

# **COMBINATION THERAPY FOR TREATING ABNORMAL CELL GROWTH**

## **CROSS REFERENCE TO RELATED APPLICATIONS**

**[0001]** This application claims the benefit of and priority to U.S. Provisional Patent Application No. 63/272,899 filed October 28, 2021, the entire contents of which are incorporated herein by reference.

## **BACKGROUND**

**[0002]** Components of the RAS/RAF/MEK/ERK (MAPK) signal transduction pathway represent opportunities for the treatment of abnormal cell growth, e.g., cancer. Mutations in RAS/RAF/MEK/ERK are frequently found in human cancers. These mutants result in a constitutively active MAPK kinase cascade, leading to tumor cell proliferation, differentiation, survival, and migration. Selective inhibitors of certain components of the RAS/RAF/MEK/ERK signal transduction pathway, such as RAS, RAF, MEK and ERK, are useful in the treatment of abnormal cell growth, in particular cancer, in mammals.

**[0003]** Due to the severity and breadth of diseases and disorders associated with abnormal cell growth, e.g., cancer, there is a need for effective therapeutic means and methods for treatment. The compounds, compositions, and methods described herein are directed toward this end.

## **SUMMARY**

**[0003a]** In a first aspect of the present disclosure, there is provided a use of a dual RAF/MEK inhibitor, in combination with a BRAF V600 inhibitor, in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer is identified as having a BRAF V600 mutation.

**[0003b]** In another aspect of the present disclosure, there is provided a use of a dual RAF/MEK inhibitor, in combination with a pan-RAF inhibitor, in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer is identified as having ARAF, BRAF, CRAF, KRAS, NRAS, HRAS, EGFR, ALKR, FGFR, PDGFR, NF1, SOS1, SOS2, MEK1, and/or MEK2 mutation.

**[0003c]** In yet another aspect of the present disclosure, there is provided a use of a dual RAF/MEK inhibitor, in combination with a CRAF inhibitor, in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer is identified as having ARAF, BRAF, CRAF, KRAS, NRAS, HRAS, EGFR, ALKR, FGFR, PDGFR, NF1, SOS1, SOS2, MEK1, and/or MEK2 mutation.

**[0003d]** In a further aspect of the present disclosure, there is provided a use of a dual RAF/MEK inhibitor, in combination with a RAF inhibitor, in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer is identified as having RAF, BRAF, CRAF, KRAS, NRAS, HRAS, EGFR, ALKR, FGFR, PDGFR, NF1, SOS1, SOS2, MEK1, and/or MEK2 mutation.

**[0004]** The present disclosure provides, in part, combinations (e.g., combinations of compounds as described herein, e.g., a BRAF V600 inhibitor, a pan-RAF inhibitor, a CRAF inhibitor, or a RAF inhibitor, and a dual RAF/MEK inhibitor), which can be used, for example, in methods of treating abnormal cell growth (e.g., cancer) in a subject in need thereof.

**[0005]** In some examples, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a dual RAF/MEK inhibitor and an effective amount of a BRAF V600 inhibitor.

**[0006]** In some examples, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a dual RAF/MEK inhibitor and an effective amount of a BRAF V600 inhibitor, wherein the

cancer is identified as having a BRAF V600 mutation. In some examples, the BRAF V600 mutation is BRAF V600E, BRAF V600K, BRAF V600D, BRAF V600R, and/or BRAF V600M mutation.

**[0007]** In some examples, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a dual RAF/MEK inhibitor and an effective amount of a pan-RAF inhibitor.

**[0008]** In some examples, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a dual RAF/MEK inhibitor and an effective amount of a pan-RAF inhibitor, wherein the cancer is identified as having ARAF, BRAF, CRAF, KRAS, NRAS, HRAS, EGFR, ALKR, FGFR, PDGFR, NF1, SOS1, SOS2, MEK1, and/or MEK2 mutation.

