COMBINATION THERAPY FOR TREATING ABNORMAL CELL GROWTH

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the priority to and benefit of U.S. Provisional Patent Application No. 63/146,349 filed February 5, 2021, U.S. Provisional Patent Application No. 63/185,651 filed May 7, 2021, U.S. Provisional Patent Application No. 63/146,352 filed February 5, 2021, U.S. Provisional Patent Application No. 63/185,672 filed May 7, 2021, U.S. Provisional Patent Application No. 63/146,395 filed February 5, 2021, U.S. Provisional Patent Application No. 63/185,695 filed May 7, 2021, U.S. Provisional Patent Application No. 63/146,357 filed February 5, 2021, U.S. Provisional Patent Application No. 63/185,704 filed May 7, 2021, U.S. Provisional Patent Application No. 63/146,369 filed February 5, 2021, and U.S. Provisional Patent Application No. 63/146,376 filed February 5, 2021, the entire contents of which are incorporated herein by reference.

BACKGROUND

Components of the RAS/RAF/MEK/ERK (MAPK) pathway represent opportunities for the treatment of abnormal cell growth, e.g., cancer. Selective inhibitors of certain components of the RAS/RAF/MEK/ERK pathway, such as RAS, RAF, MEK and ERK, are useful in the treatment of abnormal cell growth, in particular cancer, in mammals. Simultaneous targeting of multiple nodes in the MAPK pathway (vertical inhibition) may improve response (e.g., antitumor response, e.g., in depth and/or duration) compared to blocking a single node in the pathway. Additionally, the efficacy of MAPK pathway blockade may be circumvented through activation of resistance pathways, and thus co-targeting the MAPK pathway and relevant parallel pathways may be needed.

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

SUMMARY

In an aspect of the present disclosure, there is provided a use of a) an effective amount of a CDK4/6 inhibitor; and b) an effective amount of a dual RAF/MEK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof.

In another aspect of the present disclosure, there is provided a use of a) an effective amount of a SOS1 inhibitor; and b) an effective amount of a dual RAF/MEK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof.

In a further aspect of the present disclosure, there is provided a use of a) an effective amount of an ERK1/2 inhibitor; and b) an effective amount of a dual RAF/MEK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof.

In another aspect of the present disclosure, there is provided a use of a) an effective amount of a SHP2 inhibitor; and b) an effective amount of a dual RAF/MEK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof.

In a further aspect of the present disclosure, there is provided a use of a) an effective amount of an AKT inhibitor; and b) an effective amount of a dual RAF/MEK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof.

In another aspect of the present disclosure, there is provided a use of a) an effective amount of an mTOR inhibitor; and b) an effective amount of a dual RAF/MEK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof.

In a further aspect of the present disclosure, there is provided a use of a) an effective amount of a pan-HER inhibitor; and b) an effective amount of a dual RAF/MEK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof.

In another aspect of the present disclosure, there is provided a use of a) an effective amount of an EGFR inhibitor; and b) an effective amount of a dual RAF/MEK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof.

Simultaneous targeting of multiple nodes in the MAPK pathway, for example with SHP2 inhibitors, SOS1 inhibitors, ERK1/2 inhibitors, pan-HER inhibitors, or EGFR inhibitors, or co-targeting the MAPK pathway and relevant parallel pathways, for example with CDK4/6 inhibitors, AKT inhibitors, or mTOR inhibitors, may improve response (e.g., antitumor response, e.g., in depth and/or duration). Thus, provided herein, in part, are

combinations (e.g., combinations of compounds as described herein, e.g., a SHP2 inhibitor, a SOS1 inhibitor, an ERK1/2 inhibitor, a CDK4/6 inhibitor, an AKT inhibitor, an mTOR inhibitor, a pan-HER inhibitor, or an EGFR inhibitor in combination with 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.

Thus, in an ~~aspect~~example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a SHP2 inhibitor in combination with a MEK inhibitor, thereby treating the subject.

In another ~~aspect~~example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a SHP2 inhibitor in combination with a dual RAF/MEK inhibitor, thereby treating the subject.

In another ~~aspect~~example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a SOS1 inhibitor in combination with a MEK inhibitor, thereby treating the subject.

In another ~~aspect~~example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a SOS1 inhibitor in combination with a dual RAF/MEK inhibitor, thereby treating the subject.

In another ~~aspect~~example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a ERK1/2 inhibitor in combination with a MEK inhibitor, thereby treating the subject.

