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(54) Titre : PROCEDE DE TRAITEMENT D'UNE MALADIE PROLIFERATIVE
(54) Title: METHOD OF TREATING A PROLIFERATIVE DISEASE

(57) Abrégé/Abstract:
The present invention relates to a method of treating a patient with a serine/threonine kinase inhibitor wherein resistance to the treatment with a serine/threonine kinase inhibitor is suppressed by administering the serine/threonine kinase inhibitor on an intermittent dosing schedule.

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(54) Title: METHOD OF TREATING A PROLIFERATIVE DISEASE

(57) Abstract: The present invention relates to a method of treating a patient with a serine/threonine kinase inhibitor wherein resistance to the treatment with a serine/threonine kinase inhibitor is suppressed by administering the serine/threonine kinase inhibitor on an intermittent dosing schedule.

METHOD OF TREATING A PROLIFERATIVE DISEASE

SUMMARY

The present invention relates to a method of suppressing resistance to treatment with inhibitors of BRAF.

BACKGROUND

The involvement of kinases in proliferative diseases is well known. For example, kinases associated with tumorigenesis include the receptor tyrosine kinases and the serine/threonine kinase, Raf kinase. These kinases play critical roles in signal transduction pathways that influence and regulate many cellular functions such as proliferation, differentiation, and survival.

The development of therapies for the treatment of proliferative diseases remains a formidable challenge. A continuing need exists for improved therapeutic methods, particularly in view of the many variations amongst cancer cells with respect to their underlying mechanisms of growth and survival, their response to therapeutic agents, and their ability to mutate and become refractory or resistant to such agents.

Raf kinase is part of the Mitogen-Activated Protein Kinase (MAPK) signaling pathway comprising the Ras-Raf-MEK1-ERK signaling molecules. Raf has three distinct isoforms A-Raf, B-Raf, and C-Raf as distinguished by their ability to interact with its upstream modulator Ras. An activating mutation of one of the Ras genes can be seen in about 20% of all tumors and the Ras/Raf/MEK/ERK pathway is activated in about 30% of all tumors (Bos et al., Cancer Res. 49:4682-4689, 1989; Hoshino et al., Oncogene 18:813-822, 1999). Activating mutation in the kinase domain of B-Raf occurs in about 66% of melanomas, 12% of colon carcinoma and 14% of liver cancer (Davies et al., Nature 417:949-954, 2002; Yuen et al., Cancer Research 62:6451-6455, 2002; Brose et al., Cancer Research 62:6997-7000, 2002).

Small molecule RAF inhibitors, such as vemurafenib, have demonstrated proof-of-concept that BRAFV600E is a key driver of proliferation and survival in melanoma, as evidenced by tumor regression and prolonged survival in patients in late stage clinical trials. Unfortunately, the tumor response can be short-lived when resistance to a RAF inhibitor rapidly develops.

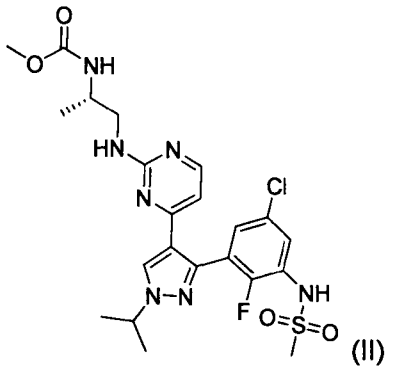
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 Comparison of continuous and intermittent dosing of a BRAF inhibitor of formula II shows that taking away a growth advantage for the resistant cells by intermittent dosing delays

or prevents the onset of resistance to the BRAF inhibitor.

