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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 February 2021 (18.02.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/030405 A1

(51) International Patent Classification:
A61K 31/4375 (2006.01) *A61P 35/00* (2006.01)
A61K 45/06 (2006.01)

(21) International Application Number:
PCT/US2020/045876

(22) International Filing Date:
12 August 2020 (12.08.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/885,797	12 August 2019 (12.08.2019)	US
62/904,198	23 September 2019 (23.09.2019)	US
62/926,281	25 October 2019 (25.10.2019)	US
62/936,018	15 November 2019 (15.11.2019)	US
62/968,927	31 January 2020 (31.01.2020)	US
62/968,945	31 January 2020 (31.01.2020)	US
63/023,921	13 May 2020 (13.05.2020)	US
63/023,936	13 May 2020 (13.05.2020)	US

(71) Applicant: **DECIPHERA PHARMACEUTICALS, LLC** [US/US]; 200 Smith Street, Waltham, MA 02451 (US).

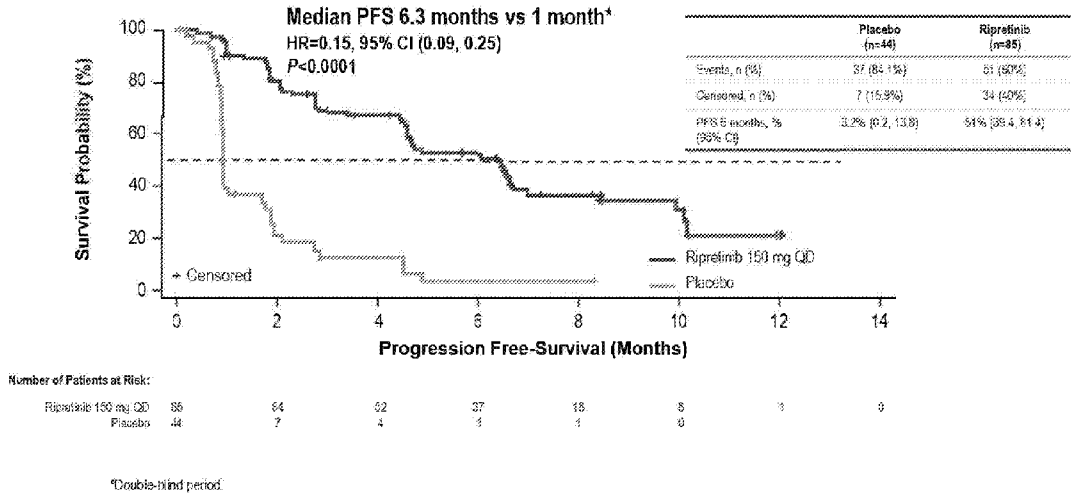
(72) Inventors: **SOTO, Rodrigo Ruiz**; 200 Smith Street, Waltham, MA 02451 (US). **ROSEN, Oliver**; 200 Smith Street, Waltham, MA 02451 (US). **PITMAN, Jama**; 200 Smith Street, Waltham, MA 02451 (US).

(74) Agent: **KAVANAUGH, Theresa, C.**; Goodwin Procter LLP, 100 Northern Avenue, IP Docketing Dept./7th Fl, Boston, MA 02210 (US).

(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, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, 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.

(54) Title: RIPRETINIB FOR TREATING GASTROINTESTINAL STROMAL TUMORS

FIG. 1



(57) Abstract: The present disclosure relates to methods of treating gastrointestinal stromal tumors to a subject in need thereof, comprising administering to the subject a therapeutically effective amount of ripretinib or a pharmaceutically acceptable salt thereof.

[Continued on next page]

WO 2021/030405 A1

(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).

Published:

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

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S.S.N. 62/885,797 filed August 12, 2019, U.S.S.N. 62/904,198 filed September 23, 2019, U.S.S.N. 62/926,281 filed October 25, 2019, U.S.S.N. 62/936,018 filed November 15, 2019, U.S.S.N. 62/968,927 January 31, 2020, U.S.S.N. 62/968,945 filed January 31, 2020, U.S.S.N. 63/023,921 filed May 13, 2020, and U.S.S.N. 63/023,936 filed May 13, 2020, the contents of each of which are incorporated herein by reference in their entirety.

