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.

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, compound combinations, compositions, and methods described herein are directed toward this end.

SUMMARY

Provided herein, in part, are combinations (e.g., combinations of compounds as described herein, e.g., KRAS G12C inhibitor in combination with a FAK inhibitor and/or a MEK inhibitor or 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.

In one aspect of the present disclosure, there is provided a use of a KRAS G12C inhibitor or a pharmaceutically acceptable salt and a FAK inhibitor or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for combination therapy to treat cancer in a subject in need thereof.

In another aspect of the present disclosure, there is provided a use of a KRAS G12C inhibitor or a pharmaceutically acceptable salt and a dual RAF/MEK inhibitor or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for combination therapy to treat cancer in a subject in need thereof.

In an example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a KRAS G12C inhibitor (e.g., ARS-853, ARS-1620, ARS-3248, LY3499446, AMG-510, and MRTX849) or a pharmaceutically acceptable salt thereof in combination with a FAK inhibitor (e.g., defactinib, TAE226, BI-853520 (IN10018), GSK2256098, PF-03814735, BI-4464, VS-4718, and APG-2449) or a pharmaceutically acceptable salt thereof, thereby treating the subject.

In another example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a KRAS G12C inhibitor (e.g., ARS-853, ARS-1620, ARS-3248, LY3499446, AMG-510, and MRTX849) or a pharmaceutically acceptable salt thereof in combination with a MEK inhibitor (e.g., trametinib,

cobimetinib, binimetinib, selumetinib, PD-325901, CI-1040, CH5126766, MEK162, AZD8330, GDC-0623, refametinib, pimasertib, WX-554, HL-085, CH4987655, TAK-733, CInQ-03, G-573, PD184161, PD318088, PD98059, RO5068760, U0126, and SL327, e.g., CH5126766) or a pharmaceutically acceptable salt thereof, thereby treating the subject.

In one example, disclosed herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a KRAS G12C inhibitor (e.g., ARS-853, ARS-1620, ARS-3248, LY3499446, AMG-510, and MRTX849) or a pharmaceutically acceptable salt thereof in combination with a dual RAF/MEK inhibitor (e.g., CH5126766) or a pharmaceutically acceptable salt thereof, thereby treating the subject.

Also provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a KRAS G12C inhibitor (e.g., ARS-853, ARS-1620, ARS-3248, LY3499446, AMG-510, and MRTX849) or a pharmaceutically acceptable salt thereof in combination with a FAK inhibitor (e.g., defactinib, TAE226, BI-853520 (IN10018), GSK2256098, PF-03814735, BI-4464, VS-4718, and APG-2449) or a pharmaceutically acceptable salt thereof and a MEK inhibitor (e.g., trametinib, cobimetinib, binimetinib, selumetinib, PD-325901, CI-1040, CH5126766, 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, thereby treating the subject.

In some examples, the KRAS G12C inhibitor is selected from the group consisting of ARS-853, ARS-1620, ARS-3248, LY3499446, AMG-510, and MRTX849, or a pharmaceutically acceptable salt thereof. In some examples, the KRAS G12C inhibitor is AMG-510 or a pharmaceutically acceptable salt thereof. In some examples, the KRAS G12C inhibitor is MRTX849 or a pharmaceutically acceptable salt thereof.

In some examples, 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 examples, the FAK inhibitor is defactinib or a pharmaceutically acceptable salt thereof.

In some examples, the method further comprises administering a MEK inhibitor.

In some examples, the MEK inhibitor is selected from the group consisting of trametinib, cobimetinib, binimetinib, selumetinib, PD-325901, CI-1040, CH5126766, 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 examples, the MEK inhibitor is a dual RAF/MEK inhibitor.

In some examples, the MEK inhibitor is CH5126766 or a pharmaceutically acceptable salt thereof.

In some examples, the KRAS G12C inhibitor is dosed at about 100 mg to about 2000 mg. In some examples, the KRAS G12C inhibitor is administered once daily. In some examples, the KRAS G12C inhibitor is administered twice daily. In some examples, the KRAS G12C inhibitor is administered orally.

In some examples, the FAK inhibitor (e.g., defactinib) is dosed twice daily. In some examples, the FAK inhibitor (e.g., defactinib) is dosed once daily. In some

examples, the FAK inhibitor (e.g., defactinib) is dosed at about 100 mg to about 1000 mg. In some examples, the FAK inhibitor (e.g., defactinib) is dosed at about 200 mg to about 400 mg. In some examples, the FAK inhibitor (e.g., defactinib) is administered orally.

In some examples, the FAK inhibitor is administered before the KRAS G12C inhibitor is administered. In some examples, the FAK inhibitor is administered after the KRAS G12C inhibitor is administered. In some examples, the FAK inhibitor is administered concurrently with the KRAS G12C inhibitor.