In another ~~aspect~~example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a ERK1/2 inhibitor in combination with a dual RAF/MEK inhibitor, thereby treating the subject.

In another ~~aspect~~example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a CDK4/6 inhibitor in combination with a MEK inhibitor, thereby treating the subject.

In another ~~aspect~~example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a CDK4/6 inhibitor in combination with a dual RAF/MEK inhibitor, thereby treating the subject.

In another ~~aspect~~example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject an AKT inhibitor in combination with a MEK inhibitor, thereby treating the subject.

In another ~~aspect~~example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject an AKT inhibitor in combination with a dual RAF/MEK inhibitor, thereby treating the subject.

In another ~~aspect~~example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject an mTOR inhibitor in combination with a MEK inhibitor, thereby treating the subject.

In another ~~aspect~~example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject an mTOR inhibitor in combination with a dual RAF/MEK inhibitor, thereby treating the subject.

In another ~~aspect~~example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a pan-HER inhibitor in combination with a MEK inhibitor, thereby treating the subject.

In another ~~aspect~~example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a pan-HER inhibitor in combination with a dual RAF/MEK inhibitor, thereby treating the subject.

In another ~~aspect~~example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a EGFR inhibitor in combination with a MEK inhibitor, thereby treating the subject.

In an ~~aspect~~example, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject a EGFR inhibitor in combination with a dual RAF/MEK inhibitor, thereby treating the subject.

In some ~~embodiment~~examples, the dual RAF/MEK inhibitor is a compound of formula (I), or a pharmaceutically acceptable salt thereof. In some ~~embodiment~~examples, the dual RAF/MEK inhibitor is a potassium salt of the compound of formula (I). Other pharmaceutically acceptable salts of the compound of formula (I) are contemplated herein in the disclosed methods of treatment.

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. 1A shows an exemplary CellTiter-Glo assay to evaluate cell viability on a 16 KRAS G12C, G12D or G12V mutant cell lines (9 NSCLC and 7 PDAC) grown in 3D conditions in a 7-day assay for VS-6766, RMS-4550, and TNO155.

FIG. 1B shows IC50 for VS-6766, TNO155, and RMC-4550.

CLAIMS

1. ~~A method of treating a cancer in a subject in need thereof, the method comprising administering to the subject~~Use of a) an effective amount of a CDK4/6 inhibitor; and b) an effective amount of a dual RAF/MEK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof ~~thereby treating the subject~~.

2. The ~~method~~ use of claim 1, wherein the CDK4/6 inhibitor is GLR2007, Roniciclib, RP-CDK4/6, TQB3303, Trilaciclib, SHR-6390, Lerociclib, FCN-437c, Milciclib, PF-06873600, XZP-3287, ON-123300, ETH-155008, HEC-80797, JS-104, PF-07220060, RMC-4550, SRX-3177, VS-2370), Palbociclib, Ribociclib, Letrozole + Ribociclib, or Abemaciclib, or a pharmaceutically acceptable salt thereof.

3. The ~~method~~ use of claim 1 or 2, wherein the CDK4/6 inhibitor is Abemaciclib, Palbociclib, or Ribociclib, or a pharmaceutically acceptable salt thereof.

4. The ~~method~~ use of any one of claims 1-3, wherein the CDK4/6 inhibitor is to be administered to the subject at least once daily.

5. The ~~method~~ use of any one of claims 1-4, wherein the CDK4/6 inhibitor is to be administered to the subject once daily.

6. The ~~method~~ use of any one of claims 1-4, wherein the CDK4/6 inhibitor is to be administered to the subject twice daily.

7. The ~~method~~ use of any one of claims 1-6, wherein the CDK4/6 inhibitor is to be administered to the subject orally.

8. The ~~method~~ use of any one of claims 1-7, wherein the CDK4/6 inhibitor is dosed at about 1 mg to about 1000 mg per administration.

9. ~~A method of treating a cancer in a subject in need thereof, the method comprising administering to the subject~~Use of a) an effective amount of a SOS1 inhibitor; and b) an effective amount of a dual RAF/MEK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof ~~thereby treating the subject~~.

10. The ~~method~~ use of claim 9, wherein the SOS1 inhibitor is BMS-SCH, SDGR5, BI-3406, BAY-293, RMC-5845, SDGR-5, or BI-1701963, or a pharmaceutically acceptable salt thereof.

11. The ~~method~~ use of claim 9 or 10, wherein the SOS1 inhibitor is SDGR-5, BI-3406, or BI-1701963, or a pharmaceutically acceptable salt thereof.

