involved in modulating T-cell activity in e.g., peripheral tissues, e.g., via interaction with its ligands, i.e., PD-L1 and PD-L2. Blockers of the immune checkpoint pathway can enhance antitumor immunity and provide opportunities to treat abnormal cell growth and provide more effective treatment for subjects suffering from cancer.

[0005] 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

[0005a] In a first aspect of the present disclosure, there is provided a use of a dual RAF/MEK inhibitor, an anti-PD-1 antibody, and a KRAS G12C inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof, wherein the medicament is to be administered to the subject.

[0005b] In another aspect of the present disclosure, there is provided a use of a dual RAF/MEK inhibitor, an anti-PD-L1 antibody, and a KRAS G12C inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof, wherein the medicament is to be administered to the subject.

[0005c] In yet another aspect of the present disclosure, there is provided a use of a dual RAF/MEK inhibitor, an anti-PD-1 antibody, a KRAS G12C inhibitor, and a FAK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof.

[0005d] In a further aspect of the present disclosure, there is provided a use of a dual RAF/MEK inhibitor, an anti-PD-L1 antibody, a KRAS G12C inhibitor, and a FAK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof.

[0006] The present disclosure provides, in part, methods of treating abnormal cell growth (e.g., cancer) in a subject in need thereof. The methods disclosed herein, in some examples, comprise treating a cancer in a subject in need thereof by administering an effective amount of a dual RAF/MEK inhibitor (e.g., Compound 1 or a pharmaceutically acceptable salt thereof), an effective amount of an anti-PD-1 antibody or anti-PD-L1 antibody, and an effective amount of a KRAS G12C inhibitor, thereby treating the subject. The methods disclosed herein, in some examples, further comprise administering to the subject an effective amount of a FAK inhibitor (e.g., defactinib or a pharmaceutically acceptable salt thereof).

[0007] 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 an effective amount of a dual RAF/MEK inhibitor (e.g., Compound 1 or a pharmaceutically acceptable salt thereof), an effective amount of an anti-PD-1 antibody, and an effective amount of a KRAS G12C inhibitor, thereby treating the subject.

[0008] 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 an effective amount of a dual RAF/MEK inhibitor (e.g., Compound 1 or a pharmaceutically acceptable salt thereof), an effective amount of an anti-PD-L1 antibody, and an effective amount of a KRAS G12C inhibitor, thereby treating the subject.

[0009] 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 an effective amount of a dual RAF/MEK inhibitor (e.g., Compound 1 or a pharmaceutically acceptable salt thereof), an effective amount of an anti-PD-1 antibody, an effective amount of a KRAS G12C inhibitor, and an effective amount of a FAK inhibitor, thereby treating the subject.

[00010] 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 an effective amount of a dual RAF/MEK inhibitor (e.g., Compound 1 or a pharmaceutically acceptable salt thereof), an effective amount of an anti-PD-L1 antibody, an effective amount of a KRAS G12C inhibitor, and an effective amount of a FAK inhibitor, thereby treating the subject.

[00011] In some examples, the dual RAF/MEK inhibitor is Compound 1 or a pharmaceutically acceptable salt thereof. In some examples, the dual RAF/MEK inhibitor is Compound 1. In some examples, the dual RAF/MEK inhibitor is a pharmaceutically acceptable salt of Compound 1 (e.g., a potassium salt of Compound 1, i.e., VS-6766).

[00012] In some examples, the dual RAF/MEK inhibitor is dosed at least once a week. In some examples, the dual RAF/MEK inhibitor is dosed twice a week.

[00013] In some examples, the dual RAF/MEK inhibitor is dosed as a cycle, wherein the cycle comprises administering the dual RAF/MEK inhibitor for three weeks and then not administering the dual RAF/MEK inhibitor for one week. In some examples, the cycle is repeated at least once.

[00014] In some examples, the dual RAF/MEK inhibitor is dosed as a cycle, wherein the cycle comprises administering the dual RAF/MEK inhibitor twice a week for three weeks and then not administering the dual RAF/MEK inhibitor for one week. In some examples, the cycle is repeated at least once.