BACKGROUND

[0002] Gastrointestinal stromal tumors (GIST) comprise less than 1% of all gastrointestinal (GI) tumors, but constitute the most common mesenchymal tumors and soft tissue sarcomas of the GI tract. They occur anywhere along the GI tract but are found most often in the stomach (60%) or small intestine (30%) and less frequently in the rectum, colon, or mesentery. In the United States, around 3300 to 6000 new cases of GIST are diagnosed each year. The vast majority of cases are sporadic, and older age is a recognized risk factor. Mutations in KIT and platelet-derived growth factor receptor-alpha (PDGFRA) are found in over 80% of all primary GISTs. Alterations in neurofibromatosis type 1 gene (NF1) and succinate dehydrogenase (SDH) complex (SDHC) genes as well as altered methylation of SDHC promoter have been described as oncogenic drivers in GIST without activating mutations in KIT or PDGFRA, and they have been linked to familial and heritable syndromes (NF1 and Carney-Stratakis syndrome).

[0003] Despite a wide variation in tumor size, location, and histologic subtypes (spindle cell, epithelioid cells, and mixed type), approximately 85% of all GISTs share oncogenic mutations in 1 of 2 receptor tyrosine kinases (TKs): KIT or PDGFRA. Constitutive activation of either of these TKs plays a central role in the oncogenic behavior of GIST. The early characterization of GIST mutational status is important in both the localized and metastatic settings to identify imatinib-resistant mutations (such as some primary KIT exon 17 mutations or PDGFRA D842V) or mutations that require a higher dose of imatinib. Patients with GIST lacking KIT or PDGFRA mutations usually do not benefit from imatinib, and standard treatment algorithms mostly do not apply. However, other mutations may be present in these patients, with the largest group represented by SDH-deficiency frequently associated with Carney or Carney-Stratakis-Syndrome. Other subtypes have mutations in NF1 (usually associated with neurofibromatosis type I) or in BRAF or KRAS. Very recently, casuistic

cases of GIST-like tumors harboring NTRK translocations have further expanded the spectrum of molecular subtypes.

[0004] In the pre-tyrosine kinase inhibitor (TKI) era, GISTs (often categorized as gastric leiomyosarcomas or leiomyoblastomas) were treated within the subtype of agnostic sarcoma trials and lacked an effective systemic therapy. However, a deeper understanding of the molecular pathogenesis and driving role of the protooncogenes KIT and PDGFRA has transformed the treatment of both localized and metastatic diseases. Localized and resectable tumors are treated surgically which remains the mainstay of curative therapy for localized disease. Resected high-risk GIST is typically treated with adjuvant imatinib, whereas low-risk GIST is managed with surgery alone. Intermediate-risk GIST is managed on a per-case basis. In an advanced/metastatic setting, imatinib 400 mg daily is approved, with dose escalation to 800 mg at the time of progression, and has been shown to yield dramatic results in disease control. Imatinib-refractory patients are treated with sunitinib as a second-line therapy and regorafenib as third-line therapy on resistance or intolerance to sunitinib.

[0005] At diagnosis, a mutation in the KIT gene occurs in 80% of GISTs and is usually found in exon 11, and less commonly in exon 9. Both mechanisms cause ligand-independent receptor activation, which leads to uncontrolled cell growth and transformation. Primary mutations affect a loss-of-function mutation in the JM domain and lead to a shift in equilibrium toward a Type I active or on-state conformation of KIT and away from a Type II inactive or off-state conformation of KIT. Exon 11 primary mutations are the most commonly seen in GISTs (around 70% of cases), and derive significant benefit from treatment with imatinib in both the adjuvant and metastatic settings, achieving a 2-year relapse-free survival of ~90% in the adjuvant setting, and a median event-free survival just under 2 years in the metastatic setting. Primary mutations (in treatment-naïve patients) in exon 9 affect the extracellular domain of KIT, mimicking conformational changes induced by ligand binding and triggering KIT receptor homodimerization. This dimerization leads to the activation of specific intracellular signaling pathways which can lead to cancer cell proliferation, survival, and resistance. Although less common than exon 11 mutations, exon 9 mutations (10%-15% of newly diagnosed cases) are most commonly seen in GISTs arising from the small intestine. Unlike exon 11 mutations, they benefit less from imatinib in both the adjuvant and metastatic settings.