12. The ~~method~~ use of any one of claims 9-11, wherein the SOS1 inhibitor is to be administered to the subject at least once daily.

13. The ~~method~~ use of any one of claims 9-12, wherein the SOS1 inhibitor is to be administered to the subject once daily.

14. The ~~method~~ use of any one of claims 9-12, wherein the SOS1 inhibitor is to be administered to the subject twice daily.

15. The ~~method~~ use of any one of claims 9-14, wherein the SOS1 inhibitor is to be administered to the subject orally.

16. The ~~method~~ use of any one of claims 9-15, wherein the SOS1 inhibitor is dosed at about 1 mg to about 1000 mg per administration.

17. ~~A method of treating a cancer in a subject in need thereof, the method comprising administering to the subject~~Use of a) an effective amount of an ERK1/2 inhibitor; and b) an effective amount of a dual RAF/MEK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof~~thereby treating the subject~~.

18. The ~~method~~ use of claim 17, wherein the ERK1/2 inhibitor is AZ6197 , BI ERKi, CC-90003, ERAS-007, HMPL-295, IPN-ERK, KO-947, LTT462, SCH772984, TK216, ASTX-029, HH-2710, LY-3214996, ulixertinib, ASN-007, ATG-017, BPI-27336, JSI-1187, MK-8353, JRP-890, or JRF-108, or a pharmaceutically acceptable salt thereof.

19. The ~~method~~ use of claim 17 or 18, wherein the ERK1/2 inhibitor is LY-3214996, or a pharmaceutically acceptable salt thereof.

20. The ~~method~~ use of any one of claims 17-19, wherein the ERK1/2 inhibitor is to be administered to the subject at least once daily.

21. The ~~method~~ use of any one of claims 17-20, wherein the ERK1/2 inhibitor is to be administered to the subject once daily.

22. The ~~method~~ use of any one of claims 17-20, wherein the ERK1/2 inhibitor is to be administered to the subject twice daily.

23. The ~~method~~ use of any one of claims 17-22, wherein the ERK1/2 inhibitor is to be administered to the subject orally.

24. The ~~method~~ use of any one of claims 17-23, wherein the ERK1/2 inhibitor is dosed at about 1 mg to about 1000 mg per administration.

25. ~~A method of treating a cancer in a subject in need thereof, the method comprising administering to the subject~~Use of a) an effective amount of a SHP2 inhibitor; and b) an effective amount of a dual RAF/MEK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof ~~thereby treating the subject~~.

26. The ~~method~~ use of claim 25, wherein the SHP2 inhibitor is ERAS-601, TNO-155, SHP099, RMC-4630, RMC-4550, IACS-13909, JAB-3068, JAB-3312, RLY-1971, BBP-398, HBI-2376, or ICP-189, BR790, ETS-001, PF-07284892, RX-SHP2i, SH3809, TAS-ASTX, X-37-SHP2, or a pharmaceutically acceptable salt thereof.

27. The ~~method~~ use of claim 25 or 26, wherein the SHP2 inhibitor is JAB-3068, RMC-4630, TNO-155, JAB-3312, RLY-1971, BBP-398, HBI-2376, ICP-189, or RMC-4550, or a pharmaceutically acceptable salt thereof.

28. The ~~method~~ use of any one of claims 25-27, wherein the SHP2 inhibitor is to be administered to the subject at least once daily.

29. The ~~method~~use of any one of claims 25-28, wherein the SHP2 inhibitor is to be administered to the subject once daily.

30. The ~~method~~use of any one of claims 25-28, wherein the SHP2 inhibitor is to be administered to the subject twice daily.

31. The ~~method~~use of any one of claims 25-30, wherein the SHP2 inhibitor is to be administered to the subject orally.

32. The ~~method~~use of any one of claims 25-31, wherein the SHP2 inhibitor is dosed at about 1 mg to about 1000 mg per administration.

33. ~~A method of treating a cancer in a subject in need thereof, the method comprising administering to the subject~~Use of a) an effective amount of an AKT inhibitor; and b) an effective amount of a dual RAF/MEK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof ~~thereby treating the subject~~.

