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(54) Title: METHOD OF TREATING KRAS WILD-TYPE METASTATIC COLORECTAL CELL CARCINOMA USING CABOZANTINIB PLUS PANITUMUMAB

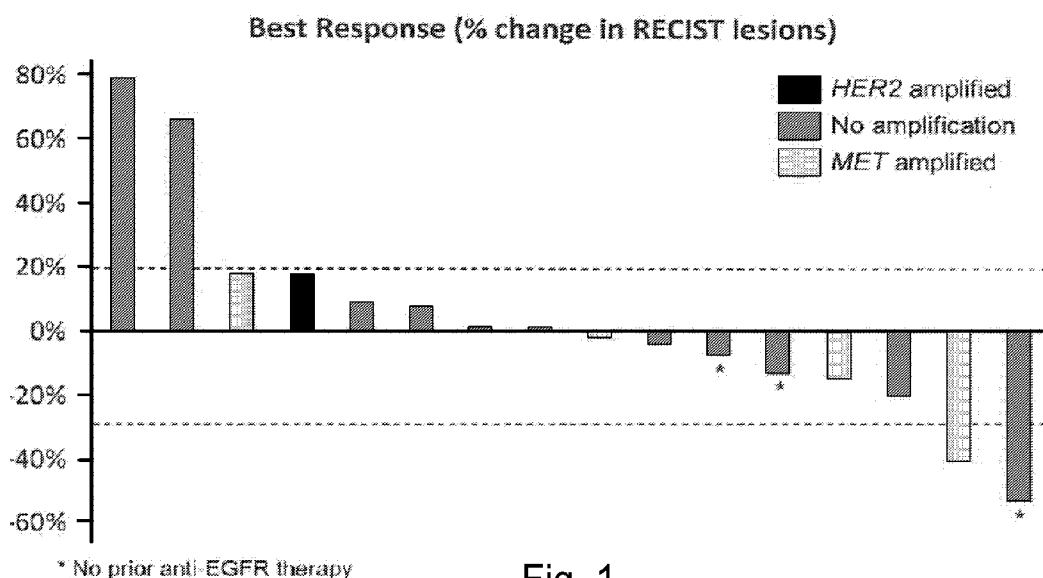


Fig. 1

(57) Abstract: The present disclosure relates to a method of treating method of treating KRAS Wild Type metastatic colorectal cancer, comprising administering to a patient in need of such treatment cabozantinib plus panitumumab.



Method of Treating KRAS Wild-Type Metastatic Colorectal Cell Carcinoma Using Cabozantinib Plus Panitumumab

CROSS-REFERENCE APPLICATIONS

[0001] The present disclosure claims priority to U.S. Provisional Application 62/338,236 filed May 18, 2016 entitled "Method of Treating KRAS Wild-Type Metastatic Colorectal Cell Carcinoma Using Cabozantinib Plus Panitumumab," the contents of which is incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] The present disclosure relates to a method of treating KRAS wild-type metastatic colorectal cancer in human patients using cabozantinib plus panitumumab.

BACKGROUND

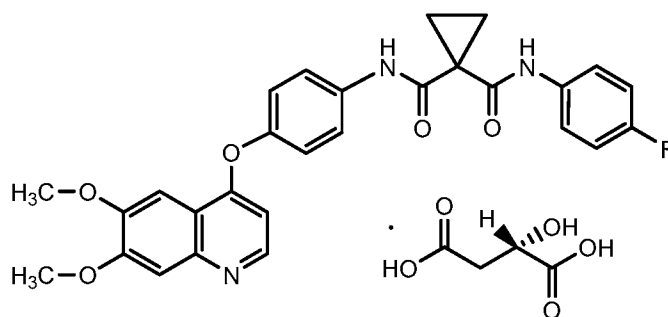
[0003] Patients with chemotherapy-refractory metastatic colorectal cancer (CRC) have modest survival benefit from standard of care therapies. Grothey, A., et al., *Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial*. Lancet, 2013. 381(9863): p. 303-12. Mayer, R.J., et al., *Randomized trial of TAS-102 for refractory metastatic colorectal cancer*. N Engl J Med, 2015. 372(20): p. 1909-19. Price, T.J., et al., *Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study*. Lancet Oncol, 2014. 15(6): p. 569-79. Although new therapies such as Panitumumab, an FDA-approved anti-EGFR monoclonal antibody are available for the treatment of KRAS and NRAS (RAS) wild-type (WT) metastatic CRC, resistance to anti-EGFR therapies due to MET amplification remains an issue. Bardelli, A., et al., *Amplification of the MET receptor drives resistance to anti-EGFR therapies in colorectal cancer*. Cancer Discov, 2013. 3(6): p. 658-73.

[0004] As a result, a need remains for therapies that overcome treatment resistance due to MET amplification in KRAS wild-type metastatic colorectal cancer.

SUMMARY

[0005] These and other needs are met by the present invention, which is directed to a method of treating KRAS wild-type metastatic colorectal cancer in human patients using cabozantinib plus panitumumab.

[0006] Cabozantinib is an oral inhibitor of tyrosine kinases including MET, VEGF receptors, and AXL. CABOMETYX is the (*S*)-malate salt of cabozantinib, a kinase inhibitor. Cabozantinib (*S*)-malate is described chemically as *N*-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2*S*)-hydroxybutanedioate. The molecular formula is $C_{28}H_{24}FN_3O_5 \cdot C_4H_6O_5$, and the molecular weight is 635.6 Daltons as malate salt. The chemical structure of cabozantinib (*S*)-malate salt is depicted below.



Cabozantinib as a capsule formulation has been approved for the treatment of medullary thyroid cancer. Cabozantinib as a tablet formulation has been approved for the treatment of advanced renal cell carcinoma who have received prior antiangiogenic therapy.

[0007] The tablet formulation (CABOMETYX) achieved a 19% increase in the C_{max} compared to the capsule formulation (COMETRIQ[®]) following a single 140 mg dose. A less than 10% difference in the AUC was observed between cabozantinib tablet (CABOMETYX) and capsule (COMETRIQ) formulations.

[0008] In one aspect, a method of treating KRAS Wild Type metastatic colorectal cancer is provided. The method comprises administering to a patient in need of such treatment an effective amount of the combination of cabozantinib or a pharmaceutically acceptable salt thereof and panitumumab.

