(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
02 February 2023 (02.02.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/009572 A1

(51) International Patent Classification:
A61K 31/33 (2006.01) *A61K 31/4433* (2006.01)
A61K 31/18 (2006.01) *A61K 31/00* (2006.01)
A61K 31/4375 (2006.01)

(21) International Application Number:
PCT/US2022/038434

(22) International Filing Date:
27 July 2022 (27.07.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/203,555 27 July 2021 (27.07.2021) US

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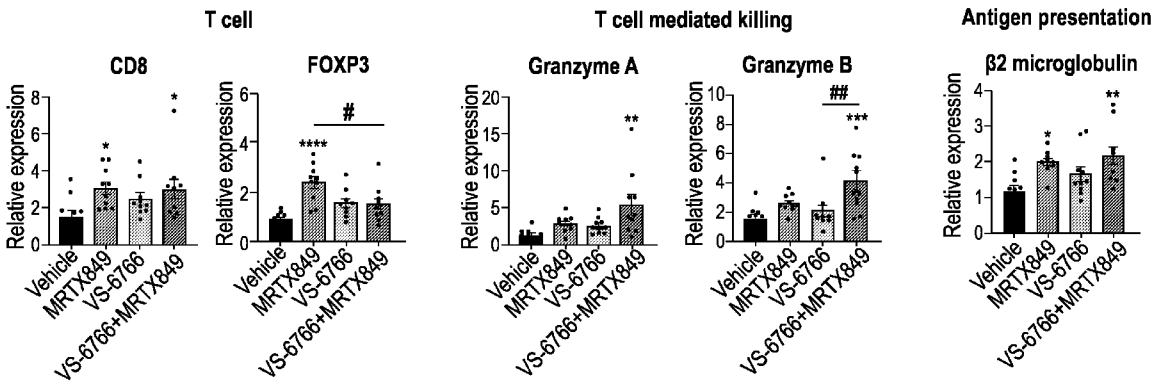
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*

(54) **Title:** COMBINATION THERAPY FOR TREATING ABNORMAL CELL GROWTH



(57) **Abstract:** The present disclosure relates to methods, compositions, and oral dosage forms of a dual RAF/MEK inhibitor, in combination with an anti-PD-1 antibody or an anti-PD-L1 antibody, and a KRAS G12C inhibitor, and optionally a FAK inhibitor, for treating abnormal cell growth (e.g., cancer).

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COMBINATION THERAPY FOR TREATING ABNORMAL CELL GROWTH

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of U.S. Provisional Patent Application Number 63/203,555, filed July 27, 2021, which is incorporated herein by reference in its entirety.

BACKGROUND

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

[0003] Kirsten Rat Sarcoma 2 Viral Oncogene Homolog (KRAS) is a small GTPase and a member of the Ras family of oncogenes. KRAS serves as a molecular switch cycling between inactive (GDP-bound) and active (GTP-bound) states to transduce upstream cellular signals received from multiple tyrosine kinases to downstream effectors to regulate a wide variety of processes, including cellular proliferation (e.g., see Alamgeer et al., (2013) *Current Opin. Pharmcol.* 13:394-401). KRAS gene mutations are common in cancers, for example, pancreatic cancer, lung adenocarcinoma, colorectal cancer (CRC), gall bladder cancer, thyroid cancer, and bile duct cancer (Kodaz et al., *EJMO* 2017).

[0004] Immune checkpoints refer to a plethora of inhibitory pathways that help maintain self-tolerance and modulate the duration and amplitude of physiological immune responses in peripheral tissues in order to minimize collateral tissue damage. Tumors co-opt certain immune checkpoint pathways as a mechanism of immune resistance, particularly against T-cells that are specific for tumor antigens. The development of checkpoint blocking antibodies, e.g., inhibitory receptors, that target or are directed against, for example, programmed death 1 receptor (PD-1), can facilitate the treatment of abnormal cell growth. PD-1 can function as negative regulators and have non-redundant roles in modulating immune responses. They are expressed on tumor-specific T-cells and can lead to compromised activation and suppressed effector functions e.g., proliferation, cytokine secretion, and tumor cell lysis. PD-1 is

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

[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 embodiments, 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 embodiments, 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 aspect, 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 aspect, 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 aspect, 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 aspect, 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 embodiments, the dual RAF/MEK inhibitor is Compound 1 or a pharmaceutically acceptable salt thereof. In some embodiments, the dual RAF/MEK inhibitor is Compound 1. In some embodiments, 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 embodiments, the dual RAF/MEK inhibitor is dosed at least once a week. In some embodiments, the dual RAF/MEK inhibitor is dosed twice a week.

[00013] In some embodiments, 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 embodiments, the cycle is repeated at least once.

[00014] In some embodiments, 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 embodiments, the cycle is repeated at least once.

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

[00016] In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the KRAS G12C inhibitor is sotorasib or a pharmaceutically acceptable salt thereof. In some embodiments, the KRAS G12C inhibitor is adagrasib or a pharmaceutically acceptable salt thereof.

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

[00020] In some embodiments, 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[00022] **FIG. 1** shows an exemplary combination of a dual RAF/MEK inhibitor and a KRAS G12C inhibitor making the immune microenvironment favorable for combining with an anti-PD-1 antibody.

DETAILED DESCRIPTION

[00023] The present disclosure provides, in some embodiments, methods and combinations of compounds useful for treating abnormal cell growth (e.g., cancer) in a subject in need thereof.

Definitions

[00024] "About" and "approximately" shall generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Exemplary degrees of error are within 20 percent (%), typically, within 10%, and more typically, within 5% of a given value or range of values.

[00025] As used herein, "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the compounds of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like. Pharmaceutically acceptable salts derived from

appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[00026] As used herein, "pharmaceutically acceptable carrier" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions described herein include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[00027] As used herein, a "subject" to which administration is contemplated includes, but is not limited to, humans (i.e., a male or female of any age group, e.g., a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle–aged adult or senior adult)) and/or a non-human animal, e.g., a mammal such as primates (e.g., cynomolgus monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats, and/or dogs. In some embodiments, the subject is a human. In some embodiments, the subject is a non-human animal. The terms "human," "patient," and "subject" are used interchangeably herein.

[00028] Disease, disorder, and condition are used interchangeably herein.

[00029] As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" contemplate an action that occurs while a subject is suffering from the specified disease, disorder or condition, which reduces the severity of the disease, disorder or condition, or retards or slows the progression of the disease, disorder or condition (also "therapeutic treatment").

[00030] In general, the "effective amount" of a compound refers to an amount sufficient to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound of the disclosure may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the

disease being treated, the mode of administration, and the age, weight, health, and condition of the subject.

[00031] As used herein, and unless otherwise specified, a "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment of a disease, disorder or condition, or to delay or minimize one or more symptoms associated with the disease, disorder or condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the disease, disorder or condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease or condition, or enhances the therapeutic efficacy of another therapeutic agent.

[00032] As used herein, "prophylactic treatment" contemplates an action that occurs before a subject begins to suffer from the specified disease, disorder or condition.

[00033] As used herein, and unless otherwise specified, a "prophylactically effective amount" of a compound is an amount sufficient to prevent a disease, disorder or condition, or one or more symptoms associated with the disease, disorder or condition, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the disease, disorder or condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[00034] The term, "oral dosage form," as used herein, refers to a composition or medium used to administer an agent to a subject. Typically, an oral dosage form is administered via the mouth, however, "oral dosage form" is intended to cover any substance which is administered to a subject and is absorbed across a membrane, e.g., a mucosal membrane, of the gastrointestinal tract, including, e.g., the mouth, esophagus, stomach, small intestine, large intestine, and colon. For example, "oral dosage form" covers a solution which is administered through a feeding tube into the stomach.

[00035] A "cycle", as used herein in the context of a cycle of administration of a drug, refers to a period of time for which a drug is administered and may further include a rest period of not administering the drug to a subject. In some embodiments, one cycle is four weeks.

[00036] A "RAS mutation" is a mutation in the RAS gene. For example, a "KRAS mutation" is a mutation of the KRAS gene (i.e., a nucleic acid mutation) or Kras protein (i.e., an amino acid mutation) that results in aberrant Kras protein function associated with increased and/or constitutive activity by favoring the active GTP-bound state of the Kras protein. The mutation may be at conserved sites that favor GTP binding and constitutively active Kras protein. In some instances, the mutation is at one or more of codons 12, 13, and 16 of the KRAS gene. For example, a KRAS mutation may be at codon 12 of the KRAS gene, for instance, as a single point substitution mutation at codon 12 (i.e., KRAS G12X mutation) (e.g., a KRAS G12V mutation arises from a single nucleotide change (c.35G>T) and results in an amino acid substitution of the glycine (G) at position 12 by a valine (V)).

Methods of Treatment

[00037] The combinations provided herein, for example, a combination of a dual RAF/MEK inhibitor, an anti-PD-1 antibody and/or an anti-PD-L1 antibody, and a KRAS G12C inhibitor, and optionally a FAK inhibitor, provide significant anti-tumor effects when compared to monotherapies alone administered for the equivalent duration and/or dosage amounts. The combinations provided herein provide opportunities for improving overall survival of subjects, reducing the risk of developing resistance to monotherapies, and reducing or preventing adverse side effects compared to prolonged administration of monotherapies. Thus, combinations of compounds described herein (e.g., an effective amount of a dual RAF/MEK inhibitor, an effective amount of an anti-PD-1 antibody and/or an anti-PD-L1 antibody, and an effective amount of a KRAS G12C inhibitor, and optionally an effective amount of a FAK inhibitor) and pharmaceutical compositions thereof are useful in methods of treating abnormal cell growth such as cancer.

[00038] In an aspect, 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, an effective amount of an anti-PD-1 antibody, and an effective amount of a KRAS G12C inhibitor, thereby treating the subject.