[0006] Despite significant improvement in outcomes compared with those in the pre–mutation-driven/TKI therapy era, response to imatinib is not experienced by all patients, and most patients with GIST will ultimately develop resistance to imatinib, most commonly due

to the development of secondary mutations in KIT. Secondary resistance mutations usually arise in the catalytic domain of the kinase: 1) at the switch pocket, which typically occur in KIT exons 13 and 14 or PDGFRA exons 14 and 15 and sterically disrupt drug binding or conformationally activate KIT, and 2) in the activation loop switch encoded by KIT exons 17 and 18 and PDGFRA 18. Activation loop mutations act by shifting the kinase into an activated Type I or on-state conformation that is less amenable to drug binding by any of the approved Type II TKIs. Although uncommon in primary GIST (1%-2% of newly diagnosed cases), mutations in exons 13, 14 and 17 are often responsible for acquired imatinib resistance, with exon 17 mutations alone accounting for as many as 50% of the acquired resistance cases to imatinib, and later to sunitinib. A need exists for a TKI that can broadly inhibit clinically relevant KIT and PDGFRA mutations.

SUMMARY

[0007] Described herein are methods of treating a gastrointestinal stromal tumor in a patient in need thereof comprising administering to the patient a therapeutically effective amount of ripretinib or a pharmaceutically acceptable salt thereof.

[0008] For example, in one embodiment described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 300 mg, e.g., 150 mg, of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

[0009] For example, in one embodiment described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 250 mg, e.g., 150 mg, of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

[00010] In another embodiment, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 600 mg, e.g., 100 mg to 250 mg, e.g., 150 mg, of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

[00011] In another embodiment, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient one or more tablets comprising ripretinib, e.g., tablets each comprising 50 mg to

100 mg of ripretinib, daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib. In some examples, the tablets comprise 50 mg of ripretinib. In some embodiments, the tablets comprise 75 mg of ripretinib. In some embodiments, the tablets comprise 100 mg of ripretinib.

[00012] In another embodiment, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient one or more tablets comprising ripretinib, e.g., tablets each comprising 50 mg to 100 mg of ripretinib, daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib, a previous second line administration of sunitinib, and a previous third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib. In some embodiments, the tablets comprise 50 mg of ripretinib. In some example, the tablets comprise 75 mg of ripretinib. In some example, the tablets comprise 100 mg of ripretinib. In another embodiment, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 250 mg of ripretinib daily, e.g., 150 mg, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

[00013] In another embodiment, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 600 mg of ripretinib daily, e.g., 100 mg to 250 mg, e.g., 100 mg to 500 mg, e.g., 100 mg to 250 mg, e.g., 150 mg, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

[00014] In another embodiment, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient to the patient, on a daily basis, one or more tablets each comprising ripretinib, e.g., tablets each comprising 50 mg to 100 mg of ripretinib, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or

wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib. In some embodiment, the tablets comprise 50 mg of ripretinib. In some embodiment, the tablets comprise 75 mg of ripretinib. In some embodiment, the tablets comprise 100 mg of ripretinib.

[00015] In another embodiment, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 600 mg of ripretinib daily, e.g., 100 mg to 250 mg, e.g., 100 mg to 500 mg, e.g., 100 mg to 250 mg, e.g., 150 mg, e.g., 300 mg, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib.

[00016] In another embodiment, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg of ripretinib once daily, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib.

[00017] In another embodiment, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient, on a daily basis, one or more tablets each comprising ripretinib, e.g., tablets each comprising 50 mg to 100 mg of ripretinib, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib. In some embodiment, the tablets comprise 50 mg of ripretinib. In some embodiment, the tablets comprise 75 mg of ripretinib. In some embodiment, the tablets comprise 100 mg of ripretinib.

[00018] In another embodiment, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg of ripretinib once daily, wherein the patient was previously administered three or more kinase inhibitors before administration of the ripretinib. In some embodiments, after at least 4 weeks of the daily ripretinib administration, the patient has at least a 5-month progression-free survival as measured using mRECIST v1.1. In some embodiments, orally administering to the patient 150 mg of ripretinib once daily comprises administering to the patient three tablets each tablet comprising 50 mg of ripretinib. In some embodiments, one of the three or more kinase inhibitors is imatinib. In some embodiments, the patient was previously administered imatinib, sunitinib and regorafenib.

[00019] In another embodiment, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg daily ripretinib, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib.

[00020] In another embodiment, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg of ripretinib once or twice daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

[00021] In another embodiment, described herein is a method for achieving at least 5 months of progression free survival as determined by mRECIST 1.1 in a patient having an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100, 150 200, or 300 mg of ripretinib daily or twice daily for at least 28 days.