[00015] In some examples, the dual RAF/MEK inhibitor is dosed at about 0.8 mg to about 10 mg per administration. In some examples, the dual RAF/MEK inhibitor is dosed at about 0.8 mg to about 5 mg per administration. In some examples, the dual RAF/MEK inhibitor is dosed at about 2.4 mg per administration In some examples, the dual RAF/MEK inhibitor is dosed at about 3.2 mg per administration. In some examples, the dual RAF/MEK inhibitor is dosed at about 4 mg per administration.

[00016] In some examples, the anti-PD-1 antibody is selected from the group consisting of balstilimab, budigalimab, cadonilimab, camrelizumab, cemiplimab, cetrelimab, dostarlimab, exabenlimab, geptanolimab, nivolumab, pembrolizumab, penpulimab, pidilizumab, pimivalimab, prolgolimab, pucotenlimab, retifanlimab, sasanlimab, serplulimab, serplulimab, sintilimab, spartalizumab, sulituzumab, tebotelimab, teripalimab, tislelizumab, toripalimab, toripalimab, zimberelimab, AK-112 (Akeso Inc), AK-123 (Akeso Inc), ALPN-202 (Alpine Immune Sciences Inc), AMG-404 (Amgen), AMP-224 (MedImunne), AMP-514 (MedImunne), ASKG-915 (AskGene Pharma), AT-16201 (AIMM Therapeutics BV), AVI-102 (AbVision Inc), AZD-7789 (Astrazeneca), BAT-1308 (Bio-Thera Solutions Ltd), BCD-

217 (Biocad), BH-2950 (Beijing Hanmi Pharmaceutical Co Ltd), BSI-050K01 (Biosion Inc), CB-201 (Crescendo Biologics Ltd), CB-213 (Crescendo Biologics Ltd), CBT-103 (Cellective BioTherapy Inc), CBT-107 (Cellective BioTherapy Inc), CS-1003 (CStone Pharmaceuticals), CYTO-101 (Cytocom Inc), DB-004 (DotBio Pte Ltd), EX-105 (Excelmab Inc), EX-108 (Excelmab Inc), F-520 (Shandong New Time Pharmaceutical), GNR-051 (Generium), GR-1405 (Genrix Biopharmaceutical), HAB-21 (Suzhou Stainwei Biotech Inc), HX-009 (Waterstone Hanxbio Pty Ltd), IBI-319 (Innovent Biologics Inc), IBI-321 (Innovent Biologics Inc), IKT-202 (Icell Kealex Therapeutics LLC), IMU-201 (Imugene Ltd), JS-201 (Shanghai Junshi Bioscience Co Ltd), KD-050 (Kadmon), KJ-101 (KisoJi Biotechnology Inc), KLS-3021 (Kolon Life Science Inc), LBL-006 (Leads Biolabs Inc), LBL-024 (Leads Biolabs Inc), LD-01 (Leidos Health Holdings LLC), LNL-005 (L&L Biopharma), LQ-005 (Shanghai Novamab Biopharmaceuticals Co Ltd), LQ-008 (Shanghai Novamab Biopharmaceuticals Co Ltd), LZM-009 (Livzon Pharmaceutical Group), MEDI-5752 (Astrazeneca), MD-402 (MD Biosciences GmbH), MGD-019 (MacoGenics) OT-2 (OncoTrap Inc), OSE-279 (OSE Immunotherapeutics), PE-0105 (Shanghai Yunyi Health Technology Development Co Ltd), PF-07209960 (Pfizer Inc), PH-762 (Phio Pharmaceuticals Corp), PSB-205 (Qilu Puget Sound), QL-1604 (Qilu Pharmaceutical Co), REGN-PD-1/XX (Regeneron), RG-6139 (Hoffmann La Roche), RO7216661 (Hoffmann La Roche), RO7284755 (Hoffmann La Roche), SAUG-1 (Juvenescence UK Ltd), SAUG-2 (Juvenescence UK Ltd), SCTI-10A (Sinocelltech), SG-001 (CSPC Pharmaceutical Group Ltd), SHR-1701 (Jiangsu Hengrui Medicine), SIB-003 (SystImmune), SL-279137 (Shattuck Labs), SOT-201 (Sotio), SSI-361 (Lyvgen Biopharma Ltd), STIA-1015 (Sorrento Therapeutics), STI-A1110 (Servier), STM-418 (Stcube Inc), Sym-021 (Symphogen A/S), T-3011 (Immvira Co Ltd), TSR-075 (GlaxoSmithKline Plc), TY101 (Tayu Huaxia Biotech), Twist-PD-1 (Twist Bioscience), XmAb-TGFβR2 (Xencor), XmAb-YYCD28 (Xencor), XmAb20717 (Xencor), XmAb23104 (Xencor), YBL-006 (Y Biologics), YBL-019 (Y Biologics), and mDX-400 (Merck & Co Inc). In some examples, the anti-PD-1 antibody is selected from the group consisting of cemiplimab, nivolumab, pembrolizumab, pidilizumab, spartalizumab, camrelizumab, sintilimab, tislelizumab, toripalimab, dostarlimab, AMP-224, and AMP-514. In some examples, the anti-PD-1 antibody is selected from the group consisting of balstilimab, budigalimab, cadonilimab, camrelizumab, cemiplimab, cetrelimab, dostarlimab, exabenlimab, geptanolimab, nivolumab, pembrolizumab, penpulimab, pidilizumab, pimivalimab, prolgolimab, pucotenlimab, retifanlimab, sasanlimab,

