positive and HER2-positive.

9. The use of any one of claims 1-8, wherein the cancer is metastatic breast cancer (mBC).

10. The use of any one of claims 1-8, wherein the cancer is advanced breast cancer.

11. The use of any one of claims 1-8, wherein the cancer is endometrioid endometrial cancer (EEC).

12. The use according to any one of claims 1-11, wherein a second therapeutic agent is to be further administered to the patient.

13. The use of claim 12, wherein the second therapeutic agent is selected from the group consisting of: abemaciclib, an aromatase inhibitor, everolimus, alpelisib, trastuzumab, and pertuzumab.

14. The use of claim 13 wherein the aromatase inhibitor is selected from the group consisting of: anastrozole, exemestane, and letrozole.

15. The use of claim 12 or 13, wherein the second therapeutic agent is abemaciclib.

16. The use of claim 12 or 13, wherein the second therapeutic agent is trastuzumab.

17. The use according to any one of claims 12-16, wherein the compound of Formula I or pharmaceutically acceptable salt thereof and second therapeutic agent are to be administered with a third therapeutic agent.

18. The use according to claim 17, wherein the third therapeutic agent is selected from the group consisting of: an aromatase inhibitor, everolimus, alpelisib, trastuzumab, and pertuzumab and wherein the third therapeutic agent differs from the second therapeutic agent.

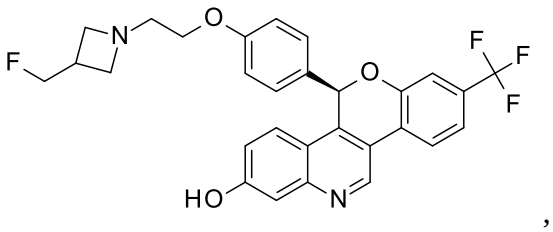
19. The use of claim 18, wherein the third therapeutic agent is selected from the group consisting of an aromatase inhibitor and trastuzumab.

20. The use of claim 18, wherein the aromatase inhibitor is selected from the group consisting of anastrozole, exemestane, and letrozole.

21. The use of claim 17, wherein the third therapeutic agent is an antidiarrheal agent.

22. The use of claim 17 or 18, wherein the third therapeutic agent is pertuzumab.

23. Use of a compound of Formula I:



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or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a patient, wherein the compound, or pharmaceutically acceptable salt thereof, is to be administered to the patient at a dose between about 200 mg and about 800 mg at least once a day for at least a week.

24. The use according to claim 23, wherein the dose is about 400 mg.

25. The use according to claim 23 or 24, wherein the patient has been identified or diagnosed as having a cancer selected from the group consisting of: breast cancer, ovarian cancer, endometrial cancer, prostate cancer, uterine cancer, gastric cancer, and lung cancer.

26. The use according to claim 25, wherein the cancer is HR-positive cancer is ER-positive and HER2-negative.

27. The use according to claim 25, wherein the HR-positive cancer is ER-positive and HER2-positive.

28. The use according to any one of claims 23 to 27, wherein the breast cancer is metastatic breast cancer (mBC).

29. The use according to any one of claims 23 to 27, wherein the breast cancer is advanced breast cancer.

30. The use according to any one of claims 23 to 27, wherein the cancer is endometrioid endometrial cancer (EEC).

31. The use according to any one of claims 23 to 30, wherein the compound, or pharmaceutically acceptable salt thereof, is to be administered in simultaneous, separate or sequential combination with a second therapeutic agent.

32. The use according to claim 31, wherein the second therapeutic agent is selected from the group consisting of: abemaciclib, an aromatase inhibitor, everolimus, alpelisib, trastuzumab, and pertuzumab.

33. The use according to claim 31 or 32, wherein the second therapeutic agent is abemaciclib.

34. The use according to claim 31 or claim 32, wherein the second therapeutic agent is trastuzumab.

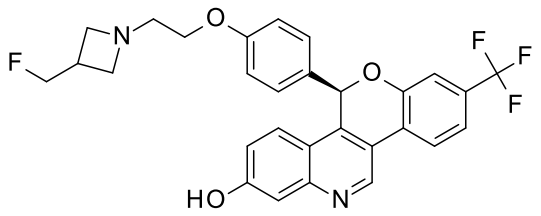
35. The use according to any one of claims 31 to 34, wherein the compound, or pharmaceutically acceptable salt thereof, and second therapeutic agent are to be administered in simultaneous, separate or sequential combination with a third therapeutic agent.

36. The use according to claim 35, wherein the third therapeutic agent is selected from the group consisting of: an aromatase inhibitor, everolimus, alpelisib, trastuzumab, and pertuzumab and wherein the third therapeutic agent differs from the second therapeutic agent.

37. The use according to claim 35 or claim 36, wherein the third therapeutic agent is selected from the group consisting of an aromatase inhibitor and trastuzumab.

38. The use according to claim 35 or 36, wherein the third therapeutic agent is pertuzumab.

39. Use of a compound of Formula I:



,

or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a patient, wherein the compound or salt is to be used in simultaneous, separate or sequential combination with a second therapeutic and a third therapeutic, wherein the second therapeutic and the third therapeutic are different and wherein the compound, or pharmaceutically acceptable salt thereof, is to be administered to the patient at a dose of between about 200 mg and about 400 mg at least once a day for at least one week.

40. The use according to claim 39, wherein the cancer is selected from the group consisting of breast cancer, ovarian cancer, endometrial cancer, prostate cancer, uterine cancer, gastric cancer, and lung cancer.

41. The use according to claim 40, wherein the cancer is ER-positive and HER2-negative.

42. The use according to claim 40, wherein the cancer is ER-positive and HER2-positive.

43. Use of a compound which is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1) in the manufacture of a medicament for treating ER+, HER2-negative breast cancer in a patient, wherein the compound is to be used in simultaneous, separate or sequential combination with pertuzumab and trastuzumab.

44. The use according to claim 43, wherein the compound is to be administered to the patient at a dose of about 400 mg.

45. Use of a compound which is (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1) in the manufacture of a medicament for treating ER+, HER2- negative breast cancer in a patient, wherein the compound is to be used in simultaneous, separate or sequential combination with abemaciclib, wherein the compound is to be administered to the patient at a dose of about 400 mg.

46. Use of (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1), pertuzumab and trastuzumab in the manufacture of a medicament for treating ER+, HER2- cancer.

47. Use of (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1) and abemaciclib in the manufacture of a medicament for treating HR+ and ER+ cancer in a patient, wherein about 400 mg of the (5R)-5-[4-[2-[3-(fluoromethyl)azetidin-1-yl]ethoxy]phenyl]-8-(trifluoromethyl)-5H-chromeno[4,3-c]quinolin-2-ol, 4-methylbenzenesulfonic acid (1/1) and abemaciclib are to be administered to the patient, wherein the cancer is selected from the group consisting of HER2- positive breast cancer, HER2-negative breast cancer and endometrioid endometrial cancer (EEC).