34. The ~~method~~use of claim 33, wherein the AKT inhibitor is capivasertib, ipatasertib, LY-2503029, afuresertib hydrochloride, COTI-2, miransertib mesylate, MK-2206, MK-2206 + selumetinib sulfate, ONC-201, PTX-200, TAS-117, trametinib dimethyl sulfoxide + uprosertib, uprosertib, ARQ-751, AT-13148, M2698, ALM-301, BAY-1125976, borussertib,

DC-120, FXY-1, JRP-890, KS-99, NISC-6, RX-0201, or RX-0301, or a pharmaceutically acceptable salt thereof.

35. The ~~method~~use of claim 33 or 34, wherein the AKT inhibitor is M2698 or ipatasertib, or a pharmaceutically acceptable salt thereof.

36. The ~~method~~use of any one of claims 33-35, wherein the AKT inhibitor is to be administered to the subject at least once daily.

37. The ~~method~~use of any one of claims 33-36, wherein the AKT inhibitor is to be administered to the subject once daily.

38. The ~~method~~use of any one of claims 33-36, wherein the AKT inhibitor is to be administered to the subject twice daily.

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

40. The ~~method~~use of any one of claims 33-39, wherein the AKT inhibitor is dosed at about 1 mg to about 1000 mg per administration.

41. ~~A method of treating a cancer in a subject in need thereof, the method comprising administering to the subject~~Use of a) an effective amount of an mTOR inhibitor; and b) an effective amount of a dual RAF/MEK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof~~thereby treating the subject~~.

42. The ~~method~~use of claim 41, wherein the mTOR inhibitor is everolimus, zortress, sirolimus, temsirolimus, sirolimus albumin-bound, dactolisib tosylate, onatasertib, DTRMWXHS-12 + everolimus + pomalidomide, bimiralisib, CC-115, monepantel, sapanisertib, sirolimus, vistusertib, detorsertib, FP-208, HEC-68498, LXI-15029, ME-344, PTX-367, WXFL-10030390, XP-105, paclitaxel + sirolimus + tanespimycin, AL-58805, AL-58922, AUM-302, CA-102, CA-103, CT-365, DFN-529, DHM-25, FT-1518, NSC-765844, omipalisib, OSU-53, OT-043, PQR-514, purinostat mesylate, QR-213, RMC-5552, SN-202, SPR-965, TAM-03, or OSI-027, or a pharmaceutically acceptable salt thereof.

43. The ~~method~~use of claim 41 or 42, wherein the mTOR inhibitor is everolimus, or a pharmaceutically acceptable salt thereof.

44. The ~~method~~use of any one of claims 41-43, wherein the mTOR inhibitor is to be administered to the subject at least once daily.

45. The ~~method~~use of any one of claims 41-44, wherein the mTOR inhibitor is to be administered to the subject once daily.

46. The ~~method~~use of any one of claims 41-44, wherein the mTOR inhibitor is to be administered to the subject twice daily.

47. The ~~method~~use of any one of claims 41-46, wherein the mTOR inhibitor is to be administered to the subject orally.

48. The ~~method~~use of any one of claims 41-47, wherein the mTOR inhibitor is dosed at about 1 mg to about 1000 mg per administration.

49. ~~A method of treating a cancer in a subject in need thereof, the method comprising administering to the subject~~Use of a) an effective amount of a pan-HER inhibitor; and b) an effective amount of a dual RAF/MEK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof~~thereby treating the subject~~.

50. The ~~method~~use of claim 49, wherein the pan-HER inhibitor is ZW49, PB 357, MP 0274, VRN 07, BDTX 189, sapitinib, zenocutuzumab, poziotinib, mobocertinib, valitinib, pyrotinib, lapatinib, afatinib, neratinib, or dacomitinib, or a pharmaceutically acceptable salt thereof.

51. The ~~method~~use of claim 49 or 50, wherein the pan-HER inhibitor is sapitinib, zenocutuzumab, poziotinib, mobocertinib, valitinib, pyrotinib, lapatinib, afatinib, neratinib, or dacomitinib, or a pharmaceutically acceptable salt thereof.

52. The ~~method~~use of any one of claims 49-51, wherein the pan-HER inhibitor is to be administered to the subject at least once daily.

53. The ~~method~~use of any one of claims 49-52, wherein the pan-HER inhibitor is to be administered to the subject once daily.

54. The ~~method~~use of any one of claims 49-52, wherein the pan-HER inhibitor is to be administered to the subject twice daily.

55. The ~~method~~use of any one of claims 49-54, wherein the pan-HER inhibitor is to be administered to the subject orally.

56. The ~~method~~use of any one of claims 49-55, wherein the pan-HER inhibitor is dosed at about 1 mg to about 1000 mg per administration.