[0009] In another aspect, a method of treating a patient with KRAS wildtype metastatic colorectal cancer which is resistant to anti-EGFR therapies is provided. The method comprising (a) determining the patient has metastatic colorectal cancer that is at least partially resistant to

anti-EFGR therapy, and (b) administering an effective amount of the combination of cabozantinib or a pharmaceutically acceptable salt thereof and panitumumab, wherein the metastatic colorectal cancer is treated.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. 1 depicts the best response to cabozantinib plus panitumumab therapy (% change in RECIST lesions).

[0011] FIG. 2 depicts the total target lesion size over time.

[0012] FIG. 3 depicts radiographic images from a 57 year old male with metastatic rectal cancer and baseline and during cabozantinib plus panitumumab treatment.

DETAILED DESCRIPTION

[0013] The present invention provides methods of treating KRAS Wild Type metastatic colorectal cancer. The method comprises, consist essentially of or consists of administering to a patient in need of such treatment an effective amount of the combination of cabozantinib or a pharmaceutically acceptable salt thereof and panitumumab. The administration of the combination increases the reduction or inhibition of cancer cell growth, reduction and/or inhibition of metastasis, or reduction in invasiveness of the cancer cells or metastasis as compared to treatment with panitumumab alone. In some instances, cancer cell growth or tumor volume is decreased by at least 10% in the patient treated with the combination, alternatively at least 20%, alternatively at least 30%, alternatively at least 40%, alternatively at least 50%, alternatively at least 60%, alternatively at least 80% reduction in tumor cell volume or tumor cell growth. The reduction or inhibition of cancer cell growth may also be assessed by no change or no increase in tumor volume/size over time, and/or reduction in the size and/or number of metastatic tumors.

[0014] In some embodiments, the reduction in tumor cells or tumor volume is determined by RECIST guidelines version 1.1, which can be found in "New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)" by E. A. Eisenhouer et al., European Journal of Cancer, 45 (2009) 228-247, which is incorporated by reference in its entirety. Suitably, treatment may consist of a reduction in tumor burden by RECIST of at least 10%, alternatively at least 20%, alternatively at least 25%, alternatively at least 30%, alternatively at least 40%,

alternatively at least 50%, alternatively at least 60%, alternatively at least 70%, alternatively at least 80% change in RECIST lesions.

[0015] The terms "subject" and "patient" are used interchangeably and refer to any animal (e.g., a mammal), including, but not limited to, humans, non-human primates, rodents, and the like, which is to be the recipient of a particular treatment. Typically, the terms "subject" and "patient" are used interchangeably herein in reference to a human subject. A suitable subject is a patient who has chemotherapy-refractory metastatic colorectal cancer. In some embodiments, the subject is a patient that is characterized by colorectal cancer that is resistant and/or is less responsive to anti-EGFR treatment alone.

[0016] For example, in some instances the subject is a patient that has previously been administered anti-EGFR treatment and found to be resistant to anti-EGFR therapies due to MET amplification. The increase in MET amplification may be detected by increased detection of MET in the bloodstream and/or an increase expression of MET on cancer cells. c-Met, also called tyrosine-protein kinase Met or hepatocyte growth factor receptor (HGFR) is encoded by the MET gene.

[0017] In other instances, the patient is a patient that has not been previously administered anti-EGFR therapies.

[0018] The combination of cabozantinib and panitumumab are administered separately as cabozantinib is administered orally and panitumumab is administered intravenously in an effective amount to treat the cancer.

[0019] The terms "effective amount" or "therapeutically effective amount" refer to an amount sufficient to effect beneficial or desirable biological and/or clinical results.

[0020] For oral administration, the cabozantinib or pharmaceutical salt thereof may be combined with one or more solid inactive ingredients for the preparation of tablets, capsules, pills, powders, granules or other suitable oral dosage forms. For example, the active agent may be combined with at least one excipient such as fillers, binders, humectants, disintegrating agents, solution retarders, absorption accelerators, wetting agents absorbents or lubricating agents. Suitable forms of cabozantinib are CABOMETYX® and COMETRIQ®.

[0021] The pharmaceutical composition is preferably in unit dosage form. In such form the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities

of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form. Suitable dosages of cabozantinib include, but are not limited to, for example, 20 mg to 200 mg, preferably 20 mg to about 140 mg, alternatively 20 mg to about 60 mg, alternatively about 20 mg, about 40 mg, about 60 mg, 80mg, 100mg, 140mg, daily and include amounts and ranges inbetween. In a preferred embodiment, the patient is administered about 20 mg to about 140 mg once a day, more preferably about 60 mg once daily.

[0022] Panitumumab is a fully human monoclonal antibody specific to the epidermal growth factor receptor (EGFR), and can be found manufactured by Amgen as VECTIBIX®.

[0023] Suitably, panitumumab is administered intravenously by IV infusion, suitably it is administered in an amount of about 5.5 mg/kg body weight to about 6.5 mg/kg body weight, preferably about 6 mg/kg body weight over a time period of about 30-90 minutes (suitably over 60 minutes) every 14 days with a physiologically acceptable salt solution. For example, the panitumumab can be dilute to a total volume of 100 mL with 0.9% sodium chloride injection, USP. Doses higher than 1000 mg should be diluted to 150 mL with 0.9% sodium chloride injection, USP. Preferably, the dilution should not exceed a final concentration of 10 mg/mL.

[0024] The terms "tumor cell growth" or "tumor cell proliferation" are used herein interchangeably to refer to the increase in number of tumor cells.

[0025] The term "metastasis" or "secondary tumor" refers to cancer cells that have spread to a secondary site, e.g., outside of the colon or rectal tissue. Secondary sites include, but are not limited to, the lymphatic system, skin, distant organs (e.g., liver, stomach, pancreas, brain, etc.) and the like.

[0026] In some aspects, the method of treating KRAS wild-type metastatic colorectal cancer comprises administering the combination of cabozantinib and panitumumab.

[0027] In some aspects, methods of reducing, inhibiting or preventing colorectal cancer cell growth in a patient are provided. The method comprises administering an effective amount of the combination provided here, including, for example, a combination comprising cabozantinib or a pharmaceutical salt thereof and panitumumab, wherein the combination is administered in an effective amount to reduce, inhibit or prevent colorectal cancer cell growth.