[00039] In another aspect, 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, an effective amount of an anti-PD-L1 antibody, and an effective amount of a KRAS G12C inhibitor, thereby treating the subject.

[00040] In another aspect, 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

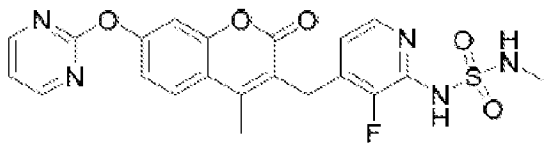
dual RAF/MEK inhibitor, an effective amount of an anti-PD-1 antibody, an effective amount of a KRAS G12C inhibitor, and a FAK inhibitor, thereby treating the subject.

[00041] In another aspect, 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 dual RAF/MEK inhibitor, an effective amount of an anti-PD-L1 antibody, an effective amount of a KRAS G12C inhibitor, and a FAK inhibitor, thereby treating the subject.

Dual RAF/MEK Inhibitors

[00042] An exemplary dual RAF/MEK inhibitor described herein is VS-6766 (also referred to as CKI27, CH5126766, or RO5126766).

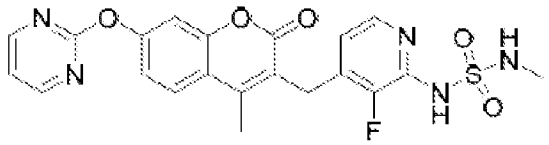
[00043] In some embodiments, the dual RAF/MEK inhibitor is a compound of formula (I):



(I),

or a pharmaceutically acceptable salt thereof.

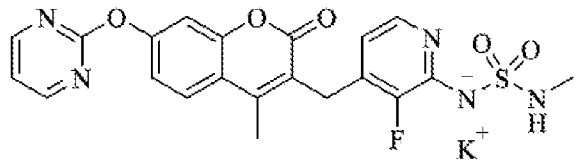
[00044] In some embodiments, the compound of formula (I) is:



(I),

which is also referred to herein as Compound 1 or VS-6766 free form.

[00045] In some embodiments, the dual RAF/MEK inhibitor is a pharmaceutically acceptable salt of the compound of formula (I). In some embodiments, the dual RAF/MEK inhibitor is a potassium salt of the compound of formula (I), which is also referred to as VS-6766. In some embodiments, VS-6766 has the following structure:



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[00046] Other pharmaceutically acceptable salts of the compound of formula (I) are contemplated herein.

[00047] In some embodiments, the dual RAF/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 embodiments, the dual RAF/MEK inhibitor is dosed once a week. In some embodiments, the dual RAF/MEK inhibitor is dosed twice a week. In some embodiments, the dual RAF/MEK inhibitor is dosed three times a week.

[00048] In some embodiments, the dual RAF/MEK inhibitor is dosed at about 0.1 mg to about 100 mg, e.g., about 0.1 mg to about 50 mg, about 0.1 mg to about 10 mg, about 0.1 mg to about 5 mg, about 0.1 mg to about 4 mg, about 0.1 mg to about 3 mg, about 0.1 mg to about 2 mg, about 0.1 mg to about 1 mg, about 1 mg to about 10 mg, about 1 mg to about 20 mg, about 1 mg to about 40 mg, about 1 mg to about 60 mg, about 1 mg to about 80 mg, about 1 mg to about 100 mg, about 10 mg to about 100 mg, about 20 mg to about 100 mg, about 40 mg to about 100 mg, about 60 mg to about 100 mg, or about 80 mg to about 100 mg per administration. In some embodiments, the dual RAF/MEK inhibitor is dosed at about 0.5 mg to about 10 mg per administration. In some embodiments, dual RAF/MEK inhibitor is dosed at about 0.8 mg to about 10 mg per administration. In some embodiments, the dual RAF/MEK inhibitor is dosed at about 0.1 mg, 0.2 mg, 0.5 mg, 1 mg, 1.5 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, or 100 mg per administration. In some embodiments, the dual RAF/MEK inhibitor is dosed at about 0.8 mg to about 10 mg per administration. In some embodiments, the dual RAF/MEK inhibitor is dosed at about 0.8 mg to about 5 mg per administration. In some embodiments, the dual RAF/MEK inhibitor is dosed at about 1 mg to about 4 mg per administration. In some embodiments, the dual RAF/MEK inhibitor is dosed at about 1 mg to about 3 mg per administration. In some embodiments, the dual RAF/MEK inhibitor is dosed at about 2 mg to about 5 mg per administration. In some embodiments, the dual RAF/MEK inhibitor is dosed at about 2 mg to about 4 mg per administration. In some embodiments, the dual RAF/MEK inhibitor is dosed at about 2 mg to about 3 mg per administration. In some embodiments, dual RAF/MEK inhibitor is dosed at about 4 mg per administration. In some embodiments, the dual RAF/MEK inhibitor is dosed at about 3.2 mg per administration. In some embodiments, the dual RAF/MEK inhibitor is dosed at about 2.4 mg per administration. In some embodiments, the dual RAF/MEK inhibitor is administered orally.

[00049] In some embodiments, the dual RAF/MEK inhibitor is dosed as a cycle comprising administering the dual RAF/MEK inhibitor for three weeks and then not administering the dual RAF/MEK inhibitor for one week. In some embodiments, the dual

RAF/MEK inhibitor is dosed twice a week. In some embodiments, the dual RAF/MEK inhibitor is dosed three times a week. In some embodiments, the dual RAF/MEK inhibitor is dosed at about 0.8 mg to about 10 mg (e.g., about 4 mg or about 3.2 mg or about 2.4 mg) per administration.

[00050] In some embodiments, the dual RAF/MEK inhibitor is dosed as a cycle comprising administering the dual RAF/MEK inhibitor twice a week at a dose of about 0.8 mg to about 10 mg per administration (e.g., about 4 mg or about 3.2 mg or about 2.4 mg per administration) for three weeks and then not administering the dual RAF/MEK inhibitor for one week. In some embodiments, the cycle is repeated at least once.

[00051] In some embodiments, the dual RAF/MEK inhibitor is dosed as a cycle comprising administering the dual RAF/MEK inhibitor three times a week at a dose of about 0.8 mg to about 10 mg per administration (e.g., about 4 mg or about 3.2 mg or about 2.4 mg per administration) for three weeks and then not administering the dual RAF/MEK inhibitor for one week. In some embodiments, the cycle is repeated at least once.

[00052] In alternative embodiments, the dual RAF/MEK inhibitor is dosed continuously (i.e., without the one week of not administering the dual RAF/MEK inhibitor). In some embodiments, the dual RAF/MEK inhibitor is dosed twice a week. In some embodiments, the dual RAF/MEK inhibitor is dosed three times a week. In some embodiments, the dual RAF/MEK inhibitor is dosed at about 0.8 mg to about 10 mg (e.g., about 4 mg or about 3.2 mg or about 2.4 mg) per administration. In some embodiments, the dual RAF/MEK inhibitor is dosed for at least four weeks. In some embodiments, the dual RAF/MEK inhibitor is dosed for four weeks.

[00053] In some embodiments, the dual RAF/MEK inhibitor is administered to the subject twice a week at a dose of about 0.8 mg to about 10 mg per administration (e.g., about 4 mg or about 3.2 mg or about 2.4 mg per administration) then dosed cyclically (as a cycle comprising administering the dual RAF/MEK inhibitor for three weeks and then not administering the dual RAF/MEK inhibitor for one week), wherein the cycle is repeated at least once. In some embodiments, the dual RAF/MEK inhibitor when dosed as a cycle comprises administering the dual RAF/MEK inhibitor twice a week at a dose of about 0.8 mg to about 10 mg per administration (e.g., about 4 mg or about 3.2 mg or about 2.4 mg per administration) for three weeks and then not administering the dual RAF/MEK inhibitor for one week.

[00054] In some embodiments, the dual RAF/MEK inhibitor is administered to the patient three times a week at a dose of about 0.8 mg to about 10 mg per administration (e.g.,

about 4 mg or about 3.2 mg or about 2.4 mg per administration) then dosed cyclically (as a cycle comprising administering the dual RAF/MEK inhibitor for three weeks and then not administering the dual RAF/MEK inhibitor for one week), wherein the cycle is repeated at least once. In some embodiments, the dual RAF/MEK inhibitor when dosed as a cycle comprises administering the dual RAF/MEK inhibitor three times a week at a dose of about 0.8 mg to about 10 mg per administration (e.g., about 4 mg or about 3.2 mg or about 2.4 mg per administration) for three weeks and then not administering the dual RAF/MEK inhibitor for one week.

Anti-PD-1 Antibodies/Anti-PD-L1 Antibodies

[00055] Antibody therapies are antibody proteins produced by the immune system and that bind to a target antigen on the surface of a cell. Antibodies are typically encoded by an immunoglobulin gene or genes, or fragments thereof. In normal physiology antibodies are used by the immune system to fight pathogens. Each antibody is specific to one or a few proteins, and those that bind to cancer antigens are used, e.g. , for the treatment of cancer. Antibodies are capable of specifically binding an antigen or epitope. (Fundamental Immunology, 3rd Edition, W.e., Paul, ed., Raven Press, N.Y. (1993)). Specific binding occurs to the corresponding antigen or epitope even in the presence of a heterogeneous population of proteins and other biologies. Specific binding of an antibody indicates that it binds to its target antigen or epitope with an affinity that is substantially greater than binding to irrelevant antigens. The relative difference in affinity is often at least 25% greater, more often at least 50% greater, most often at least 100% greater. The relative difference can be at least 2-fold, at least 5-fold, at least 10-fold, at least 25-fold, at least 50-fold, at least 100-fold, or at least 1000-fold, for example.