serplulimab, serplulimab, sintilimab, spartalizumab, sulituzumab, tebotelimab, teripalimab, tislelizumab, toripalimab, toripalimab, and zimberelimab.

[00017] In some examples, the anti-PD-L1 antibody is selected from the group consisting of atezolizumab, bintrafusp alfa, avelumab, cosibelimab, durvalumab, envafolimab, lazertinib, lodapolimab, pacmilimab, socazolimab, sugemalimab, ABL-501 (ABL Bio) ABM-101 (Abeome Corp), ABP-160 (Abpro Corp), ABM-101 (Abeome Corp), ABSK-043 (Abbisko Therapeutics), ACE-1708 (Acepodia), ADG-104 (Adagene Suzhou Ltd), AP-505 (AP Biosciences Inc), APL-502 (Apollomics, Inc), APL-801 (Apollomics Inc), ASC-61 (Ascletis Pharma), ASC-63 (Ascletis Pharma), ATG-101 (Antengene Corp Ltd), AVA-004 (Avacta Life Sciences), AVA-021 (Avacta Life Sciences), AVA-027 (Avacta Life Sciences Ltd), AVA-040 (Avacta Life Sciences), AUNP12 (Aurigene), B-1961 (AP Biosciences Inc), BAT-7104 (Bio-Thera), BBI-801 (Sumitomo Dainippon Pharma Oncology, Inc), BH-3012 (Hanmi Pharmaceuticals Co Ltd), BH-3120 (Hanmi Pharmaceuticals Co Ltd), BMS-986189 (Bristol Myers Squibb), BMX-101 (Onward Therapeutics SA), BNT-311 (BioNTech), BPI-9220 (Beta Pharma Inc), BPI-9320 (Beta Pharma Inc), CA-170 (Curis Inc), CCX-559 (ChemoCentryx Inc), CDR-1 (CDR-Life Inc), KJ-CDX-527 (Celldex Therapeutics), CK-301 (cosibelimab), CS-17938 (Shenzhen Chipscreen Biosciences Co Ltd), CTX-8371 (Compass Therapeutics Inc), CYTCDR-2 (CytImmune Sciences Inc), DB-002 (DotBio Pte Ltd), DB-003 (DotBio Pte Ltd), DF-002 (Suzhou Dingfu Target Biotechnology Co Ltd), DPDL-1E (Shanghai Hycharm Inc), DR-30207 (Zhejiang Doer Biologics Corp), DSP-105 (KAHR medical Ltd), DSP-502 (KAHR medical Ltd), EI-011 (Elixiron Immunotherapeutics Inc), EI-014 (Elixiron Immunotherapeutics Inc), EMB-08 (EpimAb Biotherapeutics Inc), ENN-101 (Ennovabio), ENN-102 (Ennovabio), EPIM-001 (Elpis Biopharmaceuticals Corp), FAZ-053 (Novartis), FS-118 (F-star Therapeutics Inc), GB-262 (Genor BioPharma Co Ltd), GB-7003 (Shanghai GeneChem Co Ltd), GR-1405 (Genrix (Shanghai) Biopharmaceutical Co Ltd), GS-19 (Gensun Biopharma Inc), GS-4224 (Gilead Sciences), Gensci-047 (GeneScience Pharmaceuticals Co Ltd), HB-0025 (Huabo Biopharm (Shanghai) Co Ltd), HB-0028 (Huabo Biopharm (Shanghai) Co Ltd), HB-0036 (Huabo Biopharm (Shanghai) Co Ltd), HBM-7015 (Harbour BioMed (Guangzhou) Co Ltd), HLX-20 (Shanghai Henlius Biotech), HS-636 (Zhejiang Hisun), IBI-318 (Innovent Biologics), IBI-322 (Innovent Biologics), IBI-323 (Innovent Biologics), IBI-327 (Innovent Biologics Inc), IGM-7354 (IGM Biosciences Inc), IKT-201 (Icell Kealex Therapeutics LLC), IMC-2101 (ImmuneOncia Therapeutics LLC), IMC-2102 (ImmuneOncia Therapeutics LLC), IMGS-002 (Immunogenesis Inc), IMM-2505 (ImmuneOnco Biopharmaceuticals (Shanghai) Co