SUMMARY

In one embodiment, there is provided use of a BRAF inhibitor of the Formula II



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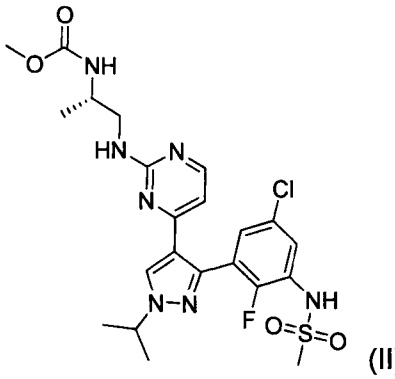
in the treatment of a proliferative disease in a subject, wherein the proliferative disease is characterized by a mutation in BRAF kinase, whereby the BRAF inhibitor of Formula II is for administration on an intermittent dosing schedule comprising a period of administration of the BRAF inhibitor of 1, 2, 3, 4, 5, or 6 weeks followed by a period of 1, 2, 3, 4, 5, or 6 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor or until resistance emerges, whereby the intermittent dosing schedule suppresses resistance to treatment with said BRAF inhibitor.

In another embodiment, there is provided the use as described herein wherein the intermittent dosing schedule improves a therapeutic effect in tumor cells already resistant to treatment with the BRAF kinase inhibitor of Formula II.

In another embodiment, there is provided the use as described herein, wherein the proliferative disease is a tumor.

In another embodiment, there is provided the use as described herein, wherein the BRAF inhibitor of Formula II is for administration once daily during the period of administration of the BRAF inhibitor of Formula II.

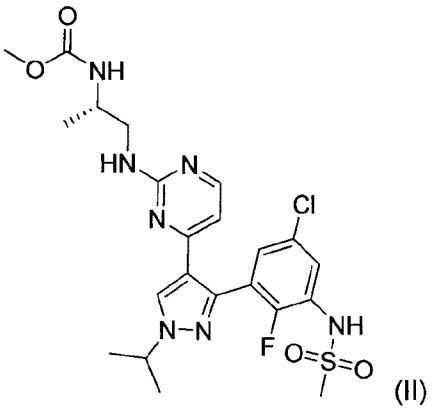
In another embodiment, there is provided use of a BRAF inhibitor of the Formula II



(II)

in inducing regression of a tumor in a patient , wherein said tumor is characterized by a mutation in BRAF kinase and wherein said tumor has become resistant to treatment with a BRAF inhibitor of the Formula II.

In another embodiment, there is provided use of a BRAF inhibitor of the Formula II



(II)

in treatment regimen for reducing dependence of a tumor on treatment with a BRAF inhibitor of the Formula II for growth, wherein said tumor is characterized by a mutation in BRAF kinase, said treatment regimen comprising withdrawal of treatment of said tumor with said BRAF inhibitor for a period of 1, 2, 3, 4, 5, or 6 weeks between periods of treatment of said tumor with said BRAF inhibitor.

In another embodiment, there is provided the use as described herein, wherein the tumor is melanoma or colorectal cancer which is characterized by a V600 mutation.

In another embodiment, there is provided the use as described herein, wherein the tumor is melanoma or colorectal cancer which is characterized by BRAFV600E.

In another embodiment, there is provided the use as described herein, wherein the BRAF inhibitor of Formula II is for administration once daily.

DETAILED DESCRIPTION

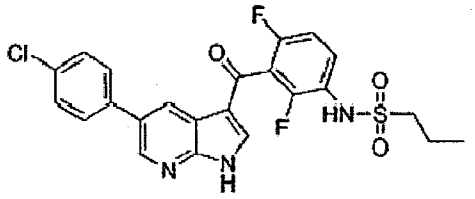
The present invention is based on the discovery that Raf kinase resistant tumor cells are 'less fit' than tumor cells which are sensitive to the Raf kinase inhibitor and have a selective disadvantage over sensitive cells in the absence of the Raf kinase inhibitor. Thus, according to the present invention resistance to treatment with a Raf kinase inhibitor is suppressed by administering the Raf kinase inhibitor on an intermittent dosing schedule.

Suppressing resistance to treatment means delaying or preventing the onset of resistance to treatment with the Raf kinase inhibitor.

