phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid (referred to herein as Compound III) are in phase I clinical trials for the treatment of solid tumors. Compound II is disclosed in US Pat. No. 7,851,626. Compound III is disclosed in US Pub 2010/0152190 A1. To the extent deemed necessary, both of these publications are herein incorporated by reference.

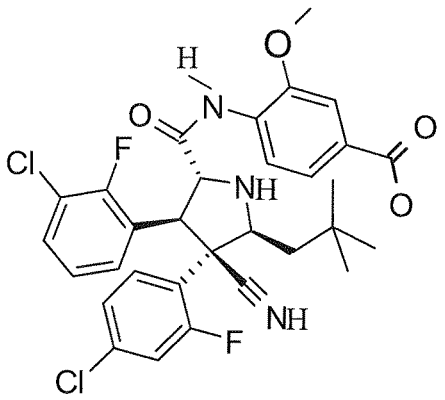
Applicants have unexpectedly found that combination therapy with vemurafenib and an MDM2 inhibitor not only is capable of overcoming resistance to vemurafenib (that is, potentiation of activity in previously vemurafenib resistant cells), but also results in improved antineoplastic effects that are significantly superior to the results obtained with each compound alone, without a significant increase in toxicity. Moreover, because these two types of compounds exert antitumor effects by affecting different cellular mechanisms, a therapeutic combination of both compounds is expected to yield improved antitumor activity in certain tumors and/or prevent or delay resistance to drug therapy.

Summary

The present disclosure~~, in a first aspect,~~ relates to a pharmaceutical product comprising (i) a first composition comprising, as an active agent, vemurafenib, or a pharmaceutically-acceptable salt thereof; and (ii) a second composition comprising, as an active agent, an MDM2 inhibitor, or a pharmaceutically acceptable salt thereof; as a combined preparation for the concomitant or sequential use in the treatment of cancer; the amount of said active agents being such that the combination thereof is therapeutically-effective in the treatment of cancer.

The present disclosure also relates to specific MDM2 inhibitors, namely compounds (II) and (III) as disclosed herein, as well as specific dosage regimen used for the combination treatment involving vemurafenib and said MDM2 inhibitors.

In a first aspect, there is provided a pharmaceutical product comprising (i) a first composition comprising, as an active agent, vemurafenib, or a pharmaceutically-acceptable salt thereof; and (ii) a second composition comprising, as an active agent, an MDM2 inhibitor which is Compound (III) of the formula

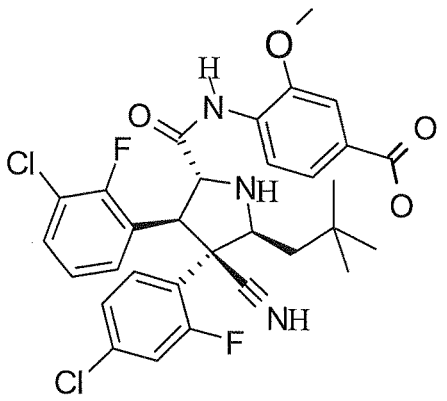


, or a pharmaceutically acceptable salt thereof; as a combined preparation for the concomitant or sequential use in the treatment of cancer; the amount of said active agents being such that the combination thereof is therapeutically-effective in the treatment of cancer, wherein said cancer is selected from the group consisting of colorectal cancer, melanoma, sarcoma and thyroid cancer and wherein said cancer involves a tumor comprising b-Raf having the V600E mutation.

The present disclosure also relates to a method of treating a patient suffering from a proliferative disorder, in particular cancer, comprising administering to the patient, either concomitantly or sequentially, (i) a first component comprising, as an active agent, vemurafenib, or a pharmaceutically-acceptable salt thereof, and (ii) a second component comprising, as an active agent, an MDM2 inhibitor, the amount of said

active agents being such that the combination thereof is therapeutically-effective in the treatment of said proliferative disorder.

The disclosure also relates to a kit comprising (i) first component comprising, as an active agent, one or more oral unit dosage forms of vemurafenib; and (ii) a second component comprising, as an active agent, one or more oral or injectable unit dosage forms of an MDM2 inhibitor. In a second aspect, there is provided a kit comprising: (i) a first component comprising, as an active agent, one or more unit dosage forms of vemurafenib, or a pharmaceutically-acceptable salt thereof; and (ii) a second component which comprises, as an active agent, one or more unit dosage forms of Compound III of the formula



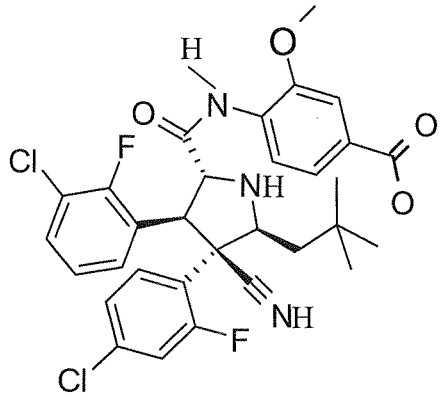
, or a pharmaceutically acceptable salt thereof.