Ltd), IMM-2510 (ImmuneOnco Biopharmaceuticals (Shanghai) Co Ltd), IMM-2520 (ImmuneOnco Biopharmaceuticals (Shanghai) Co Ltd), IMMH-010 (Tianjin Chase Sun Pharmaceutical Co Ltd), INCB-86550 (Incyte), INBRX-105 (Elpiscience Biopharmaceutical Ltd), IO-103 (IO Biotech), JBI-426 (Jubilant Therapeutics Inc), JNB-809 (JN Biosciences LLC), JNB-813 (JN Biosciences LLC), JS-003 (Shanghai Junshi Biosciences), KD-033 (Kadmon), KLA-167 (Sichuan Kelun Pharmaceutical), KN-046 (Alphamab Oncology), KN-052 (Alphamab Oncology), KY-1043 (Kymab Ltd), LP-002 (Lepu Biopharma Co Ltd), LP-008 (Lepu Biopharma Co Ltd), LQ-002 (Shanghai Novamab Biopharmaceuticals Co Ltd), LQ-004 (Shanghai Novamab Biopharmaceuticals Co Ltd), LVGN-1673 (Lyvgen Biopharma Ltd), LY-3434172 (Eli Lilly and Co), LYN-102 (LynkCell Inc), Max-10181 (Maxinovel Pharmaceuticals), MCLA-145 (Merus NV), MEDI-7526 (AstraZeneca Plc), MSB-2311 (Transcenta Holding), ND-021 (Numab Therapeutics), PF-07257876 (Pfizer), PH-790 (Phio Pharmaceuticals Corp), PM-1003 (Biotheus Inc), PM-8001 (Biotheus Inc), PMC-122 (PharmAbcine Inc), PRS-344 (Pieris Pharmaceuticals Inc), Q-1802 (QureBio), QL-301 (QLSF Biotherapeutics Inc), QLS31901 (Qilu Pharmaceutical), RC98 (RemeGen), SHR-1316 (Jiangsu Hengrui Medicine Co Ltd), SHR-1701 (Jiangsu Hengrui Medicine Co Ltd), SIM-236 (Jiangsu Simcere Pharmaceutical Co Ltd), SIM-237 (Jiangsu Simcere Pharmaceutical Co Ltd),SL-279252 (Shattuck Labs Inc), SL-279258 (Shattuck Labs Inc), SLSP-03 (Salspera LLC), SNA-02 (Oneness Biotech Co Ltd), SPX-301 (Sparx Therapeutics Inc), STIA-1014 (Sorrento Therapeutics), STIA-1015 (Sorrento Therapeutics), STT-01 (Stcube Inc), TI-1007 (Timmune Biotech), TJL-1C4 (I-Mab Biopharma), TJL-1D5 (I-Mab Biopharma), TJL-1H3 (I-Mab Biopharma), TJL-1I7 (I-Mab Biopharma), TJL-14B (I-Mab Biopharma), TS1905 (Luye Pharma Group), TST-005 (Transcenta Holding Ltd), TST-006 (Transcenta Holding Ltd), TTXsiPDL-1 (Transcode Therapeutics Inc), TXB-4BC3 (Ossianix Inc), VS-161 (Virogin Biotech), VXM-10 (Vaximm AG), WP-1066 (Moleculin Biotech), Y-111 (Wuhan YZY), YBL-007 (Y-Biologics Inc), YBL-008 (Y-Biologics Inc), YBL-009 (Y-Biologics Inc), YBL-013 (Y-Biologics Inc), YBL-016 (Y-Biologics Inc), and YBL-020 (Y-Biologics Inc). In some examples, the anti-PD-L1 antibody is selected from the group consisting of atezolizumab, bintrafusp alfa, avelumab, cosibelimab, durvalumab, envafolimab, lazertinib, lodapolimab, pacmilimab, socazolimab, and sugemalimab.