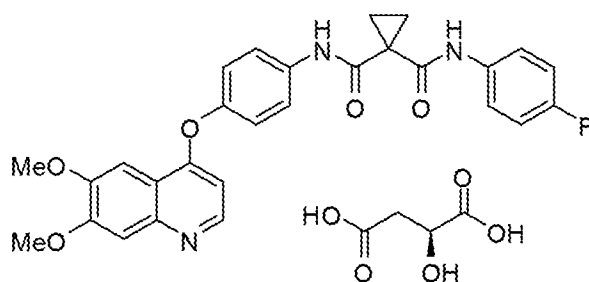
[0028] In some aspects, reducing, inhibiting or preventing colorectal cancer cell growth comprises inhibiting, reducing or preventing colorectal cancer cell proliferation, invasiveness of colorectal cancer cells, or colorectal cancer cell metastasis in a patient.

[0029] In some aspects, methods of reducing therapeutically resistant residual tumor cells in a patient suffering from colorectal cancer are described. The method comprises administering an effective amount of the combination of cabozantinib and panitumumab.

[0030] This disclosure provides kits. The kits can be suitable for use in the methods described herein. Suitable kits include a kit for treating colorectal cancer comprising a combination comprising cabozantinib or a pharmaceutically acceptable salt thereof and panitumumab. In some aspects, instructions on how to administer the combination and/or active agents.

[0031] In some embodiment, a method of treating a patient with KRAS wildtype metastatic colorectal cancer which is resistant to anti-EGFR therapies are provided. The method comprises (a) determining the patient has metastatic colorectal cancer that is at least partially resistant to anti-EGFR therapy, (b) administering an effective amount of the combination of cabozantinib or a pharmaceutically acceptable salt thereof and panitumumab, wherein the metastatic colorectal cancer is treated. In some embodiments, the method further comprises determining if the patient is characterized by the amplification of MET. Amplification of MET may be detected in a blood sample or tissue sample (e.g. tumor biopsy) from the patient. Suitable methods of detection are known in the art, including, ELISA, flow cytometry, PCR, RT-PCR, RT-qPCR (including real-time fluorescent quantitative PCR) and the like. In some aspects, the effective amount comprises about 20 mg to about 140 mg cabozantinib administered once a day orally and about 5.5-6.5 mg/kg body weight panitumumab administered once every 14 days by intravenous injection.

[0032] Cabozantinib is available as a tablet formulation under the name CABOMETYX. CABOMETYX is the (*S*)-malate salt of cabozantinib, a kinase inhibitor. Cabozantinib (*S*)-malate is described chemically as *N*-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2*S*)-hydroxybutanedioate. The molecular formula is $C_{28}H_{24}FN_3O_5 \cdot C_4H_6O_5$ and the molecular weight is 635.6 Daltons as malate salt. The chemical structure of cabozantinib (*S*)-malate salt is:



Cabozantinib (*S*)-malate salt is a white to off-white solid that is practically insoluble in aqueous media.

[0033] CABOMETYX (cabozantinib) tablets are supplied as film-coated tablets containing 20 mg, 40 mg, or 60 mg of cabozantinib, which is equivalent to 25 mg, 51 mg, or 76 mg of cabozantinib (*S*)-malate, respectively. CABOMETYX also contains the following inactive ingredients: microcrystalline cellulose, lactose anhydrous, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate as indicated below.

Ingredient	Theoretical Quantity (mg/unit dose)		
	20-mg Tablet	40-mg Tablet	60-mg Tablet
Cabozantinib (<i>S</i>)-malate	25.34	50.69	76.03
Microcrystalline Cellulose, PH-102	31.08	62.16	93.24
Lactose Anhydrous, 60M	15.54	31.07	46.61
Hydroxypropyl Cellulose, EXF	2.400	4.800	7.200
Croscarmellose Sodium	4.800	9.600	14.40
Colloidal Silicon Dioxide	0.2400	0.4800	0.7200
Magnesium Stearate (Non-Bovine)	0.6000	1.200	1.800
Opadry [®] Yellow (03K92254)	3.200	6.400	9.600
Total tablet weight	83.20	166.4	249.6

[0034] The film coating contains hypromellose, titanium dioxide, triacetin, and iron oxide yellow.

Clinical Pharmacology

Mechanism of Action

[0035] *In vitro* biochemical and/or cellular assays have shown that cabozantinib inhibits the tyrosine kinase activity of MET, VEGFR-1, -2 and -3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, drug resistance, and maintenance of the tumor microenvironment.

Pharmacodynamics

[0036] The exposure-response or -safety relationship for cabozantinib is unknown.

Cardiac Electrophysiology

[0037] The effect of orally administered cabozantinib on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled study in patients with medullary thyroid cancer administered a dose of 140 mg. A mean increase in QTcF of 10 - 15 ms was observed at 4 weeks after initiating cabozantinib. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib-treated patients in this study had a confirmed QTcF > 500 ms nor did any cabozantinib-treated patients in the RCC study (at a dose of 60 mg).

Pharmacokinetics

[0038] Repeat daily dosing of cabozantinib at 140 mg for 19 days resulted in 4- to 5-fold mean cabozantinib accumulation (based on AUC (area under the curve)) compared to a single dose administration; steady state was achieved by Day 15.

Absorption

[0039] Following oral administration of cabozantinib, median time to peak cabozantinib plasma concentrations (T_{max}) ranged from 2 to 3 hours post-dose.

[0040] A 19% increase in the C_{max} of the tablet formulation (CABOMETYX) compared to the capsule formulation (COMETRIQ®) was observed following a single 140 mg dose. A less than 10% difference in the AUC was observed between cabozantinib tablet (CABOMETYX) and capsule (COMETRIQ) formulations.

[0041] Cabozantinib C_{max} and AUC values increased by 41% and 57%, respectively, following a high-fat meal relative to fasted conditions in healthy subjects administered a single 140 mg oral dose of an investigational cabozantinib capsule formulation.

Distribution

[0042] The oral volume of distribution (V_z/F) of cabozantinib is approximately 319 L. Cabozantinib is highly protein bound in human plasma ($\geq 99.7\%$).

Elimination

[0043] The predicted terminal half-life is approximately 99 hours and the clearance (CL/F) at steady-state is estimated to be 2.2 L/hr.

Metabolism

[0044] Cabozantinib is a substrate of CYP3A4 *in vitro*.

Excretion

[0045] Approximately 81% of the total administered radioactivity was recovered within a 48-day collection period following a single 140 mg dose of an investigational ^{14}C -cabozantinib formulation in healthy subjects. Approximately 54% was recovered in feces and 27% in urine. Unchanged cabozantinib accounted for 43% of the total radioactivity in feces and was not detectable in urine following a 72 hour collection.