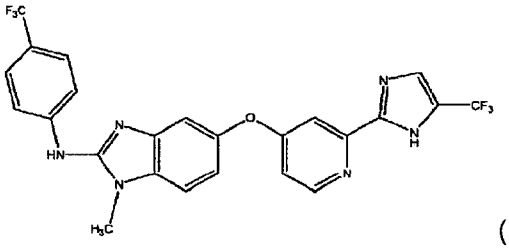
In this application, intermittent dosing schedule means that that the B-Raf kinase inhibitor is administered for a period of time followed by a period of time wherein treatment with the B-Raf kinase inhibitor is withheld. For example, the Raf kinase inhibitor is administered daily for a period of 4 weeks followed by a period of two weeks without treatment and the cycle is repeated while the patient is treated with the Raf kinase inhibitor.

BRAF inhibitors and their use for treating proliferative diseases are known in the art.

Vemurafenib (PLX4032) is a BRAF inhibitor which was approved by the FDA for the treatment of patients with melanoma whose tumors express the BRAF V600E mutation. Vemurafenib has the following chemical structure:

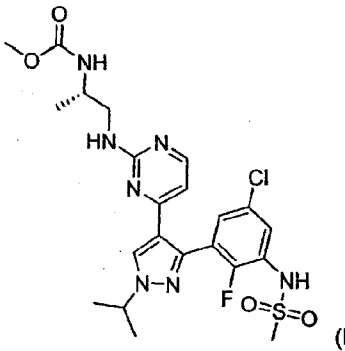


Another class of compounds that inhibits certain kinases in the MAPK pathway is the benzimidazolyl pyridyl ethers. US patent 7,482,367 discloses a B-RAF kinase inhibitor for formula I.



(I).

Another class of compounds that inhibits certain kinases in the MAPK pathway is the pyrrazole pyrimidines. WO 2011/025927, discloses the compound of formula II as an inhibitor of BRAF kinase, particularly with the BRAFV600E mutation:



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In the present method, the BRAF inhibitor is preferably a compound of formula II.

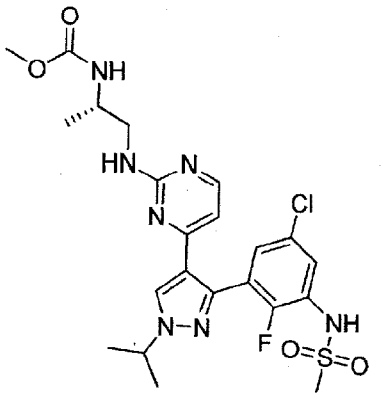
In an early passage primary human melanoma xenograft model designed to measure the emergence of resistance to a BRAF inhibitor, we have established that treatment of the xenogafts with a BRAF inhibitor on a long term continuous dosing regimen at clinically relevant doses resulted in the appearance of resistant tumors over the course of 4 to 6 weeks. Pharmacodynamic (PD) analysis within individual tumors indicated that the RAF-MEK-ERK pathway is still suppressed in resistant tumors, although the degree and duration of suppression is less than in sensitive tumors. Furthermore, the kinetics of pathway inhibition and recovery are different between each resistant tumor. Biochemical analyses indicate that serine/threonine kinases and modulation of negative feedback loops to serine/threonine kinases may be involved in resistance, as well as up-regulation of BRAF V600E expression. Pharmacological evaluation of tumor response has provided insight into tumor cell populations and the evolution of resistance. Increasing the dose of drug administered to mice bearing resistant tumors leads to a significant yet transient tumor response, followed by tumor progression. Taken together with the PD data, it is reasonable to conclude that there is a great deal of tumor cell heterogeneity, and that tumors are able to rapidly adapt to the selective pressure being applied by administration of the drug . Further support for this conclusion was obtained by suspending drug treatment from mice implanted with resistant tumors. Upon drug withdrawal, tumors initially regressed for several days to weeks, followed by re-growth. These data indicate that the adaptation which occurs within a tumor cell population under selective pressure make the cells less fit in the

absence of drug.