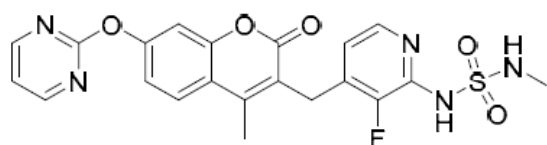
**[0009]** In some examples, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a dual RAF/MEK inhibitor and an effective amount of a CRAF inhibitor.

**[00010]** In some examples, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a dual RAF/MEK inhibitor and an effective amount of a CRAF inhibitor, wherein the cancer is identified as having ARAF, BRAF, CRAF, KRAS, NRAS, HRAS, EGFR, ALKR, FGFR, PDGFR, NF1, SOS1, SOS2, MEK1, and/or MEK2 mutation.

**[00011]** In some examples, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a dual RAF/MEK inhibitor and an effective amount of a RAF inhibitor.

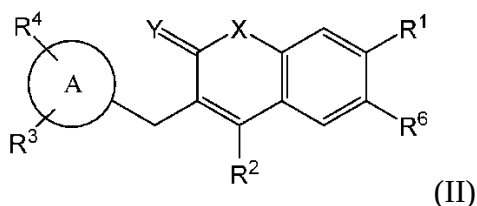
**[00012]** In some examples, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a dual RAF/MEK inhibitor and an effective amount of a RAF inhibitor, wherein the cancer is identified as having ARAF, BRAF, CRAF, KRAS, NRAS, HRAS, EGFR, ALKR, FGFR, PDGFR, NF1, SOS1, SOS2, MEK1, and/or MEK2 mutation.

**[00013]** In some examples, the dual RAF/MEK inhibitor is a compound of formula (I):



(I), or a pharmaceutically acceptable salt thereof.

**[00014]** In some examples, the dual RAF/MEK inhibitor is a compound of formula (II):



including pharmaceutically acceptable salts thereof, wherein the variables are as defined herein.

**[00015]** In some examples, the dual RAF/MEK inhibitor is IMM-1-104, or a pharmaceutically acceptable salt thereof.

**[00016]** Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing **Detailed Description, Examples, and Claims**.

#### BRIEF DESCRIPTION OF THE DRAWINGS

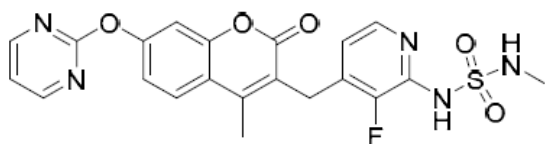
**[00017]** **FIG. 1** illustrates the synergy of VS-6766 (dual RAF/MEK inhibitor) + BRAF V600 inhibitor (BRAFi) is better than synergy of MEK inhibitor (MEKi) + BRAF V600 inhibitor (BRAFi) in BRAF V600E melanoma cell lines. 3D proliferation studies with VS-6766 + BRAFi or MEKi + BRAFi in a panel of BRAF V600E melanoma cell lines were performed to calculate synergy of VS-6766 + BRAFi and MEKi + BRAFi. Bliss, Loewe, HSA and ZIP synergy analyses were performed to generate a composite synergy score.

**[00018]** **FIG. 2** illustrates the synergy of VS-6766 (dual RAF/MEK inhibitor) + vemurafenib (BRAFi) is better than synergy of cobimetinib (MEKi) + vemurafenib (BRAFi) in BRAF V600E melanoma cell lines. Dose-response matrices were used to assess anti-proliferative effects of the combination of VS-6766 (1:5 dilutions starting at 5  $\mu$ M) + vemurafenib (1:3 dilutions starting at 5  $\mu$ M) and cobimetinib (1:5 dilutions starting at 5  $\mu$ M) + vemurafenib (1:3 dilutions starting at 5  $\mu$ M) in a panel of BRAF V600E melanoma cancer cell lines. Synergy scores were calculated using a combination of 4 different methods (Bliss, Loewe, HSA and ZIP). Bliss synergy analysis are shown. Red = synergy; Green = antagonism.