Specific Populations

[0046] The following patient characteristics did not result in a clinically relevant difference in the pharmacokinetics of cabozantinib: age (32-86 years), sex, race (Whites and non-Whites), or mild to moderate renal impairment (eGFR greater than or equal to 30 mL/min/1.73 m² as estimated by MDRD (modification of diet in renal disease equation)). The pharmacokinetics of cabozantinib is unknown in patients with worse than moderate renal impairment (eGFR less than 29 mL/min/1.73m²) as estimated by MDRD equation or renal impairment requiring dialysis.

Hepatic Impairment

[0047] Cabozantinib exposure ($AUC_{0-\text{inf}}$) increased by 81% and 63%, respectively, in patients with mild (C-P A) and moderate (C-P B) hepatic impairment. Patients with severe hepatic impairment have not been studied.

Pediatric Population

[0048] The pharmacokinetics of cabozantinib has not been studied in the pediatric population.

Drug Interactions

[0049] **CYP3A4 Inhibition on Cabozantinib:** Administration of a strong CYP3A4 inhibitor, ketoconazole, (400 mg daily for 27 days) to healthy subjects increased single-dose plasma cabozantinib exposure ($AUC_{0-\text{inf}}$) by 38%.

[0050] CYP3A4 Induction on Cabozantinib: Administration of a strong CYP3A4 inducer, rifampin, (600 mg daily for 31 days) to healthy subjects decreased single-dose plasma cabozantinib exposure (AUC_{0-inf}) by 77%.

[0051] Cabozantinib on CYP2C8 substrates: No clinically-significant effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (C_{max} and AUC) was observed when co-administered with cabozantinib at steady-state plasma concentrations (≥ 100 mg/day daily for a minimum of 21 days) in patients with solid tumors.

[0052] Gastric pH modifying agents on Cabozantinib: No clinically-significant effect on plasma cabozantinib exposure (AUC) was observed following co-administration of the proton pump inhibitor (PPI) esomeprazole (40 mg daily for 6 days) with a single dose of 100 mg cabozantinib to healthy volunteers.

In vitro Studies

Metabolic Pathways

[0053] Inhibition of CYP3A4 reduced the formation of the oxidative metabolite by $> 80\%$. Inhibition of CYP2C9 had a minimal effect on cabozantinib metabolite formation (i.e., a $<20\%$ reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation.

[0054] Although cabozantinib is an inhibitor of CYP2C8 *in vitro*, a clinical study of this potential interaction concluded that concurrent use did not result in a clinically relevant effect on CYP2C8 substrate exposure. Given this finding, other less sensitive substrates of pathways affected by cabozantinib *in vitro* (i.e., CYP2C9, CYP2C19, and CYP3A4) were not evaluated in a clinical study because, although a clinically relevant exposure effect cannot be ruled out, it is unlikely. Cabozantinib does not inhibit CYP1A2 and CYP2D6 isozymes *in vitro*.

[0055] Cabozantinib is an inducer of CYP1A1 mRNA; however, the clinical relevance of this finding is unknown. Cabozantinib does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4.

Drug Transporter Systems

[0056] Cabozantinib is an inhibitor, but not a substrate, of P-gp transport activities and has the potential to increase plasma concentrations of co-administered substrates of P-gp. The clinical relevance of this finding is unknown. Cabozantinib is a substrate of MRP2 *in vitro* and MRP2

inhibitors have the potential to increase plasma concentrations of cabozantinib. The clinical relevance of this finding is unknown.

Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

[0057] Cabozantinib was not carcinogenic in a 26-week carcinogenicity study in rasH2 transgenic mice. Cabozantinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay and was not clastogenic in both the *in vitro* cytogenetic assay using human lymphocytes or in the *in vivo* mouse micronucleus assay. Based on nonclinical findings, male and female fertility may be impaired by treatment with CABOMETYX. In a fertility study in which cabozantinib was administered to male and female rats at doses of 1, 2.5, and 5 mg/kg/day, male fertility was significantly compromised at doses equal to or greater than 2.5 mg/kg/day (approximately 13-fold of human AUC at the recommended dose), with a decrease in sperm counts and reproductive organ weights. In females, fertility was significantly reduced at doses equal to or greater than 1 mg/kg/day (5-fold of human AUC at the recommended dose) with a significant decrease in the number of live embryos and a significant increase in pre- and post-implantation losses.

[0058] Observations of effects on reproductive tract tissues in general toxicology studies were supportive of effects noted in the dedicated fertility study and included hypospermia and absence of corpora lutea in male and female dogs in a 6-month repeat dose study at plasma exposures (AUC) approximately 0.5-fold (males) and <0.1-fold (females) of those expected in humans at the recommended dose. In addition, female rats administered 5 mg/kg/day for 14 days (approximately 9-fold of human AUC at the recommended dose) exhibited ovarian necrosis.

[0059] The following non-limiting examples are included for purposes of illustration only, and are not intended to limit the scope of the range of techniques and protocols in which the compositions and methods of the present invention may find utility, as will be appreciated by one of skill in the art and can be readily implemented.

Example 1

[0060] **Phase Ib study of cabozantinib plus panitumumab in KRAS wild-type (WT) metastatic colorectal cancer (mCRC).**

[0061] **Background:** Patients with chemotherapy-refractory metastatic colorectal cancer (CRC) have modest survival benefit from standard of care therapies. Grothey, A., et al., *Regorafenib*

monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet, 2013. 381(9863): p. 303-12. Mayer, R.J., et al., *Randomized trial of TAS-102 for refractory metastatic colorectal cancer.* N Engl J Med, 2015. 372(20): p. 1909-19. Price, T.J., et al., *Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study.* Lancet Oncol, 2014. 15(6): p. 569-79. Although new therapies such as Panitumumab, an FDA-approved anti-EGFR monoclonal antibody are available for the treatment of KRAS and NRAS (RAS) wild-type (WT) metastatic CRC, resistance to anti-EGFR therapies due to MET amplification remains an issue. Bardelli, A., et al., *Amplification of the MET receptor drives resistance to anti-EGFR therapies in colorectal cancer.* Cancer Discov, 2013. 3(6): p. 658-73. Cabozantinib is a potent inhibitor of multiple receptor tyrosine kinases, including VEGFR2, AXL, and c-MET. Yakes, F.M., et al., *Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth.* Molecular cancer therapeutics, 2011. 10(12): p. 2298-308. We hypothesize that cabozantinib will enhance the activity of panitumumab, and be particularly active against MET amplified tumors.

