

G12R, KRAS G12S, or KRAS G12C. The methods comprise treating the subject by administering an effective amount of a MEK inhibitor described herein (e.g., a dual RAF/MEK inhibitor) alone or in combination with an additional agent described herein. Alternatively, the methods may comprise treating the subject by administering a pan-RAF inhibitor alone or in combination with an additional agent described herein.

In one aspect, the present disclosure provides a use of a MEK inhibitor in the manufacture of a medicament for treating a cancer in a subject identified as having a KRAS G12V mutation. In another aspect, the present disclosure provides a use of a MEK inhibitor in the manufacture of a medicament for treating a cancer in a subject identified as having a KRAS G12D mutation. In another aspect, the present disclosure provides a use of a MEK inhibitor in the manufacture of a medicament for treating a cancer characterized as having a KRAS G12V mutation in a subject in need thereof. In another aspect, the present disclosure provides a use of a MEK inhibitor in the manufacture of a medicament for treating a cancer characterized as having a KRAS G12D mutation in a subject in need thereof.

In yet another aspect, the present disclosure provides a use of a MEK inhibitor in the manufacture of a medicament for treating a cancer in a subject in need thereof, wherein the subject has previously been identified as having a KRAS G12V mutation. In yet another aspect, the present disclosure provides a use of a MEK inhibitor in the manufacture of a medicament for treating a cancer in a subject in need thereof, wherein the subject has previously been identified as having a KRAS G12D mutation. In yet another aspect, the present disclosure provides a use of a MEK inhibitor in the manufacture of a medicament for treating a cancer in a subject in need thereof, wherein the subject is selected with cancer having a KRAS G12V mutation in a tumor of the subject. In yet another aspect, the present disclosure provides a use of a MEK inhibitor in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the subject is selected with cancer having a KRAS G12D mutation in a tumor of the subject.

In a further aspect, the present disclosure provides a use of a pan-RAF inhibitor in the manufacture of a medicament for treating a cancer in a subject identified as having a KRAS G12V mutation. In a further aspect, the present disclosure provides a use of a pan-RAF inhibitor in the manufacture of a medicament for treating a cancer in a subject identified as having a KRAS G12D mutation.

In an ~~aspect~~example, provided herein is a method of treating a cancer in a subject identified as having a KRAS G12V mutation, the method comprising administering to the subject an

effective amount of a MEK inhibitor (e.g., a dual RAF/MEK inhibitor), thereby treating the subject.

In an aspectexample, provided herein is a method of treating a cancer in a subject identified as having a KRAS G12D mutation, the method comprising administering to the subject an effective amount of a MEK inhibitor (e.g., a dual RAF/MEK inhibitor), thereby treating the subject.

In an aspectexample, provided herein is a method of treating a cancer characterized as having a KRAS G12V mutation in a subject in need thereof, method comprising administering to the subject an effective amount of a MEK inhibitor (e.g., a dual RAF/MEK inhibitor), thereby treating the subject.

In an aspectexample, provided herein is a method of treating a cancer characterized as having a KRAS G12D mutation in a subject in need thereof, method comprising administering to the subject an effective amount of a MEK inhibitor (e.g., a dual RAF/MEK inhibitor), thereby treating the subject.

In some embodimentexamples, the MEK inhibitor is selected from the group consisting of trametinib, cobimetinib, binimetinib, selumetinib, PD-325901, CI-1040, VS-6766, MEK162, AZD8330, GDC-0623, refametinib, pimasertib, WX-554, HL-085, CH4987655, TAK-733, CInQ-03, G-573, PD184161, PD318088, PD98059, RO5068760, U0126, and SL327, or a pharmaceutically acceptable salt thereof.

In some embodimentexamples, the MEK inhibitor is a dual RAF/MEK inhibitor.

In some embodimentexamples, the MEK inhibitor (e.g., a dual RAF/MEK inhibitor) is VS-6766 or a pharmaceutically acceptable salt thereof.

In some embodimentexamples, the MEK inhibitor (e.g., VS-6766 or a pharmaceutically acceptable salt thereof) is dosed twice a week.