[00056] Exemplary types of antibodies include without limitation human, humanized, chimeric, monoclonal, polyclonal, single chain, antibody binding fragments, and diabodies. Once bound to a cancer antigen, antibodies can induce antibody-dependent cell-mediated cytotoxicity, activate the complement system, prevent a receptor interacting with its ligand or deliver a payload of chemotherapy or radiation, all of which can lead to cell death.

[00057] In some embodiments, 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 embodiments, 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 embodiments, 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. In some embodiments, the anti-PD-1 antibody is nivolumab. In some embodiments, the anti-PD-1 antibody is pembrolizumab.

[00058] In some embodiments, the anti-PD-1 antibody is dosed at least once a week. In some embodiments, the anti-PD-1 antibody is dosed once a week. In some embodiments, the anti-PD-1 antibody is dosed twice a week. In other embodiments, the anti-PD-1 antibody is dosed every 2 weeks. In other embodiments, the anti-PD-1 antibody is dosed every 3 weeks. In other embodiments, the anti-PD-1 antibody is dosed every 4 weeks. In other embodiments, the anti-PD-1 antibody is dosed every 5 weeks. In other embodiments, the anti-PD-1 antibody is dosed every 6 weeks.

[00059] In some embodiments, the anti-PD-1 antibody is dosed at about 10 mg to about 5000 mg, about 10 mg to about 4000 mg, about 10 mg to about 3000 g, about 10 mg to about 2000 mg, about 10 mg to about 1000 mg, about 100 mg to about 2000 mg, about 100 mg to about 1500 mg, about 100 mg to about 1000 mg, about 100 mg to about 800 mg, about 100 mg to about 500 mg, about 200 mg to about 500 mg, (e.g., about 200 mg, 240 mg, or about 480 mg) per administration.

[00060] In some embodiments, the anti-PD-1 antibody is administered parenterally (e.g., intravenous infusion).

[00061] In some embodiments, 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 embodiments, 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,

[00062] In some embodiments, the anti-PD-L1 antibody is dosed at least once a week. In some embodiments, the anti-PD-L1 antibody is dosed once a week. In some embodiments, the anti-PD-L1 antibody is dosed twice a week. In other embodiments, the anti-PD-L1 antibody is dosed every 2 weeks. In other embodiments, the anti-PD-L1 antibody is dosed every 3 weeks. In other embodiments, the anti-PD-L1 antibody is dosed every 4 weeks. In other embodiments, the anti-PD-L1 antibody is dosed every 5 weeks. In other embodiments, the anti-PD-L1 antibody is dosed every 6 weeks.

[00063] In some embodiments, the anti-PD-L1 antibody is dosed at about 10 mg to about 5000 mg, about 10 mg to about 4000 mg, about 10 mg to about 3000 g, about 10 mg to about 2000 mg, about 10 mg to about 1000 mg, about 100 mg to about 2000 mg, about 100 mg to about 1500 mg, about 100 mg to about 1000 mg, about 100 mg to about 800 mg, about 100 mg to about 500 mg, about 200 mg to about 500 mg, about 500 mg to about 1500 mg, about 500 mg to about 1200 mg, about 800 mg to about 1200 mg, about 800 mg to about 1500 mg, per administration. For example, in some embodiments, the anti-PD-L1 antibody is dosed at about 400 mg, about 800 mg, or about 1200 mg per administration.

[00064] In some embodiments, the anti-PD-L1 antibody is administered parenterally (e.g., intravenous infusion).

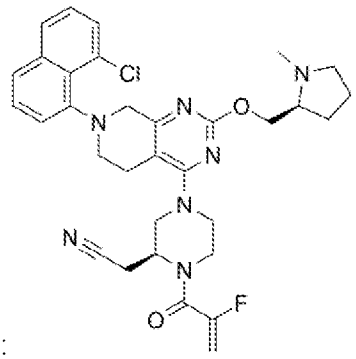
[00065] In some embodiments, the methods described herein contemplate administering to the subject in need thereof an anti-PD-1 and anti-PD-L1 bispecific antibody (e.g., wherein the bispecific antibody targets both PD-1 and PD-L1. Exemplary anti-PD-1 and

anti-PD-L1 bispecific antibodies include, but are not limited to, CTX-8371, LY 3434172, and IBI318.

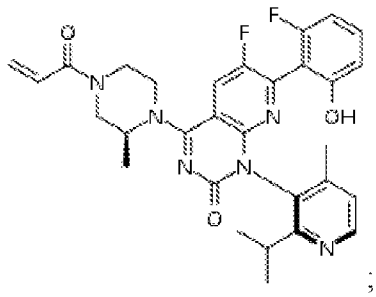
[00066] In some embodiments, the methods described herein contemplate administering to the subject in need thereof an effective amount of an anti-PD-1 antibody and an effective amount of anti-PD-L1 antibody. In some embodiments, the anti-PD-1 antibody is administered concurrently with the anti-PD-L1 antibody. In some embodiments, the anti-PD-1 antibody is administered prior to the anti-PD-L1 antibody. In some embodiments, the anti-PD-1 antibody is administered subsequent to the anti-PD-L1 antibody.

KRAS G12C inhibitors

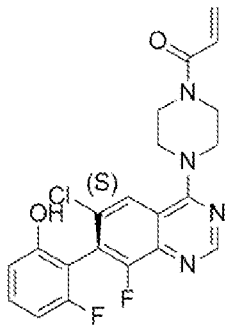
[00067] Exemplary KRAS G12C inhibitors include, but are not limited to:



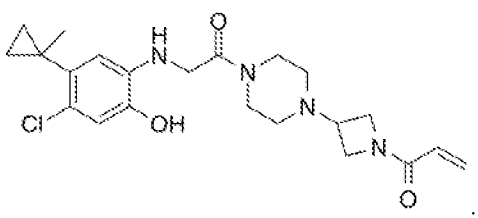
MRTX849 (adagrasib) having the following structure: ;



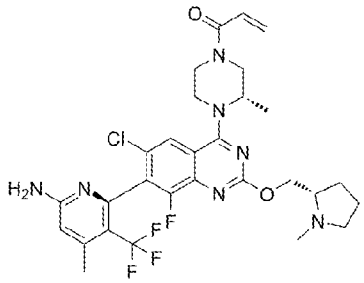
AMG-510 (sotorasib) having the following structure: ;



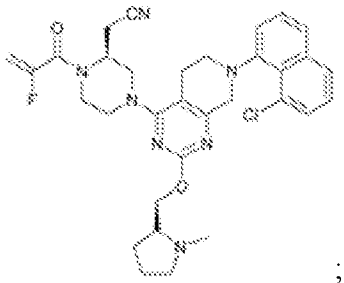
ARS-1620 having the following structure: ;



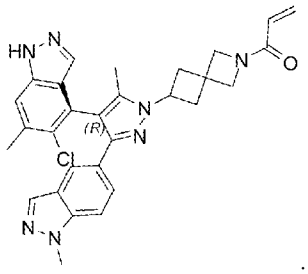
ARS-853 having the following structure: ;



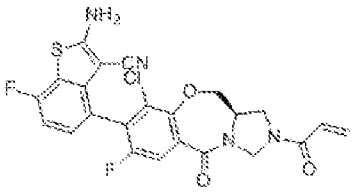
GDC-6036 having the following structure: ;



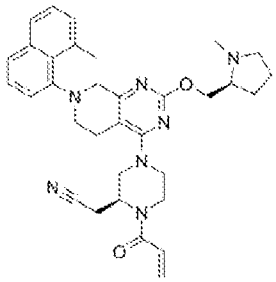
ARS-3248 having the following structure: ;



JDQ443 having the following structure: ;



LY3537982 having the following structure: ;



MRTX1257 having the following structure: ;

LY3499446 (Eli Lilly); APG-1842 (Ascentage Pharma), AST KRAS G12C inhibitor (Allist Pharmaceuticals), AZ KRAS G12C inhibitor (AstraZeneca), D-1553 (InventisBio), JAB-21000 (Jacobio Pharmaceuticals), JAB-21822 (Jacobio Pharmaceuticals), JNJ-74699157 (Janssen), 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 Bio), 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 embodiments, 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 embodiments, 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 embodiments, the KRAS G12C inhibitor is sotorasib or a pharmaceutically acceptable salt thereof. In some embodiments, the KRAS G12C inhibitor is adagrasib or a pharmaceutically acceptable salt thereof.

[00068] In some embodiments, the KRAS G12C inhibitor is administered at least once daily. In some embodiments, the KRAS G12C inhibitor is administered once daily. In some embodiments, the KRAS G12C inhibitor is administered twice daily. In some embodiments, the KRAS G12C inhibitor is administered orally.

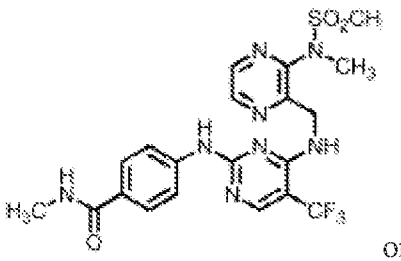
[00069] In some embodiments, the KRAS G12C inhibitor is dosed at about 10 mg to about 2000 mg, e.g., about 100 mg to about 2000 mg, about 100 mg to about 1500 mg, about 100 mg to about 1000 mg, about 100 mg to about 800 mg, about 100 mg to about 600 mg, about 100 mg to about 400 mg, about 100 mg to about 200 mg, about 200 mg to about 2000 mg, about 200 mg to about 1500 mg, about 200 mg to about 1000 mg, about 200 mg to about 800 mg, about 200 mg to about 600 mg, about 200 mg to about 400 mg, about 400 mg to about 2000 mg, about 400 mg to about 1500 mg, about 400 mg to about 1000 mg, about 400 mg to about 800 mg, about 400 mg to about 600 mg, about 600 mg to about 2000 mg, about 600 mg to about 1500 mg, about 600 mg to about 1000 mg, about 600 mg to about 800 mg, about 800 mg to about 2000 mg, 800 mg to about 1500 mg, about 800 mg to about 1000 mg, about 600 mg to about 2000 mg, about 600 mg to about 1500 mg, about 600 mg to about 1000 mg, about 600 mg to about 800 mg per administration. In some embodiments, the KRAS G12C inhibitor is dosed at about 100 mg per administration. In some embodiments, the KRAS G12C inhibitor is dosed at about 200 mg per administration. In some embodiments, the KRAS G12C inhibitor is dosed at about 300 mg per administration. In some embodiments, the KRAS G12C inhibitor is dosed at about 400 mg per administration. In some embodiments, the KRAS G12C inhibitor is dosed at about 500 mg per

administration. In some embodiments, the KRAS G12C inhibitor is dosed at about 600 mg per administration. In some embodiments, the KRAS G12C inhibitor is dosed at about 700 mg per administration. In some embodiments, the KRAS G12C inhibitor is dosed at about 800 mg per administration. In some embodiments, the KRAS G12C inhibitor is dosed at about 900 mg per administration. In some embodiments, the KRAS G12C inhibitor is dosed at about 1000 mg per administration.