[0062] Objectives. The primary objective was to define the maximum tolerated dose (MTD) and recommended phase II dose (RPTD) of cabozantinib + panitumumab. The secondary objectives were to (i) describe the dose limiting and non-dose limiting toxicities of cabozantinib + panitumumab; (ii) describe the clinical activity (objective response rate [ORR], progression free survival [PFS], and overall survival [OS]) for cabozantinib + panitumumab; and (iii) explore the relationship between tissue and blood-based biomarkers and clinical outcomes.

[0063] Methods. Eligible pts with chemotherapy refractory KRAS WT mCRC were enrolled in a 3+3 dose finding cohort (Dose Find) to identify the recommended phase II dose (RPTD). Prior anti-EGFR therapy was permitted. Cycle length was 28 days. Pts were then enrolled in a single-arm expansion cohort (EXP) and treated at the RPTD. The EXP cohort included a 2-week C monotherapy lead-in. The objectives of the EXP cohort were to better describe the safety, tolerability, and efficacy of C+P. Response assessment occurred every 2 months (mos) using RECIST version 1.1. Peripheral blood was sequenced for >54 gene mutations and focal amps, including *MET* (Guardant Health, Inc.).

[0064] Key Inclusion Criteria:

- KRAS WT adenocarcinoma of the colon or rectum that is metastatic and/or unresectable

- Prior treatment with 5-FU, oxaliplatin, irinotecan, and anti-VEGF monoclonal antibody
- Prior cetuximab or panitumumab permitted
- Adequate organ and bone marrow function

[0065] Key Exclusion Criteria:

- Prior tyrosine kinase inhibitor within 2 weeks, cytotoxic chemotherapy within 3 weeks, or any other investigational treatment within 4 weeks of study treatment
- Hypertension (BP > 140/90)
- Concomitant therapeutic doses of anticoagulants (warfarin, factor Xa inhibitors, etc.)

[0066] Trial Design:

- Dose Finding: 3+3 design to determine the MTD and RPTD of cabozantinib + panitumumab
- Dose Expansion: To define the safety, tolerability, and activity of the RPTD

[0067] Table 1 summarizes the dose and schedule of cabozantinib and panitumumab. Cycle length: cycle 1 of the Expansion cohort 6 weeks; all other cycles 4 weeks.

Table 1. Dose and schedule of cabozantinib and panitumumab

Cohort	# Evaluable subjects	Cabozantinib (mg) PO daily	Panitumumab (mg/kg) IV, Q2 weeks
Dose Finding	6	60	6
Dose Expansion	12	60	6 Started on cycle 1, day 15

[0068] Assessments:

- Adverse events (AEs) graded according to NCI CTCAE, version 4.0
- Dose-limiting toxicity (DLT) assessment window: 28 days
- Tumor assessments: Dose Finding- CT or MRI every 8 weeks (Q2 cycles); Expansion- CT or MRI after week 10 (end of cycle 2), then Q8 weeks (Q2 cycles)
- Tumors evaluated using RECIST criteria (version 1.1)

[0069] Biomarkers:

- Blood collection: Baseline, cycle 1 day 15 of Expansion cohort only, and each restaging until progression
- Plasma-EDTA cell free DNA (cfDNA) retrospectively sequenced for >54 gene mutations and focal amplifications (Guardant Health, Inc.)
- Archived paraffin-embedded tumor tissue collected from all eligible subjects
- Genomic amplification tested in tumor tissue using commercially available NGS or FISH

[0070] Results: As of 11/24/2015, 16 pts were evaluable for toxicity (6 Dose Find; 10 EXP), and 14 pts were evaluable for response (6 Dose Find; 8 EXP). 13 pts had received prior anti-EGFR therapy. There were no dose limiting toxicity events in the Dose Find cohort (0/6). The RPTD was C 60mg PO daily and P 6 mg/kg IV Q2 weeks. In the Dose Find and EXP cohorts, there were no grade 4 or 5 treatment related adverse events (TRAEs). The most frequently reported (all grades > 30%) TRAEs were (n, %) acneiform rash (10, 63%), oral mucositis (9, 56%), diarrhea (8, 50%), increased AST (7, 44%), paronychia (6, 38%), increased ALT (5, 31%), and fatigue (5, 31%). Median PFS was 3.7 mos (95% C.I., 2.3–7.4 mos). Median OS was 7.5 mos (95% C.I., 6.4–12.1 mos). 2 pts (14%) had a confirmed partial response, and 5 pts had PFS > 6 months.

[0071] Treatment Summary:

- 18 patients enrolled and dosed
- 18 subjects evaluable for toxicity, PFS, OS
- 16 subjects evaluable for response
- 17 subjects completed at least 1 cycle
- 14 of 18 pts have discontinued treatment: 11 for disease progression, 3 for toxicity
- 4 patients remain on active treatment as of cut-off date

[0072] Patient Characteristics are summarized in Table 2.

Table 2. Baseline demographics and patient characteristics

Demographic/ characteristic	Dose Finding (n= 6)	Expansion (n=12)	Overall (n= 18)
Gender, n (%)			
Male	3 (50)	3 (25)	6 (33)
Female	3 (50)	9 (75)	12 (67)
Median age, years	52.7	51.8	52.4
ECOG performance status (n,%)			
0	2 (33)	3 (25)	5 (28)
1	4 (67)	9 (75)	13 (72)
# prior treatments, (n,%)*			
2 or fewer	0 (0)	4 (33)	4 (22)
3	0 (0)	1 (9)	1 (6)
4	1 (17)	4 (33)	5 (28)
≥ 5	5 (83)	3 (25)	8 (44)
Tumor type, (n,%)			
Colon	4 (67)	11 (92)	15 (83)
Rectal	2 (33)	1 (8)	3 (17)
Prior anti-EGFR therapy, (n, %)			
Yes	6 (100)	7 (58)	13 (72)
No	0 (0)	5 (42)	5 (28)

* Excludes adjuvant chemotherapy, if completed greater than 12 months prior to treatment for metastatic disease.

[0073] Safety: Table 3 summarizes treatment-related adverse events. There were no treatment related grade 4/5 adverse events.