[00022] In another embodiment, described herein is a method for achieving at least 5 months of progression free survival as determined by mRECIST 1.1 in a patient having an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100, 150, or 200 mg of ripretinib daily or twice daily for at least 28 days.

[00023] In another embodiment, descried herein is a method of treating a patient suffering from Grade 3 palmer-plantar erythrodysesthia syndrome while being administered 150 mg ripretinib daily or twice daily, comprising withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantarplantar erythrodysesthia syndrome, then administering to the patient 100 mg daily (e.g., 100 mg once daily) ripretinib for at least 28 days.

[00024] In another embodiment, descried herein is a method of treating a patient suffering from Grade 2 palmer-plantarplantar erythrodysesthia syndrome upon administration of 150 mg ripretinib daily or twice daily, comprising a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythorysesthia syndrome within 7 days of withholding administration, then administering to the patient 150 mg daily

ripretinib or c) if the patient has not recovered, then administering to the patient 100mg daily ripretinib for at least 28 days.

[00025] In another embodiment, described herein is a method of treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a CYP3A4 inhibitor, the method comprising: orally administering to the patient 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, once or twice daily, and wherein upon administration of the ripretinib and the CYP3A4 inhibitor, provides an increased ripretinib area under the plasma concentration curve ($AUC_{0\text{-}inf}$) of 80% or more in the patient as compared to administration of ripretinib without concurrent treatment of the CYP3A4 inhibitor, and therefore the patient is at higher risk of an adverse event; and monitoring the patient more frequently, as compared to a patient not being treated with a CYP3A4 inhibitor, for the adverse event.

[00026] In another embodiment, described herein is a method of treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a proton pump inhibitor, the method comprising: orally administering to the patient 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, once or twice daily, and wherein administration of the ripretinib and proton pump inhibitor to the patient provides no clinically significant difference in the plasma exposure of ripretinib in the patient as compared to administration of ripretinib without concurrent treatment of the proton pump inhibitor.

[00027] In another embodiment, described herein is a method of treating a gastrointestinal stromal tumor in a patient in need thereof, the method comprising orally administering to the patient 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, once or twice daily, wherein the ripretinib is administered to the patient with food or without food.

BRIEF DESCRIPTION OF THE DRAWINGS

[00028] **FIG. 1** depicts a plot of survival probability with respect to progression-free survival (PFS) for patients on ripretinib and patients on placebo as described in Example 2.

[00029] **FIG. 2** depicts a plot of survival probability with respect to overall survival (OS) for patients on ripretinib and patients on placebo as described in Example 2.

[00030] **FIG. 3** depicts plots illustrating survival probability with respect to OS in patients on ripretinib, crossed over from placebo to ripretinib, and patients without cross-over.

[00031] **FIG. 4** depicts PFS by line of therapy for patients with GIST treated with 150 mg once daily of ripretinib.

[00032] **FIG. 5** depicts patient report outcome by EQ-VAS visual scale (**FIG. 5A**) and score changes from baseline (**FIG. 5B**) used to assess these scores and corresponding patient percentage distributions (**FIG. 5C**) used in the study of Example 2 at 150 mg ripretinib QD. In the study, 70 patients were receiving ripretinib and 32 were receiving placebo.

[00033] **FIG. 6** depicts EORTC QLQ-C30 physical function questions (**FIG. 6A**) and patient score changes (**FIG. 6B**) from baseline in response and corresponding patient percentage distributions (**FIG. 6C**) used in the study of Example 2 at 150 mg ripretinib QD. Physical function scores improved on average 1.6 from baseline to C2D1 among patients taking ripretinib in contrast to placebo patients who saw on average, a decline from baseline to C2D1 of 8.9 ($p=0.004$). In this study, 71 patients were receiving ripretinib and 32 were receiving placebo.

[00034] **FIG. 7** depicts EORTC QLQ-C30 role function questions (**FIG. 7A**) and patient score changes (**FIG. 7B**) from baseline in response and corresponding patient percentage distributions (**FIG. 7C**) used in the study of Example 2 at 150 mg ripretinib QD. In the study, 70 patients were receiving ripretinib and 32 were receiving placebo.