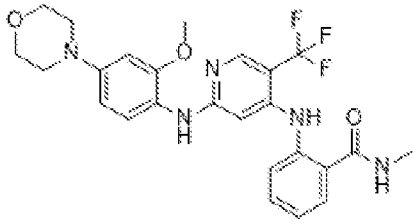
FAK Inhibitors

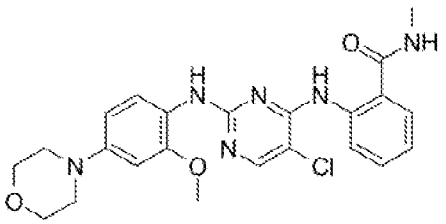
[00070] Potent inhibitors of the FAK protein tyrosine kinases may be adapted to therapeutic use as antiproliferative agents (e.g., anticancer), antitumor (e.g., effective against solid tumors), antiangiogenesis (e.g., stop or prevent proliferation of blood vessels) in mammals, particularly in humans. In some embodiments, the methods described herein further contemplate administering to the subject a FAK inhibitor described herein. The FAK inhibitors is useful in the prevention and treatment of non-hematologic malignancies, a variety of human hyperproliferative disorders such as malignant and benign tumors of the liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, lung, vulval, thyroid, hepatic carcinomas, sarcomas, glioblastomas, head and neck, and other hyperplastic conditions such as benign hyperplasia of the skin (e.g., psoriasis) and benign hyperplasia of the prostate (e.g., BPH), and in the prevention and treatment of disorders such as mesothelioma. In some embodiments, the compounds described herein, e.g., FAK inhibitors, inhibit protein tyrosine kinase 2 (PYK2).

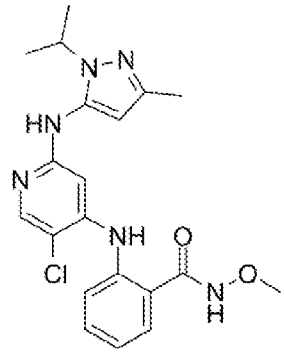
[00071] An exemplary FAK inhibitor includes, but is not limited to, defactinib having the following structure:

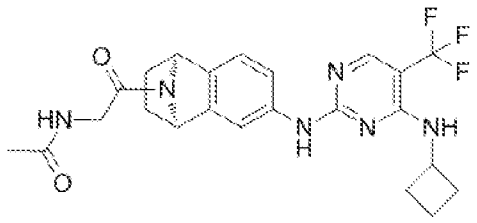


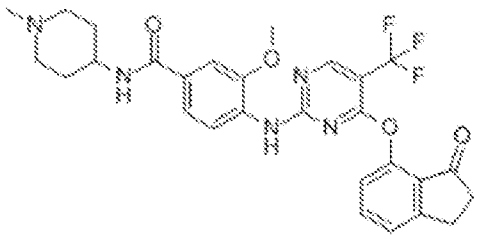
or a pharmaceutically acceptable salt thereof. Defactinib is also known as VS-6063 (e.g., VS-6063 free base) or PF-04554878. VS-6063 and related compounds are also disclosed in, for example, U.S. Patent No. 7,928,109, the content of which is incorporated herein by reference. In some embodiments, VS-6063 can form a pharmaceutically acceptable salt (e.g., VS-6063 hydrochloride).

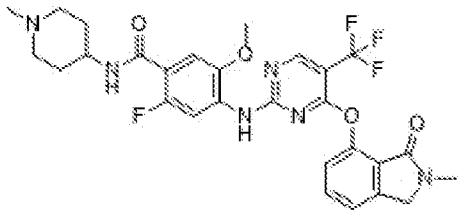
[00072] In some embodiments, the FAK inhibitor is VS-4718, having the following structure:  or a pharmaceutically acceptable salt thereof.

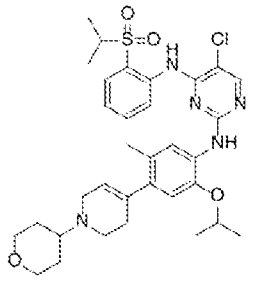
[00073] In some embodiments, the FAK inhibitor is TAE226, having the following structure:  or a pharmaceutically acceptable salt thereof.

[00074] In some embodiments, the FAK inhibitor is GSK2256098, having the following structure:  or a pharmaceutically acceptable salt thereof.

[00075] In some embodiments, the FAK inhibitor is PF-03814735, having the following structure:  or a pharmaceutically acceptable salt thereof.

[00076] In some embodiments, the FAK inhibitor is BI-4464, having the following structure:  or a pharmaceutically acceptable salt thereof.

[00077] In some embodiments, the FAK inhibitor is BI-853520 having the following structure:  or a pharmaceutically acceptable salt thereof.

[00078] In some other embodiments, the FAK inhibitor is APG-2449 having the following structure:  or a pharmaceutically acceptable salt thereof.

[00079] In some embodiments, the FAK inhibitor is selected from the group consisting of defactinib, TAE226, BI-853520, GSK2256098, PF-03814735, BI-4464, VS-4718, and APG-2449, or a pharmaceutically acceptable salt thereof. For example, in some embodiments, the FAK inhibitor is defactinib or a pharmaceutically acceptable salt thereof.

[00080] In some embodiments, the FAK inhibitor is dosed at least once daily. For example, in some embodiments, the FAK inhibitor is dosed twice daily. In some embodiments, the FAK inhibitor is dosed once daily.

[00081] In some embodiments, the FAK inhibitor is dosed at about 100 mg to about 1000 mg, e.g., about 100 mg to about 800 mg, about 100 mg to about 600 mg, about 100 mg to about 400 mg, about 100 mg to about 200 mg, about 200 mg to about 1000 mg, about 400 mg to about 1000 mg, about 600 mg to about 1000 mg, about 800 mg to about 1000 mg, about 200 mg to about 800 mg, about 200 mg to about 600 mg, about 200 mg to about 400 mg, about 400 mg to about 800 mg, or about 400 mg to about 600 mg per administration. In some embodiments, the FAK inhibitor is dosed at about 200 mg to about 400 mg per administration. In some embodiments, the FAK inhibitor is dosed at about 100 mg per administration. In some embodiments, the FAK inhibitor is dosed at about 200 mg per administration. In some embodiments, the FAK inhibitor is dosed at about 300 mg per administration. In some embodiments, the FAK inhibitor is dosed at about 400 mg per administration. In some embodiments, the FAK inhibitor is dosed at about 500 mg per administration. In some embodiments, the FAK inhibitor is dosed at about 600 mg per administration. In some embodiments, the FAK inhibitor is administered orally.

[00082] In some embodiments, the FAK inhibitor is dosed as a cycle comprising administering the FAK inhibitor for three weeks and then not administering FAK inhibitor for one week. In some embodiments, the cycle is repeated at least once.

[00083] In alternative embodiments, the FAK inhibitor is dosed continuously (i.e., without one week of not administering the FAK inhibitor). In some embodiments, the FAK inhibitor is dosed for at least four weeks.

Diseases and Disorders

Abnormal Cell Growth

[00084] Abnormal cell growth, as used herein and unless otherwise indicated, refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) that proliferate, for example, by expressing a mutated tyrosine kinase or overexpression of a receptor tyrosine kinase; (2) benign and malignant cells of other proliferative diseases, for example, in which aberrant tyrosine kinase activation occurs; (3) any tumors that proliferate, for example, by receptor tyrosine kinases; (4) any tumors mat proliferate, for example, by aberrant serine/threonine kinase activation; and (5) benign and malignant cells of other proliferative diseases, for example, in which aberrant serine/threonine kinase activation occurs. Abnormal cell growth can refer to cell growth in epithelial (e.g., carcinomas, adenocarcinomas): mesenchymal (e.g., sarcomas (e.g. leiomyosarcoma. Ewing's sarcoma)); hematopoetic (e.g., lymphomas, leukemias, myelodysplasias (e.g., pre-malignant)); or other (e.g., melanoma, mesothelioma, and other tumors of unknown origin) cell.

Neoplastic Disorders

[00085] Abnormal cell growth can refer to a neoplastic disorder. A "neoplastic disorder" is a disease or disorder characterized by cells that have the capacity for autonomous growth or replication, e.g., an abnormal state or condition characterized by proliferative cell growth. An abnormal mass of tissue as a result of abnormal cell growth or division, or a "neoplasm," can be benign, pre-malignant (carcinoma in situ) or malignant (cancer).

[00086] Exemplary neoplastic disorders include: carcinoma, sarcoma, metastatic disorders (e.g., tumors arising from prostate, colon, lung, breast and liver origin), hematopoietic neoplastic disorders, e.g., leukemias, metastatic tumors. Treatment with the compound is in an amount effective to ameliorate at least one symptom of the neoplastic disorder, e.g., reduced cell proliferation, reduced tumor mass, etc.