[00018] In some examples, the KRAS G12C inhibitor is selected from the group consisting of ARS-853 (Araxes Pharma), ARS-1620 (Araxes Pharma), ARS-3248 (Araxes Pharma), LY3499446 (Eli Lilly), AMG-510 (sotorasib), MRTX849 (adagrasib), APG-1842 (Ascentage Pharma), AST KRAS G12C inhibitor (Allist Pharmaceuticals), AZ KRAS G12C

inhibitor (AstraZeneca), D-1553 (InventisBio), GDC-6036 (Genentech), JAB-21000 (Jacobio Pharmaceuticals), JAB-21822 (Jacobio Pharmaceuticals), JDQ443 (Novartis), JNJ-74699157 (Janssen), LY3537982 (Eli Lilly), MRTX1257 (Mirati Therapeutics), RMC-6291 (Revolution Medicines), SF KRAS G12C inhibitor (Sanofi), X-Chem KRAS (X-Chem Pharmaceuticals), BI 1823911 (Boehringer Ingelheim), MK-1084 (Merck), YL-15293 (Shanghai YingLi Pharmaceutical), GFH925 (GenFleet), GH35 (Genhouse Bio), BPI-421286 (Betta Pharmaceuticals Co.), D3S-001 (D3 Bui), ZG19018 (Zejing Pharmaceuticals), HS-10370 (Jiangsu Hansoh Pharmaceutical), G12C inhibitor (Frontier Medicines), and EB160 (Shanghai Euregen Biopharma), or a pharmaceutically acceptable salt thereof. In some examples, the KRAS G12C inhibitor is ARS-853, ARS-1620, ARS-3248, sotorasib, adagrasib, APG-1842, D-1553, GDC-6036, JAB-21822, JDQ443, JNJ-74699157, LY3537982, MRTX1257, RMC-6291, BI 1823911, MK-1084 YL-15293, GFH925, GH35, BPI-421286, D3S-001, ZG19018, HS-10370, or EB160, or a pharmaceutically acceptable salt thereof. In some examples, the KRAS G12C inhibitor is ARS-853, ARS-1620, ARS-3248, sotorasib, adagrasib, GDC-6036, JDQ443, LY3537982, or MRTX1257, or a pharmaceutically acceptable salt thereof. In some examples, the KRAS G12C inhibitor is sotorasib or a pharmaceutically acceptable salt thereof. In some examples, the KRAS G12C inhibitor is adagrasib or a pharmaceutically acceptable salt thereof.

[00019] In some examples, the cancer is a cancer characterized as having a RAS mutation. In some examples, the cancer is a cancer characterized as having a KRAS mutationIn some examples, the cancer is a cancer characterized as having KRAS G12C mutation.

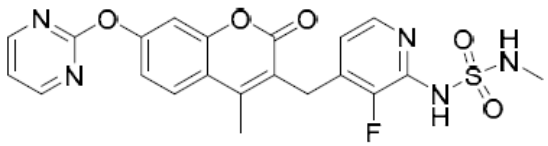
[00020] In some examples, the cancer is lung cancer, colorectal cancer, uveal melanoma, ovarian cancer, uterine endometrioid carcinoma, bladder urothelial carcinoma, breast invasive lobular carcinoma, cervical squamous cell carcinoma, cutaneous melanoma, endocervical adenocarcinoma, hepatocellular carcinoma, 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.

[00021] 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 dual RAF/MEK inhibitor, an anti-PD-1 antibody, and a KRAS G12C inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof, wherein the medicament is to be administered to the subject.

2. The use of claim 1, wherein the dual RAF/MEK inhibitor is a compound of formula (I):



(I),

or a pharmaceutically acceptable salt thereof.