57. ~~A method of treating a cancer in a subject in need thereof, the method comprising administering to the subject~~Use of a) an effective amount of an EGFR inhibitor; and b) an effective amount of a dual RAF/MEK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof.~~thereby treating the subject~~

58. The ~~method~~use of claim 57, wherein the EGFR inhibitor is doxorubicin + erlotinib, futuximab + modotuximab, abivertinib (e.g., abivertinib maleate), ABP-1119, ABP-1130, afatinib (e.g., afatinib dimaleate), AG-101, AL-6802, almonertinib (e.g., almonertinib mesylate), AM-105, amelimumab, amivantamab, AMX-3009, APL-1898, ASK-120067, AST-2818, BBT-176, BDTX-189, BEBT-108, BEBT-109, BH-2922, BLU-4810, BMX-002, BO-1978, BPI-15086, BPI-7711, brigatinib, C-005, cetuximab, CK-101, CLM-29, CLM-3, CMAB-017, CR-13626, CSHEGF-29, D-0316, D2C7-IT + PVSRIPO, dabrafenib mesylate + panitumumab + trametinib dimethyl sulfoxide, dacomitinib, DBPR-112, depatuxizumab, DGD-1202, doxitinib (e.g., doxitinib mesylate), DZD-9008, EO-1001, epertinib, erlotinib (e.g., erlotinib hydrochloride), ES-072, FCN-411, FHND-9041, FLAG-001, FLAG-003, FmAb-2, GB-263, GC-1118A, gefitinib, GS-03 + Osimertinib, HA-12128, HMPL-309, HMPL-813, HS-627, icotinib (e.g., icotinib hydrochloride), JMT-101, JRF-103, JZB-29, KBP-5209, KNP-501, KU-004, lapatinib (e.g., lapatinib ditosylate), larotinib, lazertinib, lifirafenib (e.g., lifirafenib maleate), MCLA-129, MCLA-158, MDC-22, mobocertinib, mRX-7, MTX-211, MVC-101, naquotinib (e.g., naquotinib mesylate), nazartinib (e.g., nazartinib mesylate), necitumumab, neratinib, nimotuzumab, NRC-2694, NT-004, NT-113, OBX-1012, olmutinib (e.g., olmutinib hydrochloride), osimertinib (e.g., osimertinib mesylate), panitumumab, PB-357, poziotinib, pyrotinib, QL-1105, QL-1203, RXDX-105, SAH-EJ1, sapitinib, SCT-200, selatinib (e.g., selatinib ditosilate), sirotinib, SKLB-1028, SKLB-1206, SPH-118811, SYN-004, TAS-6417, tesevatinib (e.g., tesevatinib tosylate), TGRX-360, tomuzotuximab, TQB-3804, UBP-1215, vandetanib, varlitinib, VRN-071918, VRN-6, WBP-297, WJ-13404, WSD-0922, XZP-5809, yinlitinib, YZJ-0318, ZNE-4, zorifertinib, ZR-2002, ZSP-0391, ORIC-114, DS-2087b, JS-111, LL-191, BI-4020, or BAY-2476568, or a pharmaceutically acceptable salt thereof.

59. The ~~method~~use of claim 57 or 58, wherein the EGFR inhibitor is afatinib or osimertinib, or a pharmaceutically acceptable salt thereof.

60. The ~~method~~use of any one of claims 57-59, wherein the EGFR inhibitor is to be administered to the subject at least once daily.

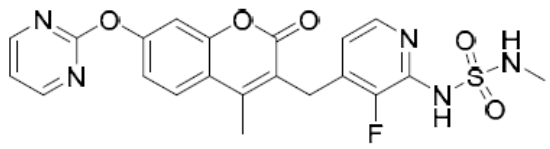
61. The ~~method~~use of any one of claims 57-60, wherein the EGFR inhibitor is to be administered to the subject once daily.

62. The ~~method~~use of any one of claims 57-60, wherein the EGFR inhibitor is to be administered to the subject twice daily.

63. The ~~method~~use of any one of claims 57-62, wherein the EGFR inhibitor is to be administered to the subject orally.

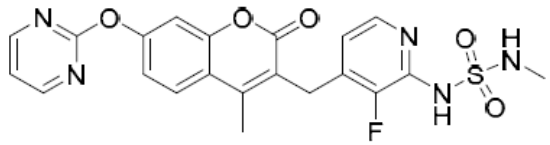
64. The ~~method~~use of any one of claims 57-63, wherein the EGFR inhibitor is dosed at about 1 mg to about 1000 mg per administration.