Table 3. Treatment-related adverse events, n (%)
(event frequency > 15%)

Adverse event	Dose Finding (n=6)		Expansion (n=12)		Overall (n=18)	
	Grade 1-2	Grade 3	Grade 1-2	Grade 3	Grade 1-2	Grade 3
Rash	3 (50)	1 (17)	8 (67)	1 (8)	11 (61)	2 (11)
Oral mucositis	5 (83)	0 (0)	2 (17)	2 (17)	7 (39)	2 (11)
Diarrhea	3 (50)	0 (0)	3 (25)	3 (25)	6 (33)	3 (17)
Fatigue	1 (17)	0 (0)	6 (50)	0 (0)	7 (39)	0 (0)
AST increased	3 (50)	0 (0)	4 (33)	0 (0)	7 (39)	0 (0)
Paronychia	3 (50)	0 (0)	3 (25)	0 (0)	6 (33)	0 (0)
ALT increased	3 (50)	0 (0)	2 (17)	0 (0)	5 (28)	0 (0)
Palmar-plantar erythrody- esthesia	2 (33)	0 (0)	0 (0)	1 (8)	2 (11)	1 (6)
Nausea	2 (33)	0 (0)	1 (8)	0 (0)	3 (17)	0 (0)
Vomiting	3 (50)	0 (0)	0 (0)	0 (0)	3 (17)	0 (0)
Hypokalemia	1 (17)	0 (0)	1 (8)	1 (8)	2 (11)	1 (6)
Hypomagnesemia	3 (50)	0 (0)	0 (0)	0 (0)	3 (17)	0 (0)

[0074] Determination of MTD/RPTD

- No DLTs in Dose Finding Cohort (0/6)
- MTD/RPTD: cabozantinib 60mg p.o. daily + panitumumab 6mg/kg I.V. Q2 weeks

[0075] The efficacy of Cabozantinib + panitumumab is summarized in Table 4.

Table 4. Clinical outcomes

	N	ORR (%) [*]	Median PFS (months) (95% CI)	Median OS (months) (95% CI)
No prior anti-EGFR therapy	5	1/3 (33)	N/A (1 event)	N/A (no events)
Prior anti-EGFR therapy	13	1/13 (8)	2.4 (1.9 – 5.6)	7.1 (4.7 – 12.1)
Overall	18	2/16 (13)	3.7 (2.3 – 7.4)	7.5 (4.9 – NE)

^{*}2 patients not assessable for response

[0076] FIG. 1 depicts the best response to cabozantinib plus panitumumab therapy (% change in RECIST lesions).

[0077] FIG. 2 depicts the total target lesion size over time.

[0078] FIG. 3 depicts baseline and post cabozantinib plus panitumumab treatment radiographic images from a case report of a 57 year old male with metastatic rectal cancer who had showed disease progression on 6 prior lines of therapy. MET amplification was detected in the patient's blood, not tissue.

[0079] Table 5 summarizes cfDNA profiles and treatment response.

Table 5. Baseline cfDNA profile and treatment response

■ Major alteration(s)
 ▨ Minor alteration(s)

	Subject	Mutations										Amplifications				Best response (%)
		APC	P53	KRAS	NRAS	BRAF	MET	EGFR*	ERBB2	PK3CA	EGFR	MET	ERBB2	KRAS		
EGFR-refractory	101	▨	■	▨		▨		▨			■	■			-40%	
	102	■					▨			■					-15%	
	105	■		■											7%	
	108	■											■		18%	
	109	■				■									8%	
	110	■													-20%	
	111											■			-2%	
	114	■			■										-4%	
	115	■				▨									-21%	
	119	■		▨		■		▨	■						2%	
EGFR-naïve	121										■	■			18%	
	125		■	▨				■			■			■	79%	
	128														65%	
	112														-41%	
	113	■													-13%	
	131									■					-7%	
	132	■													Not evaluable	
	138														Pending	

* Includes all intracellular and extracellular domain mutations
 Minor alteration: detected in less than 10% of circulating tumor DNA

[0080] Conclusions: The combination of cabozantinib + panitumumab demonstrated an acceptable safety profile. Blood-based cfDNA profiling may reveal sub-populations that are sensitive to cabozantinib + panitumumab. Enrollment to the Dose Expansion cohort will be increased to better describe the safety and activity of the combination

Other Embodiments

[0081] The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

Claims

1. A method of treating KRAS Wild Type metastatic colorectal cancer, comprising administering to a patient in need of such treatment an effective amount of the combination of cabozantinib or a pharmaceutically acceptable salt thereof and panitumumab.
2. The method of claim 1, wherein the treating is characterized by reducing, inhibiting or preventing the growth of cancer cells or reducing, inhibiting or preventing metastasis of the cancer cells or invasiveness of the cancer cells or metastasis in the patient.
3. The method of any one of the preceding claims, wherein the administration of the combination increases the reduction or inhibition of cancer cell growth, reduction and inhibition of metastasis, or invasiveness of the cancer cells or metastasis as compared to treatment with panitumumab alone.
4. The method of any one of the preceding claims, wherein the patient has chemotherapy-refractory metastatic colorectal cancer.
5. The method of any one of the preceding claims, wherein the combination of cabozantinib and panitumumab are administered separately.
6. The method of any one of the preceding claims, wherein cabozantinib is administered orally at least once a day at a dosage from about 20 mg to about 140 mg.
7. The method of claim 6, wherein cabozantinib is administered at least once a day at a dosage of about 20 mg to about 100 mg.
8. The method of claim 6 or 7, wherein cabozantinib is administered in a dosage of about 40 mg to about 60 mg per day.