[00035] **FIG. 8** depicts patient score changes from baseline (**FIG. 8A**) and percentage distributions (**FIG. 8B**) in response to Question C29 of EORTC QLQ-C30 ("How would you rate your overall health during the past week?") from a scale of 1 ("Very poor") to 7 ("Excellent") in the study of Example 2 at 150 mg ripretinib QD. In the study, 70 patients were receiving ripretinib and 32 were receiving placebo.

[00036] **FIG. 9** depicts patient score changes from baseline (**FIG. 9A**) and corresponding patient percentage distributions (**FIG. 9B**) in response to Question C30 of EORTC QLQ-C30 ("How would you rate your overall quality of life during the past week?") from a scale of 1 ("Very poor") to 7 ("Excellent") in the study of Example 2 at 150 mg ripretinib QD. In the study, 70 patients were receiving ripretinib and 32 were receiving placebo.

[00037] **FIG. 10** depicts mean changes in baseline scores in EQ-VAS across various time points, from Cycle 1, Day 15 up to Cycle 15, Day 1 of the intention-to-treat population in the study of Example 2 at 150 mg ripretinib QD.

[00038] **FIG. 11A** and **FIG. 11B** depict mean changes in baseline scores in EORTC QLQ-C30 role function and EORTC QLQ-C30 physical function, respectively, across various time

points, from Cycle 1, Day 15 up to Cycle 15, Day 1 of the intention-to-treat population in the study of Example 2 at 150 mg ripretinib QD.

[00039] **FIG. 12A** and **FIG. 12B** depict mean changes in baseline scores in EORTC QLQ-C30 question C29 response and EORTC QLQ-C30 question C30 response, respectively, across various time points, from Cycle 1, Day 15 up to Cycle 15, Day 1 of the intention-to-treat population in the study of Example 2 at 150 mg ripretinib QD.

[00040] **FIG. 13** depicts exemplary PFS data for patients who crossed over from placebo to ripretinib in the study described in Example 2 at 150 mg ripretinib QD.

[00041] **FIG. 14A** and **FIG. 14B** depict progression free survival (PFS) studies in the double-blind and open-label periods in the study of Example 2 for patients who dose escalated from 150 mg ripretinib QD 150 mg ripretinib BID. **FIG. 14C** depicting median PFS data and other parameters in these PFS studies.

[00042] **FIG. 15** shows exemplary PFS data among patients with wild-type KIT mutations in the study of Example 2.

[00043] **FIGS. 16A** and **16B** depict Progression free survival (PFS) and overall survival (OS) data based on patients with a primary Exon 11 mutation or those with a non-Exon 11 mutation in the study of Example 2 at 150 mg ripretinib QD.

[00044] **FIGS. 17A** and **17B** depicts progression free survival (PFS) and overall survival (OS) data based on patients with a primary Exon 11 mutation or a primary Exon 9 mutation in the study of Example 2 at 150 mg ripretinib QD.

[00045] **FIGS. 18A** and **18B** depicts progression free survival (PFS) and overall survival (OS) data based on patients with a primary Exon 11 mutation, or a primary Exon 9 mutation, or another mutation, or wild type (KIT and PDGFRA) in the study of Example 2 at 150 mg ripretinib QD.

[00046] **FIGS. 19A** and **19B** depicts progression free survival (PFS) studies for patients with certain primary mutations (Exon 9 or Exon 11) who dose escalated from 150 mg QD ripretinib to 150 mg BID ripretinib for the double-blind and open-label periods, respectively, in the study of Example 2.

[00047] **FIG. 20** shows exemplary progression free survival data for patients with other KIT mutations and PGDFR mutations in the study of Example 2 at 150 mg ripretinib QD.

[00048] **FIG. 21** depicts the median first appearance and worst grade of alopecia and PPES in corresponding patients receiving ripretinib in the study described in Example 2.

[00049] **FIG. 22A** depicts a mean change from baseline for physical function patient reported outcome of the EORTC-QLQ-C30 in patients receiving ripretinib, with and without

alopecia, in the study described in Example 2. **FIG. 22B** depicts a mean change from baseline for role function patient reported outcome of the EORTC-QLQ-C30 in patients receiving ripretinib, with and without alopecia, in the study described in Example 2. **FIG. 22C** depicts a mean change from baseline for physical function patient reported outcome of the EORTC-QLQ-C30 in patients receiving ripretinib, with and without palmar-plantar erythrodysesthesia syndrome (PPES), in the study described in Example 2. **FIG. 22D** depicts a mean change from baseline for role function patient reported outcome of the EORTC-QLQ-C30 in patients receiving ripretinib, with and without palmar-plantar erythrodysesthesia syndrome (PPES), in the study described in Example 2.