In some examples, the MEK inhibitor is dosed at least once a week (e.g., once a week, twice a week, three times a week, four times a week, five times a week, or six times a week). In some examples, the MEK inhibitor is dosed once a week. In some examples, the MEK inhibitor is dosed twice a week. In some examples, the MEK inhibitor is dosed once daily. In some examples, the MEK inhibitor is dosed twice daily. In some examples, the MEK inhibitor is dosed at about 0.1 mg to about 100 mg. In some examples, the MEK inhibitor is administered orally.

In some examples, the MEK inhibitor is a dual RAF/MEK inhibitor. In some examples, the dual RAF/MEK inhibitor is administered before the KRAS G12C inhibitor is administered. In some examples, the dual RAF/MEK inhibitor is administered after the KRAS G12C inhibitor is administered. In some examples, the dual RAF/MEK inhibitor is administered concurrently with the KRAS G12C inhibitor.

In some examples, the cancer is a cancer with a KRAS G12C mutation.

In some examples, the cancer is lung adenocarcinoma, non-small cell lung carcinoma, colorectal cancer (CRC), uterine endometrioid carcinoma, bladder urothelial carcinoma, breast invasive lobular carcinoma, cervical squamous cell carcinoma, cutaneous melanoma, endocervical adenocarcinoma, hepatocellular carcinoma, pancreatic adenocarcinoma, biphasic type pleural mesothelioma, renal clear cell carcinoma, renal clear cell carcinoma, stomach adenocarcinoma, tubular stomach adenocarcinoma, uterine carcinosarcoma, or uterine malignant mixed Mullerian tumor.

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

CLAIMS

1. Use of a KRAS G12C inhibitor or a pharmaceutically acceptable salt and a FAK inhibitor or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for combination therapy to treat cancer in a subject in need thereof.

2. The use of claim 1, 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.

3. The use of claim 1 or 2, wherein the FAK inhibitor is defactinib or a pharmaceutically acceptable salt thereof.

4. The use of any one of claims 1-3, wherein the KRAS G12C inhibitor is selected from the group consisting of ARS-853, ARS-1620, ARS-3248, LY3499446, AMG-510, and MRTX849, or a pharmaceutically acceptable salt thereof.

5. The use of any one of claims 1-4, wherein the KRAS G12C inhibitor is AMG-510 or a pharmaceutically acceptable salt thereof.

6. The use of any one of claims 1-4, wherein the KRAS G12C inhibitor is MRTX849 or a pharmaceutically acceptable salt thereof.

7. The use of any one of claims 1-6, wherein a MEK inhibitor is to be further administered.

8. The use of claim 7, wherein the MEK inhibitor is selected from the group consisting of trametinib, cobimetinib, binimetinib, selumetinib, PD-325901, CI-1040, CH5126766, 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.

9. The met use hod of claim 7, wherein the MEK inhibitor is a dual RAF/MEK inhibitor.

10. The use of any one of claims 7-9, wherein the MEK inhibitor is CH5126766 or a pharmaceutically acceptable salt thereof.

11. The m use ethod of any one of claims 1-10, wherein the FAK inhibitor (e.g., defactinib) is to be dosed twice daily.

12. The use of any one of claims 1-10, wherein the FAK inhibitor (e.g., defactinib) is to be dosed once daily.

13. The use of any one of claims 1-12, wherein the FAK inhibitor (e.g., defactinib) is to be dosed at about 100 mg to about 1000 mg.

14. The use of any one of claims 1-13, wherein the FAK inhibitor (e.g., defactinib) is to be dosed at about 200 mg to about 400 mg.

15. The use of any one of claims 1-14, wherein the FAK inhibitor (e.g., defactinib) is to be administered orally.

16. The use of any one of claims 1-15, wherein the KRAS G12C inhibitor is to be dosed at about 100 mg to about 2000 mg.

17. The use of any one of claims 1-16, wherein the KRAS G12C inhibitor is to be administered once daily.

18. The use of any one of claims 1-16, wherein the KRAS G12C inhibitor is to be administered twice daily.

19. The use of any one of claims 1-18, wherein the KRAS G12C inhibitor is to be administered orally.

20. The use of any one of claims 1-19, wherein the FAK inhibitor is to be administered before the KRAS G12C inhibitor is to be administered.

21. The use of any one of claims 1-19, wherein the FAK inhibitor is to be administered after the KRAS G12C inhibitor is to be administered.

22. The use of any one of claims 1-19, wherein the FAK inhibitor is to be administered concurrently with the KRAS G12C inhibitor.

23. The use of any one of claims 7-22, wherein the MEK inhibitor is to be dosed at least once a week (e.g., once a week, twice a week, three times a week, four times a week, five times a week, or six times a week).