**[00019]** **FIG. 3** illustrates the synergy of VS-6766 (dual RAF/MEK inhibitor) + dabrafenib (BRAFi) is better than synergy of trametinib (MEKi) + dabrafenib (BRAFi) in BRAF V600E melanoma cell lines. Dose-response matrices were used to assess anti-proliferative effects of the combination of VS-6766 (1:5 dilutions starting at 5  $\mu$ M) + dabrafenib (1:3 dilutions starting at 5  $\mu$ M) and trametinib (1:5 dilutions starting at 5  $\mu$ M) +

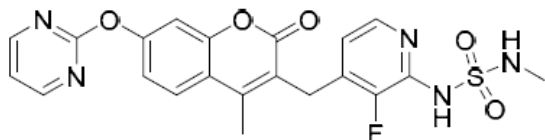
## CLAIMS

1. Use of a dual RAF/MEK inhibitor, in combination with a BRAF V600 inhibitor, in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer is identified as having a BRAF V600 mutation.
2. The use of claim 1, wherein the BRAF V600 mutation is BRAF V600E, BRAF V600K, BRAF V600D, BRAF V600R, and/or BRAF V600M mutation.
3. The use of claim 1 or 2, wherein the dual RAF/MEK inhibitor is a compound of formula (I):



(I), or a pharmaceutically acceptable salt thereof.

4. The use of claim 3, wherein the dual RAF/MEK inhibitor is a compound of formula (I):



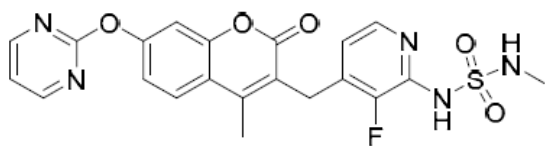
(I).

5. The use of claim 3, wherein the dual RAF/MEK inhibitor is a potassium salt of the compound of formula (I).
6. The use of any one of claims 1-5, wherein the dual RAF/MEK inhibitor is to be orally administered to the subject.
7. The use of any one of claims 1-6, wherein the dual RAF/MEK inhibitor is to be administered twice a week.
8. The use of any one of claims 1-7, wherein the dual RAF/MEK inhibitor is to be administered at a dose of 0.5 mg to about 10 mg per administration.

9. The use of any one of claims 1-8, wherein the dual RAF/MEK inhibitor is to be dosed as a cycle, wherein as part of the cycle, the dual RAF/MEK inhibitor is to be administered for three weeks and then the dual RAF/MEK inhibitor is not administered for one week.
10. The use of any one of claims 1-9, wherein the BRAF V600 inhibitor is dabrafenib, encorafenib, vemurafenib, FORE-8394 (PLX-8394), tinloragenib, AZ-304, agerafenib, KIN-2787, BGB-3245, ABM-1310, TQB-3233, UB-941, AFX-1251, ARQ 736, ASN003, AVB-BRAF, BDTX-4933, CFT1946, HLX208, RO5212054, RO7276389, or TQ-B3233, or pharmaceutically acceptable salts thereof.
11. The use of any one of claims 1-10, wherein the BRAF V600 inhibitor is dabrafenib, encorafenib, or vemurafenib, or pharmaceutically acceptable salts thereof.
12. The use of any one of claims 1-11, wherein the BRAF V600 inhibitor is to be orally administered to the subject.
13. The use of any one of claims 1-12, wherein the BRAF V600 inhibitor is to be administered once daily or twice daily.
14. The use of any one of claims 1-13, wherein the BRAF V600 inhibitor is to be dosed at 10 mg to 2000 mg per administration.
15. Use of a dual RAF/MEK inhibitor, in combination with a pan-RAF inhibitor, in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer is identified as having ARAF, BRAF, CRAF, KRAS, NRAS, HRAS, EGFR, ALKR, FGFR, PDGFR, NF1, SOS1, SOS2, MEK1, and/or MEK2 mutation.
16. The use of claim 15, wherein the pan-RAF inhibitor is BAL3833, LY3009120, REDX05358, IRICoR-Ipsen, JZP815, METiS-01, QLH11906, or SJ-C1044, or pharmaceutically acceptable salts thereof.
17. The use of claim 15 or 16, wherein the pan-RAF inhibitor is to be orally administered to the subject.
18. The use of any one of claims 15-17, wherein the pan-RAF inhibitor is to be administered once daily or twice daily.