3. The use of claim 1 or 2, wherein the dual RAF/MEK inhibitor is to be dosed at least once a week.

4. The use of any one of claims 1-3, wherein the dual RAF/MEK inhibitor is to be dosed twice a week.

5. The use of claim 1 or 2, 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 twice a week for three weeks and then the dual RAF/MEK inhibitor is not administered for one week.

6. The use of claim 5, wherein the cycle is repeated at least once.

7. The use of any one of claims 1-6, wherein the dual RAF/MEK inhibitor is to be dosed at about 0.8 mg to about 10 mg per administration.

8. The use of any one of claims 1-7, wherein the dual RAF/MEK inhibitor is to be dosed at about 2.4 mg per administration.

9. The use of any one of claims 1-7, wherein the dual RAF/MEK inhibitor is to be dosed at about 3.2 mg per administration.

10. The use of any one of claims 1-7, wherein the dual RAF/MEK inhibitor is to be dosed at about 4 mg per administration.

11. The use of any one of claims 1-10, wherein the dual RAF/MEK inhibitor is to be administered orally.

12. The use of any one of claims 1-11, wherein the anti-PD-1 antibody is selected from the group consisting of balstilimab, budigalimab, cadonilimab, camrelizumab, cemiplimab, cetrelimab, dostarlimab, exabenlimab, geptanolimab, nivolumab, pembrolizumab, penpulimab, pidilizumab, pimivalimab, prolgolimab, pucotenlimab, retifanlimab, sasanlimab, serplulimab, serplulimab, sintilimab, spartalizumab, sulituzumab, tebotelimab, teripalimab, tislelizumab, toripalimab, toripalimab, and zimberelimab.

13. The use of any one of claims 1-12, wherein the anti-PD-1 antibody is to be dosed at least once a week.

14. The use of any one of claims 1-12, wherein the anti-PD-1 antibody is to be dosed every two weeks.

15. The use of any one of claims 1-12, wherein the anti-PD-1 antibody is to be dosed every three weeks.

16. The use of any one of claims 1-12, wherein the anti-PD-1 antibody is to be dosed every four weeks.

17. The use of any one of claims 1-12, wherein the anti-PD-1 antibody is to be dosed every six weeks.

18. The use of any one of claims 1-17, wherein the anti-PD-1 antibody is to be dosed at about 100 mg to about 1000 mg per administration.

19. The use of any one of claims 1-18, wherein the anti-PD-1 antibody is to be administered parenterally.

20. The use of any one of claims 1-19, wherein the KRAS G12C inhibitor is selected from the group consisting of ARS-853, ARS-1620, ARS-3248, LY3499446, sotorasib, adagrasib, APG-1842, AST KRAS G12C inhibitor, AZ KRAS G12C inhibitor, D-1553, GDC-6036, JAB-21000, JAB-21822, JDQ443, JNJ-74699157, LY3537892, MRTX1257,

RMC-6291, SF KRAS G12C inhibitor, X-Chem KRAS, BI 1823911, MK-1084, YL-15293, GFH925, GH35, BPI-421286, D3S-001, ZG19018, HS-10370, and EB160, or a pharmaceutically acceptable salt thereof.

21. The use of any one of claims 1-20, wherein the KRAS G12C inhibitor is ARS-853, ARS-1620, ARS-3248, sotorasib, adagrasib, APG-1842, D-1553, GDC-6036, JAB-21822, JDQ443, JNJ-74699157, LY3537982, MRTX1257, RMC-6291, BI 1823911, MK-1084, YL-15293, GFH925, GH35, BPI-421286, D3S-001, ZG19018, HS-10370, or EB160, or a pharmaceutically acceptable salt thereof.

22. The use of any one of claims 1-21, wherein the KRAS G12C inhibitor is ARS-853, ARS-1620, ARS-3248, sotorasib, adagrasib, GDC-6036, JDQ443, LY3537982, or MRTX1257, or a pharmaceutically acceptable salt thereof.

23. The use of any one of claims 1-22, wherein the KRAS G12C inhibitor is sotorasib or a pharmaceutically acceptable salt thereof.

24. The use of any one of claims 1-22, wherein the KRAS G12C inhibitor is adagrasib or a pharmaceutically acceptable salt thereof.