Cancers

[00087] The methods of the present disclosure is useful in the prevention and treatment of cancer, including for example, solid tumors, soft tissue tumors, and metastases thereof. The disclosed methods are also useful in treating non-solid cancers. Exemplary solid tumors include malignancies (e.g., sarcomas, adenocarcinomas, and carcinomas) of the various organ systems, such as those of lung, breast, lymphoid, gastrointestinal (e.g., colon), and genitourinary (e.g., renal, urothelial, or testicular tumors) tracts, pharynx, prostate, and ovary. Exemplary adenocarcinomas include colorectal cancers, renal-cell carcinoma, liver cancer (e.g.. Hepatocellular carcinoma), non-small cell carcinoma of the lung, pancreatic (e.g., metastatic pancreatic adenocarcinoma) and cancer of the small intestine.

[00088] The cancer can include mesothelioma; neurofibromatosis; e.g., neurofibromatosis type 2, neurofibromatosis type 1; renal cancer; lung cancer, non small cell lung cancer; liver cancer; thyroid cancer; ovarian; breast cancer; a nervous system tumor; schwannoma; meningioma; schwannomatosis; neuroma acoustic; adenoid cystic carcinoma; ependymoma; ependymal tumors, or any other tumor which exhibits decreased merlin expression and/or mutation, and/or deletion and/or promotor hypermethylation of the NF-2 gene. In some embodiments, the cancer is renal cancer.

[00089] The cancer can include cancers characterized as comprising cancer stem cells, cancer associated mesenchymal cells, or tumor initiating cancer cells. The cancer can include cancers that have been characterized as being enriched with cancer stem cells, cancer associated mesenchymal cells, or tumor initiating cancer cells (e.g., a tumor enriched with cells that have undergone an epithelial-to-mesenchymal transition or a metastatic tumor).

[00090] The cancer can be a primary tumor, i.e., located at the anatomical site of tumor growth initiation. The cancer can also be metastatic, i.e., appearing at least a second anatomical site other than the anatomical site of tumor growth initiation. The cancer can be a recurrent cancer, i.e., cancer that returns following treatment, and after a period of time in which the cancer was undetectable. The recurrent cancer can be anatomically located locally to the original tumor, e.g., anatomically near the original tumor; regionally to the original tumor, e.g., in a lymph node located near the original tumor; or distantly to the original tumor, e.g., anatomically in a region remote from the original tumor.

[00091] The cancer can also include for example, but is not limited to, epithelial cancers, breast, lung, pancreatic, colorectal (e.g., metastatic colorectal, e.g., metastatic KRAS mutated), prostate, head and neck, melanoma (e.g., NRAS mutated locally advanced or metastatic malignant cutaneous melanoma), acute myelogenous leukemia, and glioblastoma.

Exemplary breast cancers include triple negative breast cancer, basal-like breast cancer, claudin-low breast cancer, invasive, inflammatory, metaplastic, and advanced HER-2 positive or ER-positive cancers resistant to therapy.

[00092] In some embodiments, the cancer includes a cancer characterized as having a RAS mutation. The cancer can also include a cancer characterized as having a KRAS mutation. In some embodiments, the KRAS mutation is KRAS G12C mutation.

[00093] The cancer can also include lung cancer, colorectal cancer (CRC), 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. In some embodiments, the cancer is non-small cell lung cancer, colorectal cancer, pancreatic cancer, or ovarian cancer.

[00094] In some embodiments, the cancer is unresectable or metastatic melanoma, melanoma with lymph node involvement or metastatic disease who have undergone complete resection, metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy, metastatic small cell lung cancer with progression after platinum-based chemotherapy and at least one other line of therapy, advanced renal cell carcinoma who have received prior antiangiogenic therapy, advanced renal cell carcinoma, classical Hodgkin lymphoma, recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy, locally advanced or metastatic urothelial carcinoma, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer, or hepatocellular carcinoma.

[00095] In some embodiments, the cancer is melanoma, non-small cell lung cancer, small cell lung cancer, head and neck squamous cell cancer, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability-high cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, merkel cell carcinoma, renal cell carcinoma, or endometrial carcinoma.

[00096] Other cancers include but are not limited to, uveal melanoma, brain, abdominal, esophagus, gastrointestinal, glioma, liver, tongue, neuroblastoma, osteosarcoma, ovarian, retinoblastoma, Wilm's tumor, multiple myeloma, skin, lymphoma, blood and bone marrow cancers (e.g., advanced hematological malignancies, leukemia, e.g., acute myeloid leukemia (e.g., primary or secondary), acute lymphoblastic leukemia, acute lymphocytic

leukemia, T cell leukemia, hematological malignancies, advanced myeloproliferative disorders, myelodysplastic syndrome, relapsed or refractory multiple myeloma, advanced myeloproliferative disorders), retinal, bladder, cervical, kidney, endometrial, meningioma, lymphoma, skin, uterine, lung, non small cell lung, nasopharyngeal carcinoma, neuroblastoma, solid tumor, hematologic malignancy, squamous cell carcinoma, testicular, thyroid, mesothelioma, brain vulval, sarcoma, intestine, oral, endocrine, salivary, spermatocyte seminoma, sporadic medulalry thyroid carcinoma, non-proliferating testes cells, cancers related to malignant mast cells, non-Hodgkin's lymphoma, and diffuse large B cell lymphoma.

[00097] In some embodiments, the tumor is a solid tumor. In some embodiments, the solid tumor is locally advanced or metastatic, hi some embodiments, the solid tumor is refractory (e.g., resistant) after standard therapy.

[00098] Methods described herein can reduce, ameliorate or altogether eliminate the disorder, and/or its associated symptoms, to keep it from becoming worse, to slow the rate of progression, or to minimize the rate of recurrence of the disorder once it has been initially eliminated (i.e., to avoid a relapse). A suitable dose and therapeutic regimen varies depending upon the specific compounds, combinations, and/or pharmaceutical compositions used and the mode of delivery of the compounds, combinations, and/or pharmaceutical compositions. In some embodiments, the method increases the average length of survival, increases the average length of progression-free survival, and/or reduces the rate of recurrence, of subjects treated with the combinations described herein in a statistically significant manner.

[00099] In some embodiments, the cancer is lung cancer (e.g., non-small cell lung cancer NSCLC), e.g., KRAS mutant NSCLC; metastatic cancer), bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer (e.g., unresectable low-grade ovarian, advanced or metastatic ovarian cancer), rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer (e.g., triple-negative breast cancer (e.g., breast cancer which does not express the genes for the estrogen receptor, progesterone receptor, and Her2/neu)), uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the

renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, mesothelioma (e.g., malignant pleural mesothelioma, e.g., surgical resectable malignant pleural mesothelioma) or a combination of one or more of the foregoing cancers. In some embodiments, the cancer is metastatic. In some embodiments, the abnormal cell growth is locally recurring (e.g.. the subject has a locally recurrent disease, e.g., cancer).

Additional Therapies

[000100] In some embodiments, the methods and compositions described herein is administered together with an additional therapy (e.g., cancer treatment). In one embodiment, a mixture of one or more compounds or pharmaceutical compositions may be administered with the combination described herein to a subject in need thereof. In yet another embodiment, one or more compounds or compositions (e.g., pharmaceutical compositions) may be administered with the combination described herein for the treatment or avoidance of various diseases, including, for example, cancer, diabetes, neurodegenerative diseases, cardiovascular disease, blood clotting, inflammation, flushing, obesity, aging, stress, etc. In various embodiments, combination therapies comprising a compound or pharmaceutical composition described herein may refer to (1) pharmaceutical compositions that comprise one or more compounds in combination with the combination described herein; and (2) co-administration of one or more compounds or pharmaceutical compositions described herein with the combination described herein, wherein the compound or pharmaceutical composition described herein have not been formulated in the same compositions. In some embodiments, the combinations described herein is administered with an additional treatment (e.g., an additional cancer treatment). In some embodiments, the additional treatment (e.g., an additional cancer treatment) can be administered simultaneously (e.g., at the same time), in the same or in separate compositions, or sequentially. Sequential administration refers to administration of one treatment before (e.g., immediately before, less than 5, 10, 15, 30, 45, 60 minutes; 1 , 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96 or more hours; 4, 5, 6, 7, 8, 9 or more days; 1 , 2, 3, 4, 5, 6, 7, 8 or more weeks before) administration of an additional, e.g., secondary, treatment (e.g., a compound or therapy). The order of administration of the first and secondary compound or therapy can also be reversed.

[000101] Exemplary cancer treatments include, for example: chemotherapy, targeted therapies such as antibody therapies, immunotherapy, and hormonal therapy. Examples of each of these treatments are provided below.

Chemotherapy

[000102] In some embodiments, a combination described herein is administered with a chemotherapy. Chemotherapy is the treatment of cancer with drugs that can destroy cancer cells. "Chemotherapy" usually refers to cytotoxic drugs which affect rapidly dividing cells in general, in contrast with targeted therapy. Chemotherapy drugs interfere with cell division in various possible ways, e.g., with the duplication of DNA or the separation of newly formed chromosomes. Most forms of chemotherapy target all rapidly dividing cells and are not specific for cancer cells, although some degree of specificity may come from the inability of many cancer cells to repair DNA damage, while normal cells generally can.