The present disclosure further relates to a pharmaceutical composition comprising a therapeutically effective amount of (i) vemurafenib, or a pharmaceutically-acceptable salt thereof, and (ii) an MDM2 inhibitor.

In addition, the present disclosure relates to the use of vemurafenib, or a pharmaceutically-acceptable salt thereof, and an MDM2 inhibitor for the treatment of a proliferative disorder.

The present disclosure further relates to the use of vemurafenib, or a pharmaceutically-acceptable salt thereof, and an MDM2 inhibitor for the preparation of a medicament for the treatment of a proliferative disorder.

In a third aspect, there is provided the use of vemurafenib, or a pharmaceutically-acceptable salt thereof, and an MDM2 inhibitor which is Compound (III) of the formula



, or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer, wherein said cancer is selected from the group consisting of colorectal cancer, melanoma, sarcoma and thyroid cancer and wherein said cancer involves a tumor comprising b-Raf having the V600E mutation.

Brief Description of the Drawings

Figure 1 illustrates the antitumor activity, as demonstrated by the change in mean tumor volume over time, of vemurafenib monotherapy, Compound II and Compound III monotherapy, and vemurafenib plus Compound II and vemurafenib plus Compound III combination therapy.

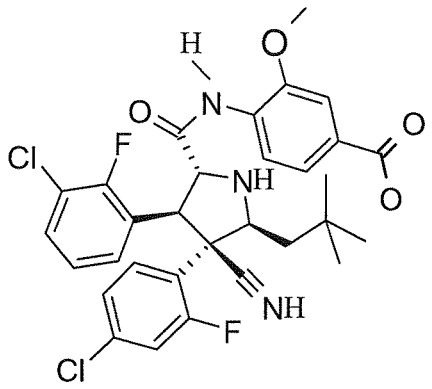
Detailed Description of the Invention

As used herein, the terms “antineoplastic” or “antitumor” mean inhibiting the development, maturation or proliferation of malignant cells.

As used herein, the terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell

Claims

1. A pharmaceutical product comprising (i) a first composition comprising, as an active agent, vemurafenib, or a pharmaceutically-acceptable salt thereof; and (ii) a second composition comprising, as an active agent, an MDM2 inhibitor which is Compound (III) of the formula



, or a pharmaceutically acceptable salt thereof; as a combined preparation for the concomitant or sequential use in the treatment of cancer; the amount of said active agents being such that the combination thereof is therapeutically-effective in the treatment of cancer, wherein said cancer is selected from the group consisting of colorectal cancer, melanoma, sarcoma and thyroid cancer and wherein said cancer involves a tumor comprising b-Raf having the V600E mutation.

2. The pharmaceutical product of claim 1, wherein the first composition is administered sequentially with the second composition.

3. The pharmaceutical product of claim 1, wherein the first composition is administered concomitantly with the second composition.

4. The pharmaceutical product of claim 1, wherein the first and second compositions are co-formulated.

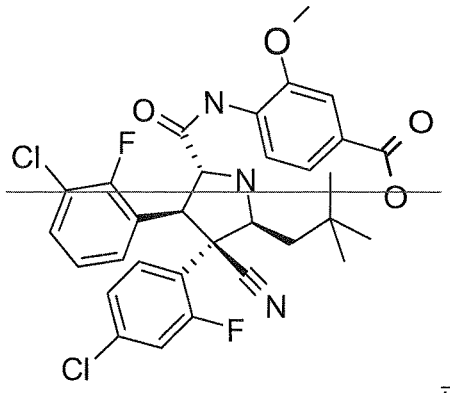
~~5. The pharmaceutical product according to any one of claim 1 to 4 for use as a medicament in the treatment of a cancer comprising V600 mutation positive b-Raf, preferably a tumor having the V600E mutation.~~

~~6. The pharmaceutical product according to claim 5, wherein said cancer is selected from the group consisting of colorectal cancer, melanoma, sarcoma and thyroid cancer and wherein said cancer involves a tumor comprising b-Raf having the V600E mutation.~~

~~7~~5. The pharmaceutical product according to any one of claims 1 to ~~6~~4 wherein vemurafenib, or a pharmaceutically-acceptable salt thereof, is administered in an amount of from about 200 mg/day to about 3000 mg/day.