25. The use of any one of claims 1-24, wherein the KRAS G12C inhibitor is to be dosed at about 100 mg to about 2000 mg per administration.

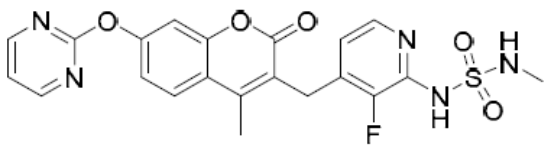
26. The use of any one of claims 1-25, wherein the KRAS G12C inhibitor is to be administered once daily.

27. The use of any one of claims 1-25, wherein the KRAS G12C inhibitor is to be administered twice daily.

28. The use of any one of claims 1-27, wherein the KRAS G12C inhibitor is to be administered orally.

29. Use of a dual RAF/MEK inhibitor, an anti-PD-L1 antibody, and a KRAS G12C inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof, wherein the medicament is to be administered to the subject.

30. The use of claim 29, wherein the dual RAF/MEK inhibitor is a compound of formula (I):



(I),

or a pharmaceutically acceptable salt thereof.

31. The use of claim 29 or 30, wherein the dual RAF/MEK inhibitor is to be dosed at least once a week.

32. The use of any one of claims 29-31, wherein the dual RAF/MEK inhibitor is to be dosed twice a week.

33. The use of claim 29 or 30, 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 twice a week for three weeks and then the dual RAF/MEK inhibitor is not administered for one week.

34. The use of claim 33, wherein the cycle is repeated at least once.

35. The use of any one of claims 29-34, wherein the dual RAF/MEK inhibitor is to be dosed at about 0.8 mg to about 10 mg per administration.

36. The use of any one of claims 29-35, wherein the dual RAF/MEK inhibitor is to be dosed at about 2.4 mg per administration.

37. The use of any one of claims 29-35, wherein the dual RAF/MEK inhibitor is to be dosed at about 3.2 mg per administration.

38. The use of any one of claims 29-35, wherein the dual RAF/MEK inhibitor is to be dosed at about 4 mg per administration.

39. The use of any one of claims 29-38, wherein the dual RAF/MEK inhibitor is to be administered orally.

40. The use of any one of claims 29-39, wherein the anti-PD-L1 antibody is selected from the group consisting of atezolizumab, bintrafusp alfa, avelumab, cosibelimab, durvalumab, envafolimab, lazertinib, lodapolimab, pacmilimab, socazolimab, and sugemalimab.

41. The use of any one of claims 29-40, wherein the anti-PD-L1 antibody is to be administered parenterally.

42. The use of any one of claims 29-41, wherein the anti-PD-L1 antibody is to be dosed at least once a week.

43. The use of any one of claims 29-41, wherein the anti-PD-L1 antibody is to be administered every two weeks.

44. The use of any one of claims 29-41, wherein the anti-PD-L1 antibody is to be administered every three weeks.

45. The use of any one of claims 29-41, wherein the anti-PD-L1 antibody is to be administered every four weeks.

46. The use of any one of claims 29-45, wherein the anti-PD-L1 antibody is to be dosed at about 100 mg to about 2000 mg per administration.

47. The use of any one of claims 29-46, wherein the KRAS G12C inhibitor is selected from the group consisting of ARS-853, ARS-1620, ARS-3248, LY3499446, sotorasib, adagrasib, APG-1842, AST KRAS G12C inhibitor, AZ KRAS G12C inhibitor, D-1553, GDC-6036, JAB-21000, JAB-21822, JDQ443, JNJ-74699157, LY3537892, MRTX1257, RMC-6291, SF KRAS G12C inhibitor, X-Chem KRAS, BI 1823911, MK-1084, YL-15293, GFH925, GH35, BPI-421286, D3S-001, ZG19018, HS-10370, and EB160, or a pharmaceutically acceptable salt thereof.

48. The use of any one of claims 29-47, wherein the KRAS G12C inhibitor is ARS-853, ARS-1620, ARS-3248, sotorasib, adagrasib, APG-1842, D-1553, GDC-6036, JAB-21822, JDQ443, JNJ-74699157, LY3537982, MRTX1257, RMC-6291, BI 1823911, MK-1084, YL-15293, GFH925, GH35, BPI-421286, D3S-001, ZG19018, HS-10370, or EB160, or a pharmaceutically acceptable salt thereof.