[000103] Examples of chemotherapeutic agents used in cancer therapy include, for example, antimetabolites (e.g., folic acid, purine, and pyrimidine derivatives) and alkylating agents (e.g., nitrogen mustards, nitrosoureas, platinum, alkyl sulfonates, hydrazines, triazenes, aziridines, spindle poison, cytotoxic agents, toposimerase inhibitors and others). Exemplary agents include Aclarubicin, Actinomycin, Alitretinon, Altretamine, Aminopterin, Aminolevulinic acid, Amrubicin, Amsacrine, Anagrelide, Arsenic trioxide, Asparaginase, Atrasentan, Belotecan, Bexarotene, endamustine, Bleomycin, Bortezomib, Busulfan, Camptotnecin, Capecitabine, Carboplatin, Carboquone, Carmofur, Carmustine, Celecoxib, Chlorambucil, Chlormethine, Cisplatin, Cladribine, Clofarabine, Crisantaspase, Cyclophosphamide, Cytarabine, Dacarbazine, Dactinomycin, Daunorubicin, Decitabine, Demecolcine, Docetaxel, Doxorubicin, Efaproxiral, Elesclomol, Elsamitrucin, Enocitabine, Epirubicin, Estramustine, Etoglucid, Etoposide, Floxuridine, Fludarabine, Fluorouracil (5FU), Fotemustine, Gemcitabine, Gliadel implants, Hydroxycarbamide, Hydroxyurea, idarubicin, Ifosfamide, Irinotecan, Irofulven, Ixabepilone, Larotaxel, Leucovorin, Liposomal doxorubicin, Liposomal daunorubicin, Lonidamine, Lomustine, Lucanthone, Mannosulfan, Masoprocol, Melphalan, Mercaptopurine, Mesna, Methotrexate, Methyl aminolevulinate, Mitobronitol, Mitoguazone, Mitotane, Mitomycin, Mitoxantrone, Nedaplatin, Nimustine, Oblimersen, Omacetaxine, Ortataxel, Oxaliplatin, Paclitaxel, Pegaspargase, Pemetrexed, Pentostatin, Pirarubicin, Pixanlrone, Plicamycin, Porfimer sodium, Prednimustine, Procarbazine, Raltitrexed, Ranimustine, Rubitecan, Sapacitabine, Semustine, Sitimagene ceradenovec, Strataplatin, Streptozocin, Talaporfm, Tegafur-uracil, Temoporfin, Temozolomide, Teniposide, Tesetaxel, Testolactone, Tetranitrate, Thiotepa, Tiazofurine, Tioguanine, Tipifarnib, Topotecan, Trabectedin, Triaziquone, Triethylenemelamine, Triplatin, Tretinoin, Treosulfan, Trofosfamide, Uramustine, Valrubicin, Verteporfin,

Vinblastine, Vincristine, Vindesine, Vinflunine, Vinorelbine, Vorinostat, Zorubicin, and other cytostatic or cytotoxic agents described herein.

[000104] Because some drugs work better together than alone, two or more drugs are often given at the same time or sequentially. Often, two or more chemotherapy agents are used as combination chemotherapy. In some embodiments, the chemotherapy agents (including combination chemotherapy) can be used in combination with a combination described herein.

Targeted Therapy

[000105] In some embodiments, a combination described herein is administered with a targeted therapy. Targeted therapy constitutes the use of agents specific for the deregulated proteins of cancer cells. Small molecule targeted therapy drugs are generally inhibitors of enzymatic domains on mutated, overexpressed, or otherwise critical proteins within the cancer cell. Prominent examples are the tyrosine kinase inhibitors such as Axitinib, Bosutinib, Cediranib, desatinib, erolotinib, imatinib, gefitinib, lapatinib, Lestaurtinib, Nilotinib, Semaxanib, Sorafenib, Sunitinib, and Vandetanib, and also cyclin-depdendent kinase inhibitors such as Alvocidib and Seliciclib. Monoclonal antibody therapy is another strategy in which the therapeutic agent is an antibody which specifically binds to a protein on the surface of the cancer cells. Examples include the anti-HER2/neu antibody trastuzumab (HERCEPTIN®) typically used in breast cancer, and the anti-CD20 antibody rituximab and Tositumomab typically used in a variety of B-cell malignancies. Other exemplary anbitodies include Ctuximab, Panitumumab, Trastuzumab, Alemtuzumab, Bevacizumab, Edrecolomab, and Gemtuzumab. Exemplary fusion proteins include Aflibercept and Denileukin diftitox. In some embodiments, the targeted therapy can be used in combination with a combination described herein.

[000106] Targeted therapy can also involve small peptides as "homing devices" which can bind to cell surface receptors or affected extracellular matrix surrounding the tumor. Radionuclides which are attached to these peptides (e.g., RGDs) eventually kill the cancer cell if the nuclide decay s in the vicinity of the cell. An example of such therapy includes BEXXAR®.

Immunotherapy

[000107] In some embodiments, a combination described herein is administered with an immunotherapy. Cancer immunotherapy refers to a diverse set of therapeutic strategies designed to induce the patient's own immune system to fight the tumor.

[000108] Contemporary methods for generating an immune response against tumors include intravesicular BCG immunotherapy for superficial bladder cancer, and use of interferons and other cytokines to induce an immune response in subjects with renal cell carcinoma and melanoma. Allogeneic hematopoietic stem cell transplantation can be considered a form of immunotherapy, since the donor's immune cells will often attack the tumor in a graft- versus-tumor effect. In some embodiments, the immunotherapy agents can be used in combination with a combination as described herein.

Hormonal Therapy

[000109] In some embodiments, a combination described is administered with a hormonal therapy. The growth of some cancers can be inhibited by providing or blocking certain hormones. Common examples of hormone-sensitive tumors include certain types of breast and prostate cancers. Removing or blocking estrogen or testosterone is often an important additional treatment. In certain cancers, administration of hormone agonists, such as progestogens may be therapeutically beneficial. In some embodiments, the hormonal therapy agents can be used in combination with a combination described herein.

Radiation Therapy

[000110] The combinations described herein can be used in combination with directed energy or particle, or radioisotope treatments, e.g., radiation therapies, e.g., radiation oncology, for the treatment of proliferative disease, e.g., cancer, e.g., cancer associated with cancer stem cells. The combinations described herein may be administered to a subject simultaneously or sequentially along with the directed energy or particle, or radioisotope treatments. For example, the combinations described herein may be administered before, during, or after the directed energy or particle, or radioisotope treatment, or a combination thereof. The directed energy or particle therapy may comprise total body irradiation, local body irradiation, or point irradiation. The directed energy or particle may originate from an accelerator, synchrotron, nuclear reaction, vacuum tube, laser, or from a radioisotope. The therapy may comprise external beam radiation therapy, teletherapy, brachy therapy, sealed source radiation therapy, systemic radioisotope therapy , or unsealed source radiotherapy. The therapy may comprise ingestion of, or placement in proximity to, a radioisotope, e.g., radioactive iodine, cobalt, cesium, potassium, bromine, fluorine, carbon. External beam radiation may comprise exposure to directed alpha particles, electrons (e.g., beta particles), protons, neutrons, positrons, or photons (e.g., radiowave, millimeter wave, microwave, infrared, visible, ultraviolet, X-ray, or gamma-ray photons). The radiation may be directed at any portion of the subject in need of treatment.

Surgery

[000111] The combinations described herein can be used in combination with surgery, e.g., surgical exploration, intervention, biopsy, for the treatment of proliferative disease, e.g., cancer, e.g., cancer associated with cancer stem cells. The combinations described herein may be administered to a subject simultaneously or sequentially along with the surgery. For example, the combinations described herein may be administered before (preoperative), during, or after (post-operative) the surgery, or a combination thereof. The surgery may be a biopsy during which one or more cells are collected for further analysis. The biopsy may be accomplished, for example, with a scalpel, a needle, a catheter, an endoscope, a spatula, or scissors. The biopsy may be an excisional biopsy, an incisional biopsy, a core biopsy, or a needle biopsy, e.g., a needle aspiration biopsy. The surgery may involve the removal of localized tissues suspected to be or identified as being cancerous. For example, the procedure may involve the removal of a cancerous lesion, lump, polyp, or mole. The procedure may involve the removal of larger amounts of tissue, such as breast, bone, skin, fat, or muscle. The procedure may involve removal of part of, or the entirety of, an organ or node, for example, lung, throat, tongue, bladder, cervix, ovary, testicle, lymph node, liver, pancreas, brain, eye, kidney, gallbladder, stomach, colon, rectum, or intestine. In one embodiment, the cancer is breast cancer, e.g., triple negative breast cancer, and the surgery is a mastectomy or lumpectomy.

Anti-Inflammatory Agents

[000112] A combination described herein can be administered with an anti-inflammatory agent. Anti-inflammatory agents can include, but are not limited to, non-steroidal anti-inflammatory agents (e.g., Salicylates (Aspirin (acetylsalicylic acid), Diflunisal, Salsalate), Propionic acid derivatives (Ibuprofen, Naproxen, Fenoprofen, Ketoprofen, Flurbiprofen, Oxaprozin, Loxoprofen), Acetic acid derivatives (Indomethacin, Sulindac, Etodolac, Ketorolac, Diclofenac, Nabumetone), Enolic acid (Oxicam) derivatives (Piroxicam, Meloxicam, Tenoxicam, Droxicam, Lomoxicam, Isoxicam), Fenamic acid derivatives (Fenamates)(Mefenamic acid, Meclofenamic acid, Flufenamic acid. Tolfenamic acid). Selective COX -2 inhibitors (Coxibs) (Celecoxib), Sulphonanilides (Nimesulide). Steriods (e.g. Hydrocortisone (Cortisol), Cortisone acetate, Prednisone, Prednisolone, Methylprednisolone, Dexamethasone, Betamethasone, Triamcinolone, Beclometasone, Fludrocortisone acetate, Deoxycorticosterone acetate, Aldosterone).