In some embodimentexamples, the MEK inhibitor (e.g., VS-6766 or a pharmaceutically acceptable salt thereof) is dosed at about 0.5 mg to about 10 mg (e.g., about 4 mg or about 3.2 mg).

In some [embodimentexamples](#), the MEK inhibitor (e.g., VS-6766 or a pharmaceutically acceptable salt thereof) is dosed cyclically for three weeks on and then one week off.

In some [embodimentexamples](#), the MEK inhibitor (e.g., VS-6766 or a pharmaceutically acceptable salt thereof) is administered in combination with an additional agent. In some [embodimentexamples](#), the additional agent is administered prior to the MEK inhibitor. In some [embodimentexamples](#), the additional agent is administered concurrently with the MEK inhibitor. In some [embodimentexamples](#), the additional agent is administered subsequent to the MEK inhibitor.

In some [embodimentexamples](#), the additional agent is a FAK inhibitor. In some [embodimentexample](#)s, the FAK inhibitor is selected from the group consisting of defactinib, TAE226, BI-853520 (IN10018), GSK2256098, PF-03814735, BI-4464, VS-4718, and APG-2449, or a pharmaceutically acceptable salt thereof. In some [embodimentexamples](#), the FAK inhibitor is defactinib or a pharmaceutically acceptable salt thereof.

In some [embodimentexamples](#), the FAK inhibitor (e.g., defactinib or a pharmaceutically acceptable salt thereof) is dosed once daily. In some [embodimentexamples](#), the FAK inhibitor (e.g., defactinib or a pharmaceutically acceptable salt thereof) is dosed twice daily.

In some [embodimentexamples](#), the FAK inhibitor (e.g., defactinib or a pharmaceutically acceptable salt thereof) is dosed at about 100 mg to about 1000 mg. In some [embodimentexamples](#), the FAK inhibitor (e.g., defactinib or a pharmaceutically acceptable salt thereof) is dosed at about 200 mg to about 400 mg (e.g., 200 mg or 400 mg).

In some [embodimentexamples](#), the FAK inhibitor (e.g., defactinib or a pharmaceutically acceptable salt thereof) is dosed daily at about 400 mg to about 800 mg. For example, the FAK inhibitor (e.g., defactinib or a pharmaceutically acceptable salt thereof) may be dosed twice daily at about 200 mg to about 400 mg (e.g., about 200 mg or about 400 mg twice daily).

In some [embodimentexamples](#), the MEK inhibitor (e.g., VS-6766 or a pharmaceutically acceptable salt thereof) is dosed as a cycle, wherein the cycle comprises administering the MEK inhibitor for three weeks and then not administering the MEK inhibitor for one week.

In some [embodimentexamples](#), the MEK inhibitor (e.g., VS-6766 or a pharmaceutically acceptable salt thereof) and the FAK inhibitor (e.g., defactinib or a pharmaceutically acceptable salt thereof) are dosed as a cycle, wherein the cycle comprises administering the MEK inhibitor and the FAK inhibitor for three weeks and then not administering the MEK inhibitor and the FAK inhibitor for one week.

In some [embodimentexamples](#), the MEK inhibitor (e.g., VS-6766 or a pharmaceutically acceptable salt thereof) and the FAK inhibitor (e.g., defactinib or a pharmaceutically

acceptable salt thereof) are independently dosed as a cycle. In some [embodimentexamples](#), the MEK inhibitor (e.g., VS-6766 or a pharmaceutically acceptable salt thereof) and the FAK inhibitor (e.g., defactinib or a pharmaceutically acceptable salt thereof) are simultaneously dosed as a cycle.

5 In some [embodimentexamples](#), the MEK inhibitor (e.g., VS-6766 or a pharmaceutically acceptable salt thereof) is dosed at about 0.5 mg to about 10 mg and the FAK inhibitor (e.g., defactinib or a pharmaceutically acceptable salt thereof) is dosed at about 200 mg to about 400 mg. In some [embodimentexamples](#), the MEK inhibitor (e.g., VS-6766 or a pharmaceutically acceptable salt thereof) is dosed at about 4 mg twice a week and the FAK inhibitor (e.g.,
10 defactinib or a pharmaceutically acceptable salt thereof) is dosed at about 200 mg twice daily.