~~8~~6. The pharmaceutical product according to any one of claims 1 to ~~6~~4 wherein vemurafenib, or a pharmaceutically-acceptable salt thereof, is administered in an amount of from about 960 mg/day to about 2000 mg/day.

~~9. The pharmaceutical product according to any one of claims 1 to 8, wherein said MDM2 inhibitor is the Compound (III) of the formula~~



~~, or~~

~~a pharmaceutically acceptable salt of said compound.~~

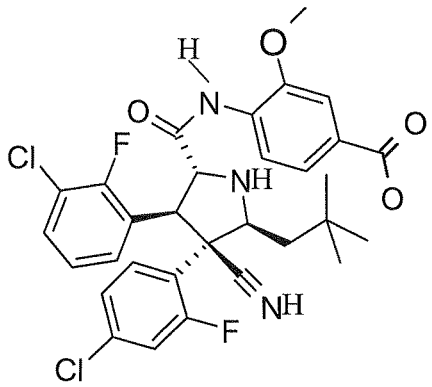
~~10~~7. The pharmaceutical product according to claim ~~9~~1, wherein Compound (III), or a pharmaceutically acceptable salt thereof, is administered in an amount of from about 100 mg/day to about 2500 mg/day.

~~11~~8. The pharmaceutical product according to claim ~~9~~1, wherein Compound (III), or a pharmaceutically acceptable salt thereof, is administered in an amount of from about 300 mg/day to about 2000 mg/day.

~~12~~9. The pharmaceutical product according to claim 1, wherein vemurafenib, or a pharmaceutically-acceptable salt thereof, is administered in an amount from about 480 mg to about 960 mg bid daily on about day 1 through about day 28 of a 28 day cycle, and Compound III, or a pharmaceutically-acceptable salt thereof, is administered once daily in an amount from 300 mg/day to about 2000 mg/day for up to 5 days on days 1-5 of a 28 day cycle.

~~13~~10. The pharmaceutical product according to claim 1, wherein vemurafenib, or a pharmaceutically-acceptable salt thereof, is administered in an amount from about 480 mg to about 960 mg bid daily from about day 1 through about day 28 of a 28 day cycle, and Compound III, or a pharmaceutically-acceptable salt thereof, is administered once weekly in an amount of about 2500 mg/day on days 1, 8 and 15 of a 28 day cycle.

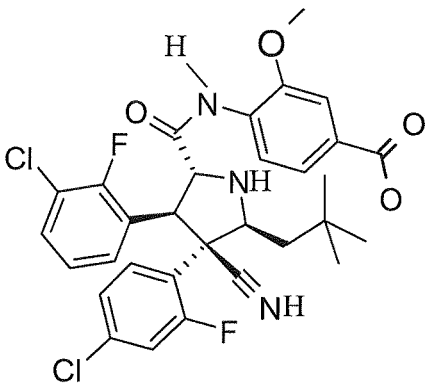
~~14~~11. A kit comprising: (i) a first component comprising, as an active agent, one or more unit dosage forms of vemurafenib, or a pharmaceutically-acceptable salt thereof; and (ii) a second component which comprises, as an active agent, one or more unit dosage forms of Compound III of the formula



, or a pharmaceutically acceptable salt thereof.

~~15~~12. A kit according to claim ~~14~~12, for use in the treatment of a proliferative disorder, preferably cancer selected from the group consisting of colorectal cancer, melanoma, sarcoma and thyroid cancer and wherein said cancer involves a tumor comprising b-Raf having the V600E mutation.

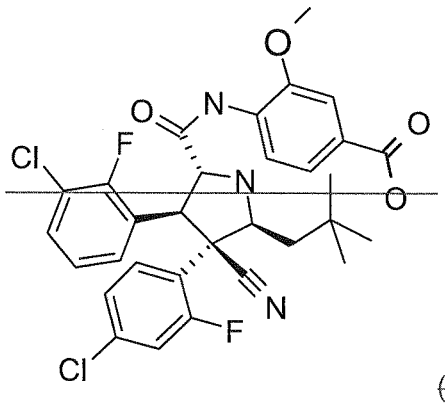
~~16~~13. The use of vemurafenib, or a pharmaceutically-acceptable salt thereof, and an MDM2 inhibitor which is Compound (III) of the formula



, or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer, wherein said cancer is selected from the group consisting of colorectal cancer, melanoma, sarcoma and thyroid cancer and wherein said cancer involves a tumor comprising b-Raf having the V600E mutation.

~~17. The use according to claim 16, wherein the cancer is selected from the group consisting of colorectal cancer, melanoma, sarcoma and thyroid cancer and wherein said cancer involves a tumor comprising b-Raf having the V600E mutation.~~

~~18. The use according to claim 16 or 17, wherein the MDM2 inhibitor is Compound (III)~~



~~(III).~~

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