Analgesic Agents

[000113] Analgesics can include but are not limited to, opiates (e.g. morphine, codeine, oxycodone, hydrocodone, dihydromorphine, pethidine, buprenorphine, tramadol, venlafaxine), paracetomal and Nonsteroidal anti-inflammatory agents (e.g., Salicylates (Aspirin (acetylsalicylic acid), Diflunisal, Salsalate), Propionic acid derivatives (Ibuprofen, Naproxen, Fenoprofen, Ketoprofen, Flurbiprofen, Oxaprozin, Loxoprofen), Acetic acid derivatives (Indomethacin, Sulindac, Etodolac, Ketorolac, Diclofenac, Nabumetone), Enolic acid (Oxicam) derivatives (Piroxicam, Meloxicam, Tenoxicam, Droxicam, Lomoxicam, Isoxicam), Fenamic acid derivatives (Fenamates)(Mefenamic acid, Meclofenamic acid, Flufenamic acid. Tolfenamic acid). Selective COX-2 inhibitors (Coxibs) (Celecoxib), Sulphonanilides (Nimesulide).

Antiemetic Agents

[000114] A combination described herein can be administered with an antiemetic agent. Antiemetic agents can include, but are not limited to, 5-HT3 receptor antagonists (Dolasetron (Anzemet), Granisetron (Kytril, Sancuso), Ondansetron (Zofran), Tropisetron (Navoban), Palonosetron (Aloxi), Mirtazapine (Remeron)), Dopamine antagonists (Domperidone, Olanzapine, Droperidol, Haloperidol, Chlorpromazine, Promethazine, Prochlorperazine, Metoclopramide (Reglan), Alizapride, Prochlorperazine (Compazine, Stemzine, Buccastem, Stemetil, Phenotil), NKl receptor antagonist (Aprepitant (Emend), Antihistamines (Cyclizine, Diphenhydramine (Benadryl), Dimenhydrinate (Gravol, Dramamine), Meclozine (Bonine, Antivert), Promethazine (Pentazine, Phenergan, Promacot), Hydroxyzine), benzodiazapines (Lorazepam, Midazolam), Anticholinergics (hyoscine), steriods (Dexamethasone).

Combinations

[000115] The phrase, "in combination with," and the terms "co-administration," "co-administering," or "co-providing", as used herein in the context of the administration of a compound described herein or a therapy described herein, means that two or more different compounds or therapies are delivered to the subject during the course of the subject's affliction with the disease or disorder (e.g., a disease or disorder as described herein, e.g., cancer), e.g., two or more different compounds or therapies are delivered to the subject after the subject has been diagnosed with the disease or disorder (e.g., a disease or disorder as described herein, e.g., cancer) and before the disease or disorder has been cured or eliminated or treatment has ceased for other reasons.

[000116] In some embodiments, the delivery of one compound or therapy is still occurring when the delivery of the second or third or fourth compound or therapy begins, so

that there is overlap in terms of administration. This is sometimes referred to herein as "simultaneous" or "concurrent delivery." In other embodiments, the delivery of one compound or therapy ends before the delivery of the other compound or therapy begins. In some embodiments of either case, the treatment (e.g., administration of compound, composition, or therapy) is more effective because of combined administration. For example, the second compound or therapy and/or the third compound or therapy and/or fourth compound or therapy is more effective, e.g., an equivalent effect is seen with less of the second compound or therapy, or the second compound or therapy and/or the third compound or therapy and/or fourth compound or therapy reduces symptoms to a greater extent, than would be seen if the second compound or therapy and/or the third compound or therapy and/or fourth compound or therapy were administered in the absence of the first compound or therapy, or the analogous situation is seen with the first compound or therapy. In some embodiments, delivery is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one compound or therapy delivered in the absence of the other. The effect of the two or three or four compounds or therapies can be partially additive, wholly additive, or great than additive (e.g., synergistic). In some embodiments, the effect of the combinations disclosed herein is synergistic. The delivery can be such that the first compound or therapy delivered is still detectable when the second and/or third and/or fourth compound or therapy is delivered.

[000117] In some embodiments, the first compound or therapy and second compound or therapy and third compound or therapy and optionally fourth compound or therapy can be administered simultaneously (e.g., at the same time), in the same or in separate compositions, or sequentially. Sequential administration refers to administration of one compound or therapy before (e.g., immediately before, less than 5, 10, 15, 30, 45, 60 minutes; 1 , 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 48, 72, 96 or more hours; 4, 5, 6, 7, 8, 9 or more days; 1 , 2, 3, 4, 5, 6, 7, 8 or more weeks before) administration of an additional, e.g., secondary compound or therapy and/or third compound or therapy and/or fourth compound or therapy. The order of administration of the first and secondary and third compound or therapy and optionally fourth compound or therapy can also be reversed or arranged in any combinatorial sequence of the compounds/therapies.

[000118] The combinations described herein can be a first line treatment for abnormal cell growth, e.g., cancer, i.e., it is used in a patient who has not been previously administered another drug intended to treat the cancer; a second line treatment for the cancer, i.e., it is used in a subject in need thereof who has been previously administered another drug intended to

treat the cancer; a third or fourth treatment for the cancer, i.e., it is used in a subject who has been previously administered two or three other drugs intended to treat the cancer.

Administration and Dosage

[000119] The combinations of this disclosure may be administered orally, parenterally, topically, rectally, or via an implanted reservoir, preferably by oral administration or administration by injection. In some cases, the pH of the composition (e.g., pharmaceutical composition) may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability or efficacy of the composition.

[000120] In some embodiments, the subject is administered the composition (e.g., pharmaceutical composition) orally. In some embodiments the composition (e.g., pharmaceutical composition) is be orally administered in any orally acceptable dosage form including, but not limited to, liqui-gel tablets or capsules, syrups, emulsions and aqueous suspensions. Liqui-gels may include gelatins, plasticisers, and/or opacifiers, as needed to achieve a suitable consistency and may be coated with enteric coatings that are approved for use, e.g., shellacs. Additional thickening agents, for example gums, e.g., xanthan gum, starches, e.g., corn starch, or glutens may be added to achieve a desired consistency of the composition (e.g., pharmaceutical composition) when used as an oral dosage. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[000121] In some embodiments, the subject is administered the composition (e.g., pharmaceutical composition) in a form suitable for oral administration such as a tablet, capsule, pill, powder, sustained release formulations, solution, and suspension. The composition (e.g., pharmaceutical composition) may be in unit dosage forms suitable for single administration of precise dosages. Pharmaceutical compositions may comprise, in addition to a compound as described herein a pharmaceutically acceptable carrier, and may optionally further comprise one or more pharmaceutically acceptable excipients, such as, for example, stabilizers, diluents, binders, and lubricants. In addition, the tablet may include other medicinal or pharmaceutical agents, carriers, and or adjuvants. Exemplary pharmaceutical compositions include compressed tablets (e.g., directly compressed tablets).

[000122] Tablets are also provided comprising the active or therapeutic ingredient (e.g., compound as described herein). Tn addition to the active or therapeutic ingredients, tablets may contain a number of inert materials such as carriers. Pharmaceutically acceptable carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, sesame oil and the like. Saline solutions and aqueous dextrose can also be employed as liquid earners. Oral dosage forms for use in accordance

with the present disclosure thus may be formulated in conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active ingredients into preparations which, can be used pharmaceutically. Excipients can impart good powder flow and compression characteristics to the material being compressed. Examples of excipients are described, for example, in the Handbook of Pharmaceutical Excipients (5th edition), Edited by Raymond C Rowe, Paul J. Sheskey, and Sian C. Owen; Publisher: Pharmaceutical Press.

[000123] For oral administration, the active ingredients, e.g., the compound as described herein can be formulated readily by combining the active ingredients with pharmaceutically acceptable carriers well known in the art. Such carriers enable the active ingredients of the disclosure to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, powders or granules, suspensions or solutions in water or non-aqueous media, and the like, for oral ingestion by a subject. Pharmacological preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries if desired, to obtain, for example, tablets. Suitable excipients such as diluents, binders or disintegrants may be desirable.

[000124] The dosage varies depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g., Fingl, et al., 1975, in "Pharmacological Basis of Therapeutics"). Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular subject will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the subject's disposition to the disease, condition or symptoms, and the judgment of the treating physician. A course of therapy can comprise one or more separate administrations of a compound as described herein. A course of therapy can comprise one or more cycles of a compound as described herein.

[000125] In some embodiments, a cycle, as used herein in the context of a cycle of administration of a drug, refers to a period of time for which a drug is administered to a patient. For example, if a drug is administered for a cycle of 21 days, the periodic administration, e.g., daily or twice daily, is given for 21 days. A drug can be administered for more than one cycle. Rest periods may be interposed between cycles. A rest cycle may be 1,

2, 4, 6, 8, 10, 12, 16, 20, 24 hours, 1 , 2, 3, 4, 5, 6, 7 days, or 1 , 2, 3, 4 or more weeks in length.

[000126] Oral dosage forms may, if desired, be presented in a pack or dispenser device, such as an FDA approved kit, which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions or human or veterinary administration. Such notice, for example, may be of labeling approved by the U.S. Food and Drug Administration for prescription drugs or of an approved product insert.

EXAMPLES

Example 1.

Tumor mouse studies

[000127] In vivo experiments were carried out using transplantable mouse models of KRAS G12C cancer (e.g., KRAS G12C lung cancer). KPAR1.3^{G12C} cells were obtained from Kras$^{G12D/WT}$; Trp53$^{fl/fl}$, Rosa26$^{APOBEC3Bi/WT}$; Rag1$^{KO/KO}$ lung tumors and prime edited to express KRAS^{G12C}. These cells form immune hot tumors which are responsive to immunotherapies (Boumelha et al, bioRxiv). Briefly, tumors were formed orthotopically in the lung by tail vein injection of KPAR1.3^{G12C} cells. Mice were sorted into 4 groups: vehicle, VS-6766 (0.3 mg/kg oral dosing, once per day), MRTX849 (50 mg/kg oral dosing, once per day), and VS-6766 + MRTX849. After 5 days of treatment, mice were euthanized, and orthotopic KPAR1.3^{G12C} lung tumors collected.

qPCR analysis

[000128] RNA was extracted and converted to cDNA using a High-Capacity cDNA Reverse Transcription Kit. To determine effects on the tumor microenvironment, TaqMan qPCR was run using CD8, FOXP3, granzyme A, granzyme B and β2-microglobulin probes from Applied Biosystems. Each PCR reaction was run in triplicate wells. Expression levels were computed as the difference (ΔCT) between the target gene CT and normalizing gene CT.