In some [embodimentexamples](#), the MEK inhibitor (e.g., VS-6766 or a pharmaceutically acceptable salt thereof) is dosed at about 3.2 mg twice a week and the FAK inhibitor (e.g., defactinib or a pharmaceutically acceptable salt thereof) is dosed at about 200 mg twice daily.

15 In some [embodimentexamples](#), the MEK inhibitor (e.g., VS-6766 or a pharmaceutically acceptable salt thereof) is dosed at about 4 mg twice a week and the FAK inhibitor (e.g., defactinib or a pharmaceutically acceptable salt thereof) is dosed at about 400 mg twice daily.

In some [embodimentexamples](#), the MEK inhibitor (e.g., VS-6766 or a pharmaceutically acceptable salt thereof) is dosed at about 3.2 mg twice a week and the FAK inhibitor (e.g., defactinib or a pharmaceutically acceptable salt thereof) is dosed at about 400 mg twice daily.

20 In some [embodimentexamples](#), the cancer is ovarian cancer, non-small cell lung cancer (e.g., NSCLC adenocarcinoma)), uterine endometrioid carcinoma, pancreatic adenocarcinoma, colorectal adenocarcinoma, or lung adenocarcinoma. In some [embodimentexamples](#), the cancer is NSCLC (e.g., KRAS G12V mutant NSCLC).

25 In another [aspectexample](#), provided herein is a method of detecting presence of a KRAS gene mutation associated with a subject having a cancer, the method comprising:

- (a) obtaining a biological sample from the subject; and
- (b) performing an assay that screens for mutation in the sample.

In another [aspectexample](#), provided herein is a method of identifying a subject having a cancer with a KRAS gene mutation, the method comprising:

- 30
- (a) obtaining a biological sample from the subject; and
 - (b) performing an assay that screen for mutation in the sample.

In some [embodimentexamples](#), the methods further comprise administering to the subject identified as having a cancer with a KRAS mutation (e.g., KRAS G12X mutation (e.g., KRAS G12V, KRAS G12D, KRAS G12A, KRAS G12R, KRAS G12S, or KRAS G12C)) an

effective amount of a MEK inhibitor described herein (e.g., a dual RAF/MEK inhibitor) alone or in combination with an additional agent (e.g., a FAK inhibitor).

In alternative embodiment examples, the methods may further comprise administering to the subject identified as having a cancer with a KRAS mutation (e.g., KRAS G12X mutation (e.g., KRAS G12V, KRAS G12D, KRAS G12A, KRAS G12R, KRAS G12S, or KRAS G12C)) an effective amount of a pan-RAF inhibitor alone or in combination with an additional agent (e.g., a FAK inhibitor).

In some embodiment examples, the KRAS gene mutation is G12A, G12C, G12D, G12R, G12S, G12V or G13D. In some embodiment examples, the KRAS gene mutation is G12V. In some embodiment examples, the cancer is NSCLC.

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

FIG. 1 shows exemplary best response by RECIST in KRAS G12V NSCLC for the monotherapy of VS-6766 and combination therapy of VS-6766 and defactinib. **FIG. 2** shows the time on treatment for KRAS G12V NSCLC. **FIG. 3** shows exemplary best response by RECIST in KRAS G12V tumors (endometrial, NSCLC, and ovarian) for the monotherapy of VS-6766 and combination therapy of VS-6766 and defactinib. **FIG. 4** shows the time on treatment for KRAS G12V tumors (endometrial, NSCLC, and ovarian).

DETAILED DESCRIPTION

As generally described herein, the present disclosure provides methods that are useful for treating abnormal cell growth (e.g., cancer) in a subject in need thereof. Contemplated subjects in need of treatment of cancer may be identified as having a KRAS mutation (e.g., KRAS G12X mutation (e.g., KRAS G12V, KRAS G12D, KRAS G12A, KRAS G12R, KRAS G12S, or KRAS G12C)).