All resistant tumors have higher levels of p-ERK in the presence of the BRAF inhibitor compound compared to sensitive tumors and have faster recovery rates post-dose. The kinetics of the recovery vary between resistant tumors. BRAF resistant tumors depend on the presence of drug for growth and removal of the drug causes tumors to regress. Resistant cells are less fit then sensitive cells in the absence of compound. The present invention utilizes this discovery to suppress resistance to treatment with a BRAF inhibitor by administering the BRAF inhibitor on an intermittent dosing schedule

Thus, the present invention includes a method of treating a proliferative disease, which comprises suppressing resistance to treatment with a BRAF kinase inhibitor by administering the BRAF kinase inhibitor on an intermittent dosing schedule.

In particular, the present invention includes A method of treating a proliferative disease characterized by a mutation in BRAF kinase, which comprises suppressing resistance to treatment with a BRAF inhibitor of the Formula II



(II)

by administering the BRAF inhibitor of Formula II on an intermittent dosing schedule.

In a preferred embodiment, the present invention further relates to a method of treating a proliferative disease characterized by a mutation in BRAF kinase, which comprises suppressing resistance to treatment with a BRAF inhibitor by administering the BRAF inhibitor on an intermittent dosing schedule.

This aspect of the invention further relates to a method wherein the BRAF mutation is a V600 mutation, such as BRAFV600E.

The proliferative diseases treated by the inventive method include cancer such as, but not limited to, bladder, breast, brain, head and neck, liver, biliary tract, carcinomas, acute and chronic lymphoid leukemias, acute and chronic myelogenous leukemias, chronic myelomonocytic leukemias, colorectal, gastric, gastrointestinal stromal, glioma, lymphomas, melanomas, multiple myeloma, myeloproliferative diseases, neuroendocrine, lung, pancreatic, ovarian, prostate, renal cell, sarcomas and thyroid, such as papillary thyroid, cancers. Other proliferative diseases include mast cell leukemia, germ cell tumors, small-cell lung carcinoma, gastrointestinal stromal tumors, neuroblastoma, and osteosarcoma.

More particularly, the proliferative disease treated by the inventive method is melanoma which is characterized by a V600 mutation, such as BRAFV600E, or colorectal cancer characterized by a V600 mutation, such as BRAFV600E.

In an important aspect, the intermittent dosing schedule comprises administering the BRAF inhibitor for a period of 4 weeks followed by a period of two weeks without treatment and repeating the cycle while the patient is treated with the BRAF inhibitor or until resistance emerges. However, additional intermittent dosing schedules include, for example, cycles of 1 one week on 1 week off, 2 weeks on 1 or 2 weeks off, 3 weeks on 1, 2 or 3 weeks off, 4 weeks on 1, 2, 3 or 4 weeks off, especially 4 weeks on 1 week off or 4 weeks on 2 weeks off, 5 weeks on 1, 2 3, 4, or 5 weeks off, 6 weeks on and 1, 2, 3, 4, 5 or 6 weeks off, and so on.

This invention further includes use of a BRAF inhibitor for the preparation of a medicament for the treatment of a proliferative disease whereby the BRAF inhibitor is administered on an intermittent dosing schedule. In particular, use of a BRAF inhibitor of the Formula II for the preparation of a medicament for the treatment of a proliferative disease whereby the BRAF inhibitor of Formula II is administered on an intemittent dosing schedule

The following Example illustrates the present invention.