65. The ~~method~~use of any one of claims 1-64, wherein the dual RAF/MEK inhibitor is a compound of formula (I):



(I), or a pharmaceutically acceptable salt thereof.

66. The ~~method~~use of claim 65, wherein the dual RAF/MEK inhibitor is a compound of formula (I):



(I).

67. The ~~method~~use of claim 65, wherein the dual RAF/MEK inhibitor is a potassium salt of the compound of formula (I).

68. The ~~method~~use of any one of claims 1-67, wherein the dual RAF/MEK inhibitor is to be orally administered to the subject.

69. The ~~method~~use of any one of claims 1-68, wherein the dual RAF/MEK inhibitor is to be administered to the subject twice a week.

70. The ~~method~~use of any one of claims 1-69, wherein the dual RAF/MEK inhibitor is to be administered to the subject at a dose of 0.5 mg to about 10 mg per administration.

71. The ~~method~~use of claim 70, wherein the dual RAF/MEK inhibitor is dosed at 3.2 mg per administration.

72. The ~~method~~use of claim 70, wherein the dual RAF/MEK inhibitor is dosed at 4 mg per administration.

73. The ~~method~~use of any one of claims 1-72, wherein the dual RAF/MEK inhibitor is dosed as a cycle, and wherein ~~comprising administering~~ the dual RAF/MEK inhibitor is to be administered to the subject for three weeks and then not ~~administering the dual RAF/MEK inhibitor~~administered for one week.

74. The ~~method~~use of any one of claims 1-73, wherein the cancer is lung adenocarcinoma, non-small cell lung carcinoma, colorectal cancer, 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.

75. The ~~method~~use of any one of claims 1-73, 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.

76. The ~~method~~use of any one of claims 1-73, wherein the cancer is melanoma, lung cancer, colorectal cancer, ovarian cancer, thyroid cancer, glioblastoma, or renal cancer.

77. The ~~method~~use of claim 76, wherein the lung cancer is non-small cell lung cancer.

78. The ~~method~~use of claim 76, wherein the lung cancer is metastatic non-small cell lung cancer.

79. The ~~method~~use of claim 76, wherein the melanoma is unresectable melanoma.

80. The ~~method~~use of claim 76, wherein the melanoma is metastatic melanoma.

81. The ~~method~~use of claim 76, wherein the cancer is colorectal cancer.

82. The ~~method~~use of claim 76, wherein the cancer is ovarian cancer.

83. The ~~method~~use of any one of claims 1-82, wherein the cancer is identified as having a RAS mutation.

84. The ~~method~~use of any one of claims 1-83, wherein the cancer is identified as having a KRAS, NRAS, or HRAS mutation.

85. The ~~method~~use of claim 84, wherein the KRAS mutation is a mutation in KRAS G12V, KRAS G12D, KRAS G12A, KRAS G12R, KRAS G12S, or KRAS G12C.

86. The ~~method~~use of claim 84, wherein the KRAS mutation is a mutation in KRAS G13V, KRAS G13D, KRAS G13A, KRAS G13R, KRAS G13S, KRAS G13E, KRAS G12 dup, or KRAS G13C.

87. The ~~method~~use of claim 84, wherein the KRAS mutation is a mutation in KRAS Q61H, KRAS Q61K, KRAS Q61L, KRAS Q61R, KRAS Q61P, or KRAS Q61E.

88. The ~~method~~use of ~~claim~~ any one of claims 1-87, wherein the cancer is identified as having RAF mutation.

89. The ~~method~~use of ~~claim~~ any one of claims 1-88, wherein the cancer is identified as having a BRAF, ARAF, or CRAF mutation.

90. The ~~method~~use of claim 89, wherein the BRAF mutation is a BRAF V600 mutation.

91. The ~~method~~use of any one of claims 1-90, wherein the cancer is identified as having a MEK1 and/or MEK2 mutation.

92. The ~~method~~use of any one of claims 1-91, wherein the cancer is identified as having NF1 alterations, KRAS amplification, and/or NRAS amplification.

93. The ~~method~~use of any one of claims 1-92, wherein the cancer is identified as having positive phosphor-ERK protein expression (e.g., ≥ 10%, ≥20%, or ≥ 30% of cells) detected by immunohistochemistry.

94. The ~~method~~use of any one of claims 1-93, wherein the cancer is identified as having a EGFR alteration.