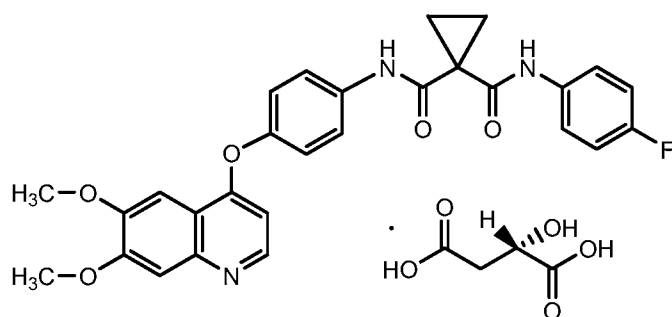
9. The method of any one of the preceding claims, wherein the panitumumab is administered intravenously in an amount of about 5 mg/kg body weight to about 7 mg/kg body weight at an interval of about once every 14 days.
10. The method of claim 9, wherein cabozantinib is administered to the patient at an oral dose of 60mg p.o. daily and panitumumab is administered to the patient at 6mg/kg I.V. Q2 weeks.
11. The method of any one of the preceding claims, wherein the combination is administered for at least 4 weeks.
12. The method of claim 11, wherein the combination is administered for at least six week.
13. The method of claim 12, wherein the combination is administered for at least 10 weeks.
14. The method of any one of the preceding claims, wherein the combination is administered for at least 24 weeks.
15. The method of any one of the preceding claims, wherein the patient has colorectal cancer is characterized by increased MET amplification.
16. The method of any one of the preceding claims, wherein the cancer is resistant to anti-EFGR therapy alone.
17. The method of any one of the preceding claim, wherein the treating is characterized by a reduction in the tumor volume by at least 50%.
18. A method of treating a patient with KRAS wildtype metastatic colorectal cancer which is resistant to anti-EGFR therapies, the method comprising
 - (a) determining the patient has metastatic colorectal cancer that is at least partially resistant to anti-EFGR therapy,

(b) administering an effective amount of the combination of cabozantinib or a pharmaceutically acceptable salt thereof and panitumumab, wherein the metastatic colorectal cancer is treated.

19. The method of claim 17, wherein the treating is characterized by reducing, inhibiting or preventing the growth of cancer cells or reducing, inhibiting or preventing metastasis of the cancer cells in the patient.

20. The method of claim 17 or 18, wherein the effective amount comprises about 20 mg to about 140 mg cabozantinib administered once a day orally and about 5.5-6.5 mg/kg body weight panitumumab administered once every 14 days by intravenous injection.