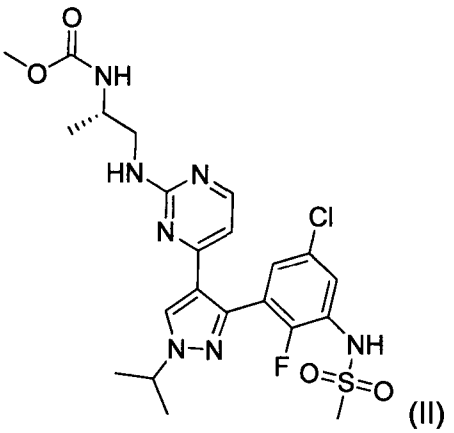
Example 1

Hmex1906 primary human melanoma tumors are implanted at passage 3 into nude mice. The mice were monitored until the implanted tumors reached 200-400mm^3. Once this size is reached, the mice are dosed bid with 5mg/kg of a Raf inhibitor (Compound of Formula II) for 4 weeks. Some of the mice continue treatment while others are subject to an ntermittent treatment schedule of 4 weeks of treatment and 2 weeks of drug holiday..

The results are shown in Figure 1. Resistance emerged in all mice receiving the Compound of Formula II on a continuous basis, but there is no evidence of resistance in the mice that were subject to an intermittent dosing schedule.

CLAIMS:

1. Use of a BRAF inhibitor of the Formula II



(II)

in the treatment of a proliferative disease in a subject, wherein the proliferative disease is characterized by a mutation in BRAF kinase, whereby the BRAF inhibitor of Formula II is for administration on an intermittent dosing schedule comprising a period of administration of the BRAF inhibitor of 1, 2, 3, 4, 5, or 6 weeks followed by a period of 1, 2, 3, 4, 5, or 6 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor or until resistance emerges, whereby the intermittent dosing schedule suppresses resistance to treatment with said BRAF inhibitor.

2. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 4 weeks followed by a period of two weeks without treatment and repetition of the cycle while the patient is to be treated with the BRAF inhibitor or until resistance emerges.

3. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of Formula II of 4 weeks followed by a period of 2 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld, and repetition of the cycle while the patient is to be treated with the BRAF inhibitor of Formula II.

4. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 1 week followed by a period of 1 week wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

5. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 2 weeks followed by a period of 1 week wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

6. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 2 weeks followed by a period of 2 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

7. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 3 weeks followed by a period of 1 week wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

8. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 3 weeks followed by a period of 2 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

9. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 3 weeks followed by a period of 3 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

10. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 4 weeks followed by a period of 1 week wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

11. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 4 weeks followed by a period of 3 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

12. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 4 weeks followed by a period of 4 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

13. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 5 weeks followed by a period of 1 week wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

14. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 5 weeks followed by a period of 2 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

15. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 5 weeks followed by a period of 3 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

16. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 5 weeks followed by a period of 4 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

17. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 5 weeks followed by a period of 5 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

18. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 6 weeks followed by a period of 1 week wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

19. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 6 weeks followed by a period of 2 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

20. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 6 weeks followed by a period of 3 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

21. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 6 weeks followed by a period of 4 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

22. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 6 weeks followed by a period of 5 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

23. The use of claim 1, wherein the intermittent dosing schedule comprises a period of administration of the BRAF inhibitor of 6 weeks followed by a period of 6 weeks wherein treatment with the BRAF inhibitor of Formula II is to be withheld and repetition of the cycle while the patient is to be treated with the BRAF inhibitor.

24. The use of claim 1 wherein the intermittent dosing schedule improves a therapeutic effect in tumor cells already resistant to treatment with the BRAF kinase inhibitor of Formula II.