CLAIMS

We claim:

- 5 1. ~~A method of treating a cancer in a subject identified as having a KRAS G12V mutation, the method comprising administering to the subject an effective amount~~Use of a MEK inhibitor in the manufacture of a medicament for treating a cancer in a subject identified as having a KRAS G12V mutation, thereby treating the subject.
- 10 2. ~~A method of treating a cancer in a subject identified as having a KRAS G12D mutation, the method comprising administering to the subject an effective amount~~Use of a MEK inhibitor in the manufacture of a medicament for treating a cancer in a subject identified as having a KRAS G12D mutation, thereby treating the subject.
- 15 3. ~~A method of treating a cancer characterized as having a KRAS G12V mutation in a subject in need thereof, the method comprising administering to the subject an effective amount~~Use of a MEK inhibitor in the manufacture of a medicament for treating a cancer characterized as having a KRAS G12V mutation in a subject in need thereof, thereby treating the subject.
- 20 4. ~~A method of treating a cancer characterized as having a KRAS G12D mutation in a subject in need thereof, the method comprising administering to the subject an effective amount~~Use of a MEK inhibitor in the manufacture of a medicament for treating a cancer characterized as having a KRAS G12D mutation in a subject in need thereof, thereby treating the subject.
- 25 5. ~~A method of treating a cancer in a subject in need thereof, comprising administering to the subject an effective amount~~Use of a MEK inhibitor in the manufacture of a medicament for treating a cancer in a subject in need thereof, wherein the subject has previously been identified as having a KRAS G12V mutation.
- 30 6. ~~A method of treating a cancer in a subject in need thereof, comprising administering to the subject an effective amount~~Use of a MEK inhibitor in the manufacture of a

medicament for treating a cancer in a subject in need thereof, wherein the subject has previously been identified as having a KRAS G12D mutation.

7. ~~A method of treating a cancer in a subject in need thereof, comprising selecting a~~
5 ~~subject with cancer having a KRAS G12V mutation in a tumor of the subject; and treating the~~
~~subject with an effective amount~~ Use of a MEK inhibitor in the manufacture of a medicament
for treating a cancer in a subject in need thereof, wherein the subject is selected with cancer
having a KRAS G12V mutation in a tumor of the subject.

10 8. ~~A method of treating cancer in a subject in need thereof, comprising selecting a~~
~~subject with cancer having a KRAS G12D mutation in a tumor of the subject; and treating the~~
~~subject with an effective amount~~ Use of a MEK inhibitor in the manufacture of a medicament
for treating cancer in a subject in need thereof, wherein the subject is selected with cancer
having a KRAS G12D mutation in a tumor of the subject.

15 9. The ~~method~~ use of any one of claims 1-8, wherein the MEK inhibitor is selected from
the group consisting of trametinib, cobimetinib, binimetinib, selumetinib, PD-325901, CI-
1040, VS-6766, MEK162, AZD8330, GDC-0623, refametinib, pimasertib, WX-554, HL-085,
CH4987655, TAK-733, ClnQ-03, G-573, PD184161, PD318088, PD98059, RO5068760,
20 U0126, and SL327, or a pharmaceutically acceptable salt thereof.

10. The ~~use~~ method of any one of claims 1-9, wherein the MEK inhibitor is a dual
RAF/MEK inhibitor.

11. The ~~use~~ method of any one of claims 1-10, wherein the MEK inhibitor is VS-6766 or a
pharmaceutically acceptable salt thereof.

25 12. The ~~use~~ method of any one of claims 1-11, wherein the MEK inhibitor is to be dosed
once a week.

13. The ~~use~~ method of any one of claims 1-11, wherein the MEK inhibitor is to be dosed
twice a week.

30 14. The ~~use~~ method of any one of claims 1-11, wherein the MEK inhibitor is to be dosed
once daily.