[000129] In **FIG. 1**, mice bearing orthotopic KPAR1.3^{G12C} lung tumors were treated for 5 days with vehicle, VS-6766 (0.3 mg/kg), MRTX849 (50 mg/kg), and VS-6766 +

MRTX849. Tumors were collected and mRNA levels were analyzed by qPCR using specific primers for CD8, FOXP3, granzyme A, granzyme B and β2-microglobulin.

[000130] FIG. 1 shows that the combination of VS-6766 and KRAS G12C inhibitor makes the immune microenvironment more favorable for combining with an anti-PD-1 antibody. Contemplated anti-PD-1 antibodies are disclosed herein (see, e.g., paragraph [00057]). Also contemplated are combinations with an anti-PD-L1 antibody.

Example 2.

Tumor mouse studies

[000131] KRAS G12C mutant tumor mouse models (e.g., CT26 KRAS G12C mutant colorectal model) are used. Tumor challenge is initiated by subcutaneous inoculation of tumor cell suspensions into mice. Tumor sizes (mm3) are measured. Once tumors reach an average volume of 50-80 mm3, mice are sorted into 8 groups: vehicle; VS-6766; G12C inhibitor (G12Ci); anti−PD-1; VS-6766 + G12Ci; VS-6766 + anti-PD-1; G12Ci + anti-PD-1; VS-6766 + G12Ci + anti-PD-1. Tumors and body weights are measured for the duration of the study. The animals are checked for any effects of tumor growth and treatments on normal behavior such as mobility, food and water consumption (by looking only), and body weight gain/loss, eye/hair matting and any other abnormal effect.

EQUIVALENTS AND SCOPE

[000132] In the claims articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The disclosure includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[000133] Furthermore, the disclosure encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in

any other claim that is dependent on the same base claim. Where elements are presented as lists, e.g., in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the disclosure, or aspects of the disclosure, is/are referred to as comprising particular elements and/or features, some embodiments of the disclosure or aspects of the disclosure consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms "comprising" and "containing" are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub–range within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

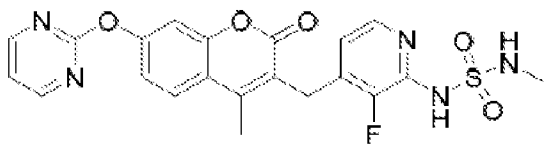
[000134] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present disclosure that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the disclosure can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[000135] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present disclosure, as defined in the following claims.

CLAIMS

1. 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, an effective amount of an anti-PD-1 antibody, and an effective amount of KRAS G12C inhibitor, thereby treating the subject.

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



(I),

or a pharmaceutically acceptable salt thereof.

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

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

5. The method of claim 1 or 2, wherein 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

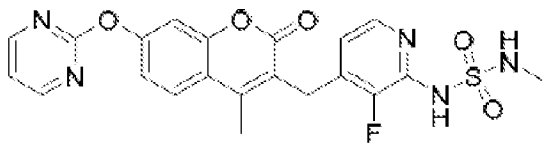
26. The method of any one of claims 1-25, wherein the KRAS G12C inhibitor is administered once daily.

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

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

29. 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, an effective amount of an anti-PD-L1 antibody, and an effective amount of KRAS G12C inhibitor, thereby treating the subject.

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



(I),

or a pharmaceutically acceptable salt thereof.

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

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

33. The method of claim 29 or 30, wherein 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.

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

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

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

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

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

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

40. The method 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 method of any one of claims 29-40, wherein the anti-PD-L1 antibody is administered parenterally.

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

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

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

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

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

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

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

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

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

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

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

56. The method of any one of claims 1-55, wherein the method further comprises administering to the subject an effective amount of a FAK inhibitor.

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

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

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

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

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

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

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

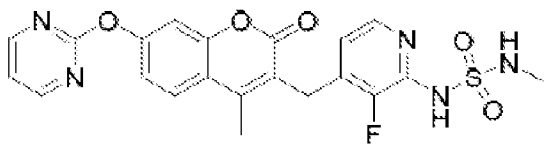
64. The method of any one of claims 56-63, wherein the FAK inhibitor is administered orally.

65. The method of any one of claims 56-64, wherein the FAK inhibitor is dosed as a cycle, wherein the cycle comprises administering the FAK inhibitor for three weeks and then not administering the dual RAF/MEK inhibitor for one week.

66. 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, an effective amount of an anti-PD-1 antibody, and an effective amount of a KRAS G12C inhibitor, and an effective amount of a FAK inhibitor, thereby treating the subject.

67. A method of treating a cancer in a subject in need thereof, the method comprising administering to the subject administering to the subject an effective amount of a dual RAF/MEK inhibitor, 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.

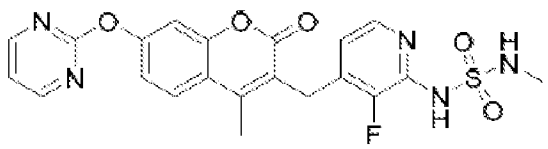
68. The method of claim 66 or 67, wherein the dual RAF/MEK inhibitor is a compound of formula (I):



(I),

or a pharmaceutically acceptable salt thereof.

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

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

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

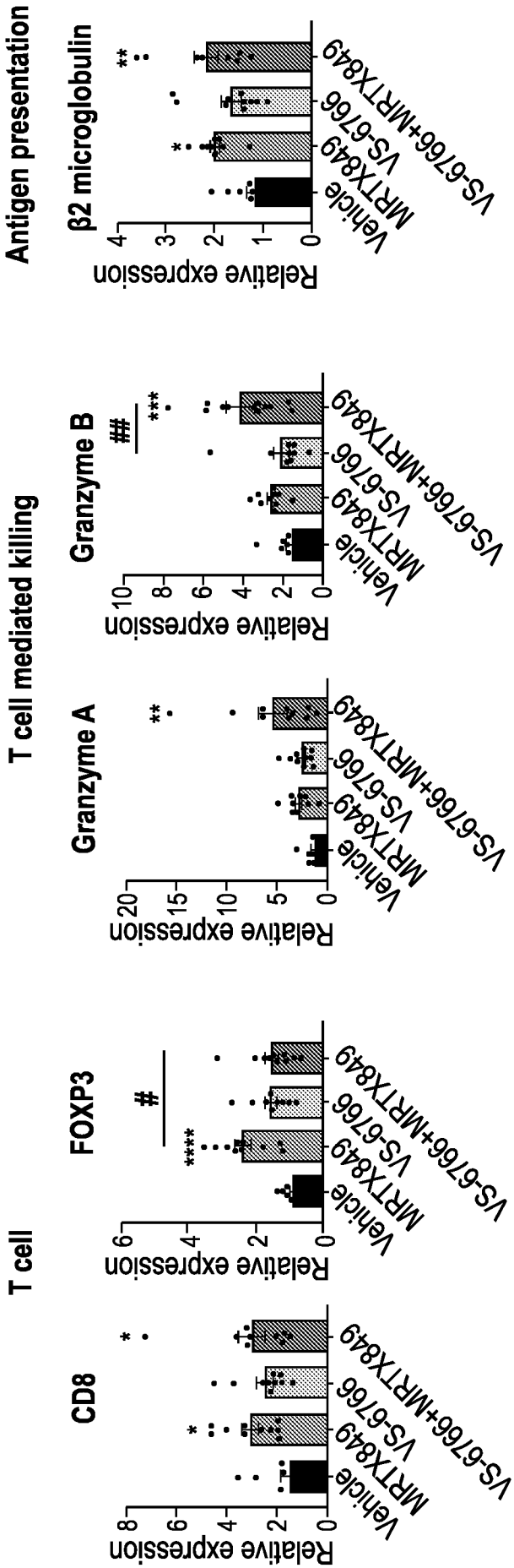
73. The method of any one of claims 1-72, wherein the cancer is lung cancer, colorectal cancer, pancreatic cancer, uveal melanoma, ovarian cancer, uterine endometrioid carcinoma, bladder urothelial carcinoma, breast invasive lobular carcinoma, cervical squamous cell carcinoma, cutaneous melanoma, endocervical 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 method of any one of claims 1-73, wherein the cancer is lung cancer, colorectal cancer, pancreatic cancer, or ovarian cancer.

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

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

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


T cell
CD8
FOXP3
T cell mediated killing
Granzyme A
Granzyme B
Antigen presentation
β2 microglobulin
Relative expression
Vehicle
MRTX849
VS-6766
VS-6766+MRTX849
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/38434

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4, 7-28, 32-65, 69-77
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/38434

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/33, A61K 31/18, A61K 31/4375, A61K 31/4433 (2022.01)
ADD. A61K 31/00 (2022.01)

CPC - INV. A61K 31/33, A61K 31/18, A61K 31/4375, A61K 31/4433
ADD. A61K 31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2021/047783 A1 (The Institute Of Cancer Research: Royal Cancer Hospital) 18 March 2021 (18.03.2021); p2 p4 p20 p25 p26	1-3, 5-6, 29-31, 66-68
Y	WO 2016/115376 A1 (The Regents Of The University Of California) 21 July 2016 (21.07.2016); para[003] para[0045] para[0047]	1-3, 5-6, 29-31, 66-68
A	WO 2021/142144 A1 (Immuneering Corporation) 15 July 2021 (15.07.2021); entire document	1-3, 5-6, 29-31, 66-68

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 September 2022	OCT 06 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300