25. The use according to any one of claims 1-24, wherein the BRAF mutation is a V600 mutation.

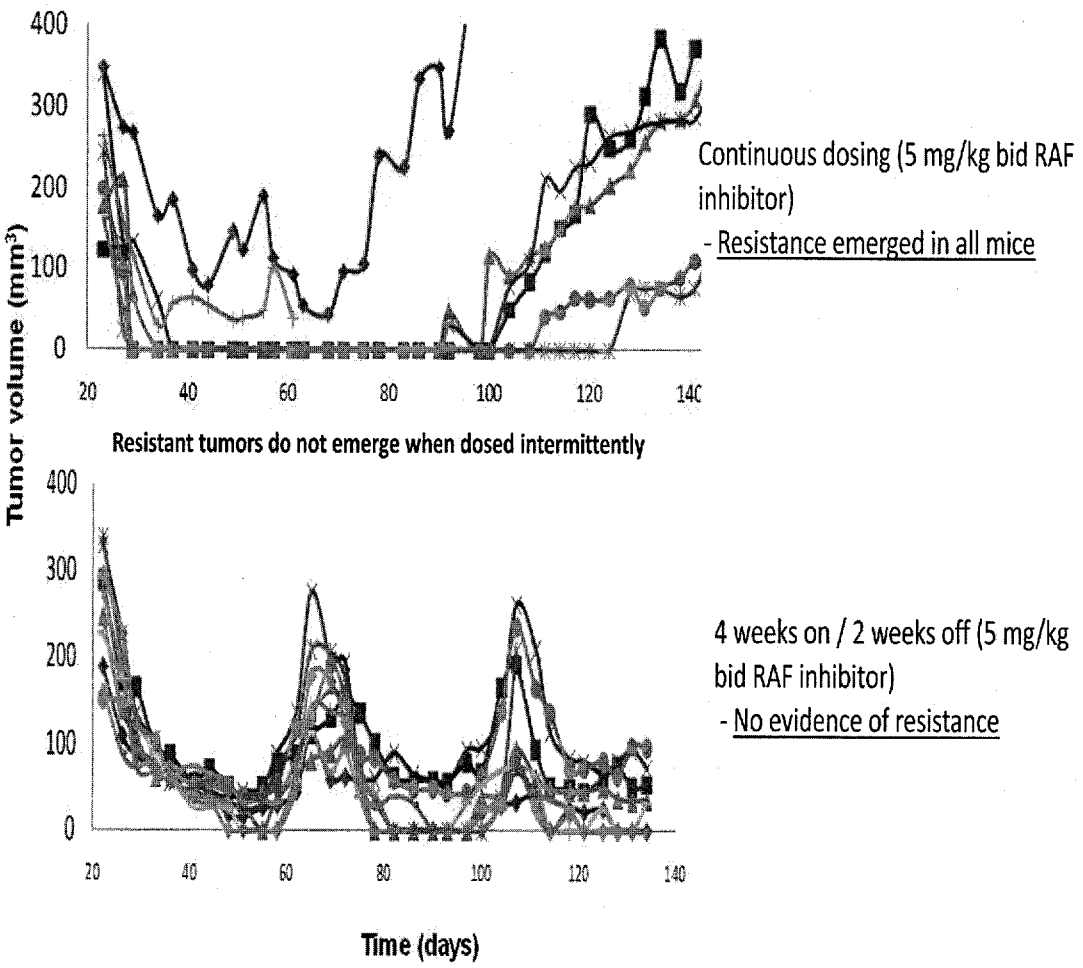
26. The use according to any one of claims 1-25, wherein the proliferative disease is a tumor.

27. The use according to claim 26, wherein the tumor is melanoma or colorectal cancer which is characterized by a V600 mutation.

28. The use according to claim 27, wherein the tumor is melanoma or colorectal cancer which is characterized by BRAFV600E.

29. The use according to any one of claims 1-28, wherein the BRAF inhibitor of Formula II is for administration once daily during the period of administration of the BRAF inhibitor of Formula II.

Figure 1


Tumor volume (mm3)
400
300
200
100
0
20
40
60
80
100
120
140
Continuous dosing (5 mg/kg bid RAF inhibitor)
- Resistance emerged in all mice
Resistant tumors do not emerge when dosed intermittently
4 weeks on / 2 weeks off (5 mg/kg bid RAF inhibitor)
- No evidence of resistance
Time (days)