19. The use of any one of claims 15-18, wherein the pan-RAF inhibitor is to be dosed at 10 mg to 2000 mg per administration.
20. Use of a dual RAF/MEK inhibitor, in combination with a CRAF inhibitor, in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer is identified as having ARAF, BRAF, CRAF, KRAS, NRAS, HRAS, EGFR, ALKR, FGFR, PDGFR, NF1, SOS1, SOS2, MEK1, and/or MEK2 mutation.
21. The use of claim 20, wherein the CRAF inhibitor is MG005, Quanta-RAF1, or STX200, or pharmaceutically acceptable salts thereof.
22. The use of claim 20 or 21, wherein the CRAF inhibitor is to be orally administered to the subject.
23. The use of any one of claims 20-22, wherein the CRAF inhibitor is to be administered once daily or twice daily.
24. The use of any one of claims 20-23, wherein the CRAF inhibitor is to be dosed at 10 mg to 2000 mg per administration.
25. Use of a dual RAF/MEK inhibitor, in combination with a RAF inhibitor, in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer is identified as having RAF, BRAF, CRAF, KRAS, NRAS, HRAS, EGFR, ALKR, FGFR, PDGFR, NF1, SOS1, SOS2, MEK1, and/or MEK2 mutation.
26. The use of claim 25, wherein the RAF inhibitor is donafenib, lifirafenib, rigosertib, BMS-908662, XP-102, ABM-2526, DDC-PanRAF, FNX006, or VRN-XX, or pharmaceutically acceptable salts thereof.
27. The use of claim 25 or 26, wherein the RAF inhibitor is to be orally administered to the subject.
28. The use of any one of claims 25-27, wherein the RAF inhibitor is to be administered once daily or twice daily.
29. The use of any one of claims 25-28, wherein the RAF inhibitor is to be dosed at 10 mg to 2000 mg per administration.

30. The use of any one of claims 15-29, wherein the dual RAF/MEK inhibitor is a compound of formula (I):



(I), or a pharmaceutically acceptable salt thereof.

31. The use of any one of claims 1-30, wherein the cancer is pancreatic cancer, gynecologic cancer (e.g., cervical cancer, ovarian cancer, uterine cancer, vaginal cancer, endometrial cancer, or vulvar cancer), liver cancer, prostate cancer, mesothelioma, breast cancer, bladder cancer, melanoma, lung cancer, colorectal cancer, thyroid cancer, glioblastoma, or renal cancer.

32. The use of any one of claims 1-31, wherein the cancer is melanoma, lung cancer, colorectal cancer, thyroid cancer, glioblastoma, or renal cancer, optionally wherein the lung cancer is non-small cell lung cancer (e.g., metastatic non-small cell lung cancer), the melanoma is unresectable melanoma or metastatic melanoma, or the thyroid cancer is papillary thyroid cancer, follicular thyroid cancer, or anaplastic thyroid cancer.

33. The use of any one of claims 1-32, wherein the medicament is to be administered to the subject, and wherein a FAK inhibitor is to be further administered to the subject.

34. The use of claim 33, wherein the FAK inhibitor is defactinib, or a pharmaceutically acceptable salt thereof.

35. The use of claim 33 or 34, wherein the FAK inhibitor is to be dosed at about 100 mg to about 1000 mg.

36. The use of claim 35, wherein the FAK inhibitor is to be dosed at about 100 mg to about 400 mg per administration (e.g., 200 mg or 400 mg per administration).

37. The use of any one of claims 33-36, wherein the FAK inhibitor is to be administered once daily or twice daily.

38. The use of any one of claims 33-37, wherein the FAK inhibitor is to be dosed as a cycle, wherein, as part of the cycle, the FAK inhibitor is to be administered for three weeks and then the FAK inhibitor is not administered for one week.

39. The use of any one of claims 33-38, wherein the FAK inhibitor is to be orally administered to the subject.