15. The ~~method-use~~ of any one of claims 1-11, wherein the MEK inhibitor is to be dosed twice daily.

16. The ~~usemethod~~ of any one of claims 1-15, wherein the MEK inhibitor is to be dosed for at least three weeks.

17. The ~~usemethod~~ of any one of claims 1-16, wherein the MEK inhibitor is to be dosed as a cycle, wherein the cycle comprises ~~administering-that~~ the MEK inhibitor is to be administered for three weeks and then not to be administered ~~administering the MEK inhibitor~~ for one week.

18. The ~~usemethod~~ of any one of claims 1-17, wherein the MEK inhibitor is to be dosed at ~~about~~ 0.1 mg to ~~about~~ 100 mg.

19. The ~~usemethod~~ of any one of claims 1-18, wherein the MEK inhibitor is to be dosed at ~~about~~ 0.5 mg to ~~about~~ 10 mg.

20. The ~~usemethod~~ of any one of claims 1-19, wherein the MEK inhibitor is to be dosed at about 4 mg.

21. The ~~usemethod~~ of any one of claims 1-19, wherein the MEK inhibitor is to be dosed at about 3.2 mg.

22. The ~~usemethod~~ of any one of claims 1-21, wherein the MEK inhibitor is to be administered orally.

23. The ~~usemethod~~ of any one of claims 1-22, further comprising ~~that administering to the subject~~ an additional agent is to be administered to the subject.

24. The ~~usemethod~~ of claim 23, wherein the additional agent is to be administered prior to the MEK inhibitor.

25. The ~~usemethod~~ of claim 23, wherein the additional agent is to be administered concurrently with the MEK inhibitor.

26. The ~~usemethod~~ of claim 23, wherein the additional agent is to be administered subsequent to the MEK inhibitor.

27. The ~~use~~method of any one of claims 23-26, wherein the additional agent is a FAK inhibitor.

28. The ~~use~~method of claim 27, wherein the FAK inhibitor is selected from the group consisting of defactinib, TAE226, BI-853520 (IN10018), GSK2256098, PF-03814735, BI-4464, VS-4718, and APG-2449, or a pharmaceutically acceptable salt thereof.

29. The ~~use~~method of claim 27 or 28, wherein the FAK inhibitor is defactinib or a pharmaceutically acceptable salt thereof.

30. The ~~use~~method of any one of claims 27-29, wherein the FAK inhibitor is to be dosed twice daily.

31. The ~~use~~method of any one of claims 27-29, wherein the FAK inhibitor is to be dosed once daily.

32. The ~~use~~method of any one of claims 27-31, wherein the FAK inhibitor is to be dosed at ~~about~~ 100 mg to ~~about~~ 1000 mg.

33. The ~~use~~method of any one of claims 27-32, wherein the FAK inhibitor is to be dosed at ~~about~~ 200 mg to ~~about~~ 400 mg.

34. The ~~method~~use of any one of claims 27-33, wherein the FAK inhibitor is to be dosed at about 200 mg.

35. The ~~use~~method of any one of claims 27-33, wherein the FAK inhibitor is to be dosed at about 400 mg.

36. The ~~use~~method of any one of claims 27-35, wherein the FAK inhibitor is to be administered orally.

37. The ~~use~~method of any one of claims 1-36, wherein the cancer is ovarian cancer, non-small cell lung cancer (e.g., NSCLC adenocarcinoma)), uterine endometrioid carcinoma, pancreatic adenocarcinoma, colorectal adenocarcinoma, or lung adenocarcinoma.

38. The ~~use~~method of any one of claims 1-37, wherein the cancer is non-small cell lung cancer.

39. ~~A method of treating a cancer in a subject identified as having a KRAS G12V mutation, the method comprising administering to the subject an effective amount Use of a pan-RAF inhibitor in the manufacture of a medicament for treating a cancer in a subject identified as having a KRAS G12V mutation, thereby treating the subject.~~

5 40. ~~A method of treating a cancer in a subject identified as having a KRAS G12D mutation, the method comprising administering to the subject an effective amount Use of a pan-RAF inhibitor in the manufacture of a medicament for treating a cancer in a subject identified as having a KRAS G12D mutation, thereby treating the subject.~~