21. The method of any of the preceding claims, wherein the cabozantinib is cabozantinib (S)-malate of the formula:



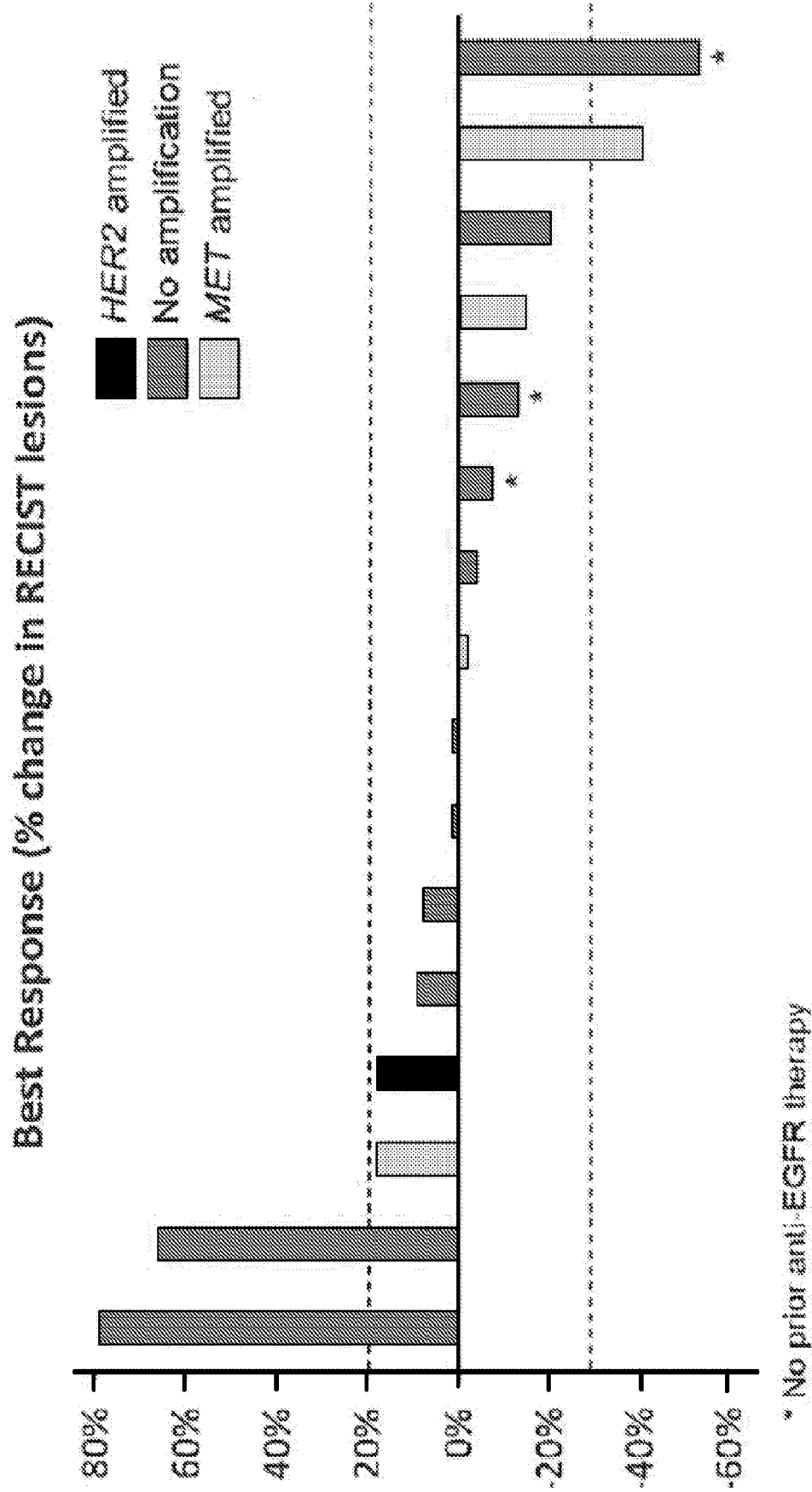


Fig. 1

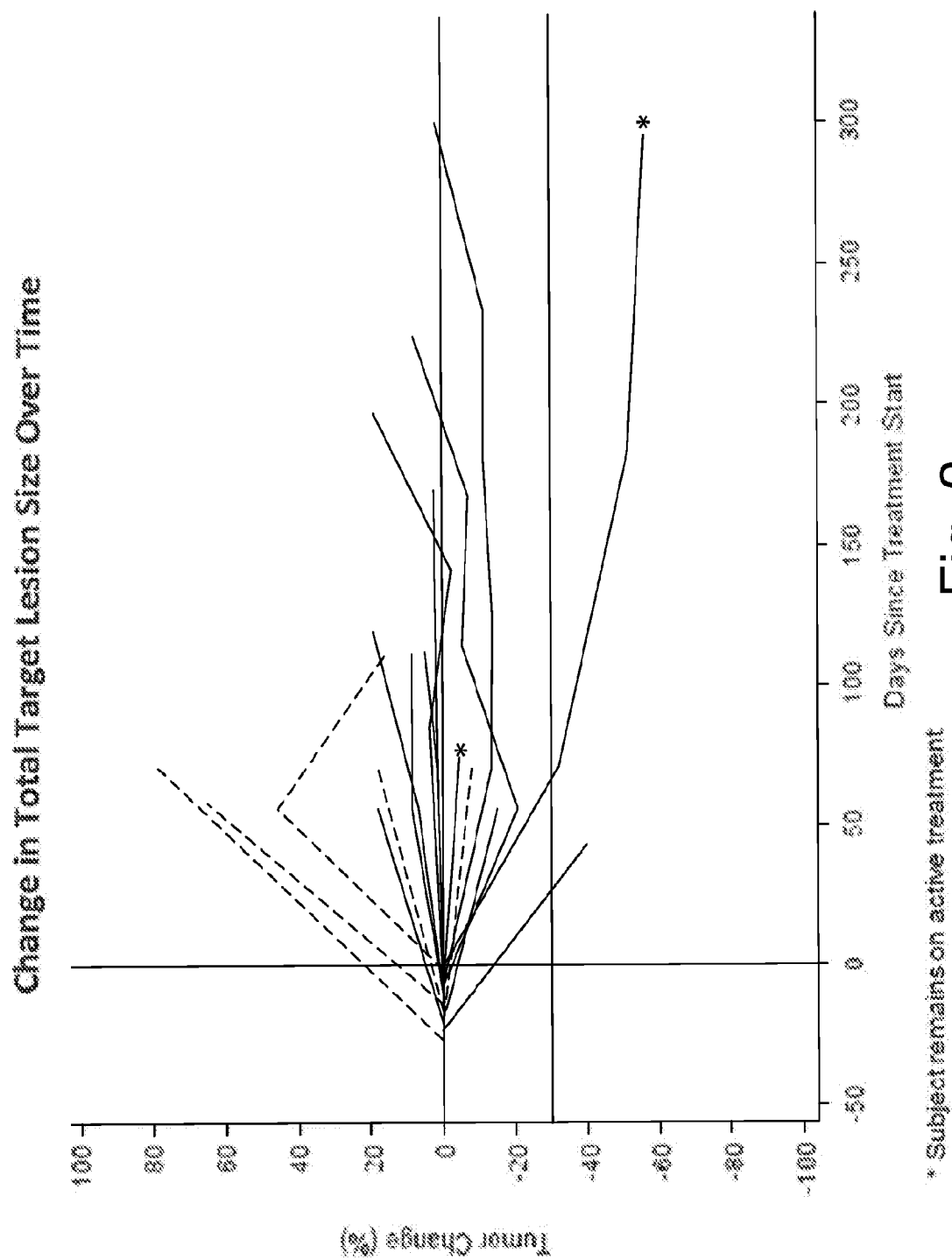


Fig. 2

3/3

57 Year Old Male with Metastatic Rectal Cancer

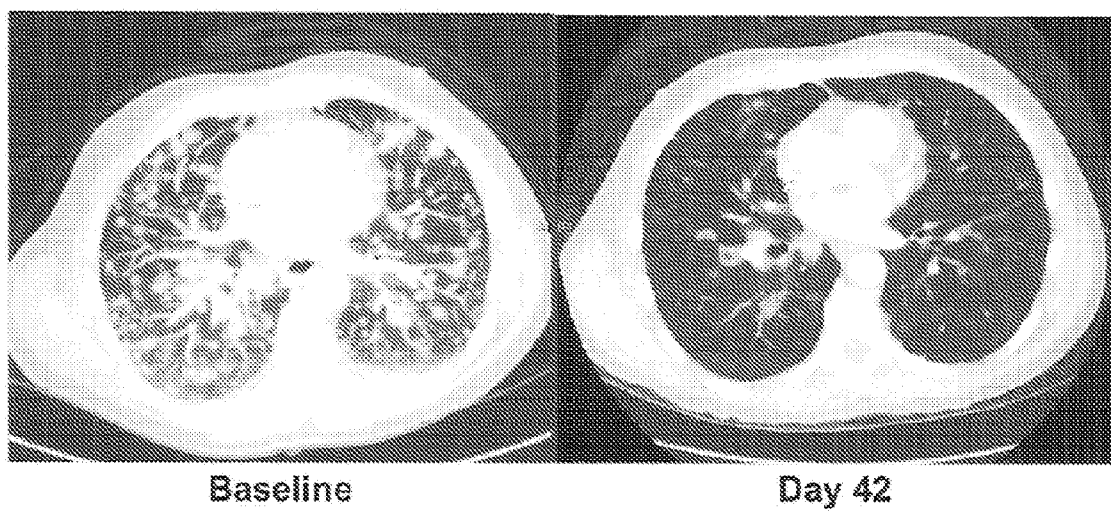


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/33085

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/395, A61P 35/00, A61P 35/04, A61K 31/47, A61K 45/00, A61P 43/00 (2017.01)
 CPC - A61K 39/395, A61K 31/47, C07D 215/22

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.
X	WO 2010/039248 A1 (JOHNS) 08 April 2010 (08.04.2010), [090], [0141], [0143], [0191]-[0192], [0196]	1-3
X	US 2012/0225870 A1 (JANNE et al) 06 September 2012 (06.09.2012), [0005], [0052], [0057]-[0058], [0061], [0069], [0071], [0084], [0193]	18
A	WO 2009/111691 A2 (FILVAROFF et al) 11 September 2009 (11.09.2009), entire document.	1-3, 18
A	MISALE et al, "Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer" Nature, volume 486, 28 June 2012 (28.06.2012), pg 532-536.	1-3, 18
A	AMADO et al, "Wild-Type KRAS Is Required for Panitumumab Efficacy in Patients With Metastatic Colorectal Cancer" Journal of Clinical Oncology, volume 26, issue 10, 03 March 2008 (03.03.2008), pg 1626-1634.	1-3, 18

☐ 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

"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

18 July 2017

Date of mailing of the international search report

22 AUG 2017

Name and mailing address of the ISA/US

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 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/33085

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.: 4-17, 19-21
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.