49. The use of any one of claims 29-48, wherein the KRAS G12C inhibitor is ARS-853, ARS-1620, ARS-3248, sotorasib, adagrasib, GDC-6036, JDQ443, LY3537982, or MRTX1257, or a pharmaceutically acceptable salt thereof.

50. The use of any one of claims 29-49, wherein the KRAS G12C inhibitor is sotorasib or a pharmaceutically acceptable salt thereof.

51. The use of any one of claims 29-49, wherein the KRAS G12C inhibitor is adagrasib or a pharmaceutically acceptable salt thereof.

52. The use of any one of claims 29-51, wherein the KRAS G12C inhibitor is to be dosed at about 100 mg to about 2000 mg per administration.

53. The use of any one of claims 29-52, wherein the KRAS G12C inhibitor is to be administered once daily.

54. The use of any one of claims 29-52, wherein the KRAS G12C inhibitor is to be administered twice daily.

55. The use of any one of claims 29-54, wherein the KRAS G12C inhibitor is to be administered orally.

56. The use of any one of claims 1-55, wherein a FAK inhibitor is to be further administered to the subject.

57. The use of claim 56, wherein the FAK inhibitor is defactinib or a pharmaceutically acceptable salt thereof.

58. The use of claim 56 or 57, wherein the FAK inhibitor is to be dosed twice daily.

59. The use of claim 56 or 57, wherein the FAK inhibitor is to be dosed once daily.

60. The use of any one of claims 56-59, wherein the FAK inhibitor is to be dosed at about 100 mg to about 1000 mg per administration.

61. The use of any one of claims 56-60, wherein the FAK inhibitor is to be dosed at about 200 mg to about 400 mg per administration.

62. The use of any one of claims 56-61, wherein the FAK inhibitor is to be dosed at about 200 mg per administration.

63. The use of any one of claims 56-61, wherein the FAK inhibitor is to be dosed at about 400 mg per administration.

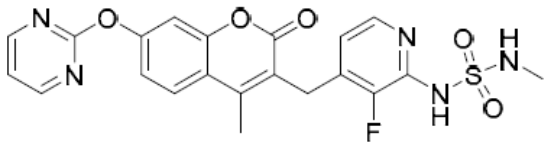
64. The use of any one of claims 56-63, wherein the FAK inhibitor is to be administered orally.

65. The use of any one of claims 56-64, 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 dual RAF/MEK inhibitor is not administered for one week.

66. Use of a dual RAF/MEK inhibitor, an anti-PD-1 antibody, a KRAS G12C inhibitor, and a FAK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof.

67. Use of a dual RAF/MEK inhibitor, an anti-PD-L1 antibody, a KRAS G12C inhibitor, and a FAK inhibitor, in the manufacture of a medicament for treating a cancer in a subject in need thereof.

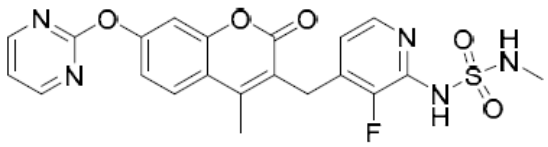
68. The use of claim 66 or 67, wherein the dual RAF/MEK inhibitor is a compound of formula (I):



(I),

or a pharmaceutically acceptable salt thereof.

69. The use of any one of claims 1-68, wherein the dual RAF/MEK inhibitor is a potassium salt of the compound of formula (I):



(I).

70. The use of any one of claims 1-69, wherein the cancer is a cancer characterized as having a RAS mutation.

71. The use of claim 70, wherein the RAS mutation is a KRAS mutation.

72. The use of claim 71, wherein the KRAS mutation is KRAS G12C mutation.

73. The use of any one of claims 1-72, wherein the cancer is lung cancer, colorectal cancer, pancreatic cancer, uveal melanoma, ovarian 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.

74. The use of any one of claims 1-73, wherein the cancer is lung cancer, colorectal cancer, pancreatic cancer, or ovarian cancer.

75. The use of claim 73 or 74, wherein the lung cancer is non-small cell lung cancer.

76. The use of claim 73 or 74, wherein the ovarian cancer is low grade serous ovarian cancer.

77. The use of claim 73 or 74, wherein the cancer is colorectal cancer.