24. The use of any one of claims 7-23, wherein the MEK inhibitor is to be dosed once a week.

25. The use of any one of claims 7-23, wherein the MEK inhibitor is to be dosed twice a week.

26. The use of any one of claims 7-22, wherein the MEK inhibitor is to be dosed once daily.

27. The use of any one of claims 7-22, wherein the MEK inhibitor is to be dosed twice daily.

28. The use of any one of claims 7-27, wherein the MEK inhibitor is to be dosed at about 0.1 mg to about 100 mg.

29. The use of any one of claims 7-28, wherein the MEK inhibitor is to be administered orally.

30. The use of any one of claims 7-29, wherein the FAK inhibitor is defactinib or a pharmaceutically acceptable salt thereof, the KRAS G12C inhibitor is MRTX849 or a pharmaceutically acceptable salt thereof, and the MEK inhibitor is CH5126766 or a pharmaceutically acceptable salt thereof.

31. The use of any one of claims 7-29, wherein the FAK inhibitor is defactinib or a pharmaceutically acceptable salt thereof, the KRAS G12C inhibitor is AMG-510 or a pharmaceutically acceptable salt thereof, and the MEK inhibitor is CH5126766 or a pharmaceutically acceptable salt thereof.

32. Use of a KRAS G12C inhibitor or a pharmaceutically acceptable salt and a dual RAF/MEK inhibitor or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for combination therapy to treat cancer in a subject in need thereof.

33. The use of claim 32, wherein the KRAS G12C inhibitor is selected from the group consisting of ARS-853, ARS-1620, ARS-3248, LY3499446, AMG-510, and MRTX849, or a pharmaceutically acceptable salt thereof.

34. The use of claim 32 or 33, wherein the KRAS G12C inhibitor is AMG-510 or a pharmaceutically acceptable salt thereof.

35. The use of claim 32 or 33, wherein the KRAS G12C inhibitor is MRTX849 or a pharmaceutically acceptable salt thereof.

36. The use of any one of claims 32-35, wherein the dual RAF/MEK inhibitor is CH5126766 or a pharmaceutically acceptable salt thereof.

37. The use of any one of claims 32-36, wherein the KRAS G12C inhibitor is to be dosed at about 100 mg to about 2000 mg.

38. The use of any one of claims 32-37, wherein the KRAS G12C inhibitor is to be administered once daily.

39. The use of any one of claims 32-37, wherein the KRAS G12C inhibitor is to be administered twice daily.

40. The use of any one of claims 32-39, wherein the KRAS G12C inhibitor is to be administered orally.

41. The use of any one of claims 32-40, wherein the dual RAF/MEK inhibitor is to be dosed at least once a week (e.g., once a week, twice a week, three times a week, four times a week, five times a week, or six times a week).

42. The use of any one of claims 32-41, wherein the dual RAF/MEK inhibitor is to be dosed once a week.

43. The use of any one of claims 32-41, wherein the dual RAF/MEK inhibitor is to be dosed twice a week.

44. The use of any one of claims 32-41, wherein the dual RAF/MEK inhibitor is to be dosed once daily.

45. The use of any one of claims 32-41, wherein the dual RAF/MEK inhibitor is to be dosed twice daily.

46. The use of any one of claims 32-45, wherein the dual RAF/MEK inhibitor is to be dosed at about 0.1 mg to about 100 mg.

47. The use of any one of claims 32-46, wherein the dual RAF/MEK inhibitor is to be administered orally.

48. The use of any one of claims 32-47, wherein the dual RAF/MEK inhibitor is to be administered before the KRAS G12C inhibitor is to be administered.

49. The use of any one of claims 32-47, wherein the dual RAF/MEK inhibitor is to be administered after the KRAS G12C inhibitor is to be administered.

50. The use of any one of claims 32-47, wherein the dual RAF/MEK inhibitor is to be administered concurrently with the KRAS G12C inhibitor.

51. The use of any one of claims 1-50, wherein the cancer is a cancer with a KRAS G12C mutation.

52. The use of any one of claims 1-51, wherein the cancer is lung adenocarcinoma, non-small cell lung carcinoma, colorectal cancer (CRC), uterine endometrioid carcinoma, bladder urothelial carcinoma, breast invasive lobular carcinoma, cervical squamous cell carcinoma, cutaneous melanoma, endocervical adenocarcinoma, hepatocellular carcinoma, pancreatic adenocarcinoma, biphasic type pleural mesothelioma, renal clear cell carcinoma, renal clear cell carcinoma, stomach adenocarcinoma, tubular stomach adenocarcinoma, uterine carcinosarcoma, or uterine malignant mixed Mullerian tumor.