[00050] **FIG. 23A** depicts a mean change from baseline for overall health patient reported outcome of the EORTC-QLQ-C30 in patients receiving ripretinib, with and without alopecia, in the study described in Example 2. **FIG. 23B** depicts a mean change from baseline for overall quality of life patient reported outcome of the EORTC-QLQ-C30 in patients receiving ripretinib, with and without alopecia, in the study described in Example 2. **FIG. 23C** depicts a mean change from baseline for overall health patient reported outcome of the EORTC-QLQ-C30 in patients receiving ripretinib, with and without palmar-plantar erythrodysesthesia syndrome (PPES), in the study described in Example 2. **FIG. 23D** depicts a mean change from baseline for overall quality of life patient reported outcome of the EORTC-QLQ-C30 in patients receiving ripretinib, with and without palmar-plantar erythrodysesthesia syndrome (PPES), in the study described in Example 2.

[00051] **FIG. 24A** depicts a mean change from baseline for state of health (VAS) patient reported outcome of the EORTC-QLQ-C30 in patients receiving ripretinib, with and without alopecia, in the study described in Example 2. **FIG. 24B** depicts a mean change from baseline for state of health (VAS) patient reported outcome of the EORTC-QLQ-C30 in patients receiving ripretinib, with and without palmar-plantar erythrodysesthesia syndrome (PPES), in the study described in Example 2.

[00052] **FIG. 25A** and **FIG. 25B** depict exemplary PFS of subjects who dose escalated to 150 mg BID, PFS before (PFS1) and after (PFS2) dose escalation.

[00053] **FIG. 26A-D** depicts an exemplary comparison of PFS of patient subgroups with Exon 9 (**FIG. 26A**), Exon 11 (**FIG. 26B**), Exon 13 (**FIG. 26C**), or Exon 17 (**FIG. 26D**) KIT mutations. This exemplary data show that ripretinib showed PFS benefit in all assessed patient subgroups compared to placebo.

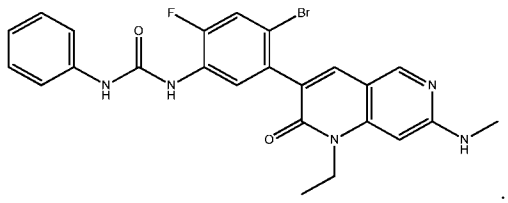
[00054] **FIG. 27** shows PFS data of exemplary second and third-line patients with Exons 9, 11, 13, or 17 KIT mutations. The data show that, in second and third line populations, patients with such various KIT mutations have comparable PFS.

DETAILED DESCRIPTION

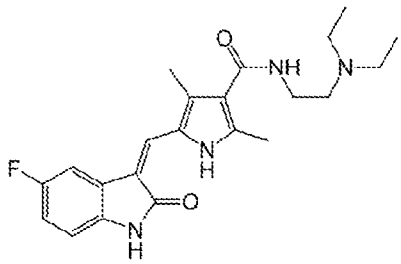
[00055] The features and other details of the disclosure will now be more particularly described. Certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

Definitions

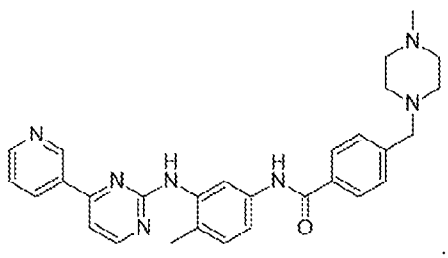
[00056] As used herein, "ripretinib" is a compound represented by the following structure:



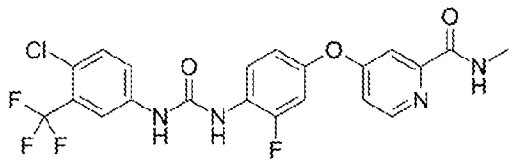
[00057] As used herein, "sunitinib" is a compound represented by the following structure:



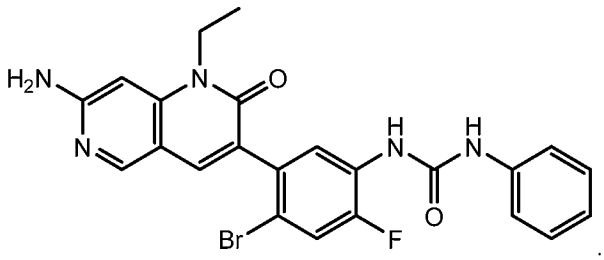
[00058] As used herein, "imatinib" is a compound represented by the following structure:



[00059] As used herein, "regorafenib" is a compound represented by the following structure:



[00060] As used herein, "Compound A" is a compound represented by the following structure:



[00061] "Individual," "patient," or "subject" are used interchangeably herein and include any animal, including mammals, including mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and humans. The compounds described herein can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of veterinary treatment, *e.g.*, domestic animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, and the like). The mammal treated in the methods described herein is desirably a mammal in which treatment of a disorder described herein is desired, such as a human.

[00062] The term "pharmaceutically acceptable salt(s)" as used herein refers to salts of acidic or basic groups that may be present in compounds used in the compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including, but not limited to, malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate,

methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e., 1,1'-methylene-*bis*-(2-hydroxy-3-naphthoate)) salts.

[00063] As used herein, "treating" includes any effect, e.g., lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder and the like.

[00064] Therapeutically effective amount" includes the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. A compound described herein, *e.g.*, ripretinib is administered in therapeutically effective amounts to treat a condition described herein, *e.g.*, gastrointestinal stromal tumors. Alternatively, a therapeutically effective amount of a compound is the quantity required to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in the prevention of or a decrease in the symptoms associated with the condition.

[00065] As used herein, "$AUC_{0\text{-}24h}$" refers to the area under the plasma concentration-time curve from time zero to 24 hours for a compound described herein. As used herein, "$AUC_{0\text{-}inf}$" refers to the area under the plasma concentration-time curve from time zero to infinite time for a compound described herein. As used herein, "C_{max}" refers to the maximum plasma concentration of a compound described herein.

[00066] A compound described herein, *e.g.*, ripretinib, can be formulated as a pharmaceutical composition using a pharmaceutically acceptable carrier and administered by a variety of routes. In some embodiments, such compositions are for oral administration. In some embodiments, compositions formulated for oral administration are provided as tablets. In some embodiments, such compositions are for parenteral (by injection) administration (*e.g.*, a composition formulated for local injection at the site of a tumor, *e.g.*, a diffuse-type giant cell tumor). In some embodiments, such compositions are for transdermal administration. In some embodiments, such compositions are for topical administration. In some embodiments, such compositions are for intravenous (IV) administration. In some embodiments, such compositions are for intramuscular (IM) administration. Such pharmaceutical compositions and processes for preparing them are well known in the art. See, e.g., REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (A. Gennaro, et al., eds., 19th ed., Mack Publishing Co., 1995).

Methods of Treatment

[00067] Described herein are methods of treating gastrointestinal stromal tumors in a patient in need thereof. For example, the present disclosure relates to a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg or more of ripretinib daily, e.g., 100 mg to 5000 mg, e.g., 100 mg to 500 mg, 100 mg to 250 mg, e.g., 150 mg, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib. In some embodiments, the method comprises administering to the patient 110 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 120 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 130 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 140 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 150 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 200 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 250 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 300 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 350 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 400 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 450 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 500 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 550 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 600 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 650 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 700 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 750 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 800 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 850 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 900 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 950 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 1000 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 150

mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 200 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 250 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 300 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 350 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 400 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 450 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 500 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 550 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 600 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 650 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 700 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 750 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 800 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 850 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 900 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 950 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 1000 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 150 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 200 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 250 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 300 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 350 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 400 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 450 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 500 mg of ripretinib twice daily.

[00068] In some embodiments, a patient was only previously treated with a first line administration of imatinib, e.g., only imatinib and no other therapeutic compounds had been administered to the patient before administration of ripretinib to the patient. For example, a

patient was not previously administered with sunitinib and/or regorafenib, e.g., the patient was not previously given a second line administration of sunitinib therapy and/or a third-line administration of regorafenib therapy.

[00069] In some embodiments, the patient has a non-nodal tumor lesion of greater than or equal to 1.0 cm in the long axis or greater than or equal to double the slide thickness in the long axis, within 21 days prior to the first dose of ripretinib. Contemplated methods of treatment include administering ripretinib on a 42-day cycle, comprising daily administrations of ripretinib without administering sunitinib. After at least one 42-day cycle comprising daily administrations of ripretinib, the patient may have progression-free survival as measured using mRECIST v1.1. In some embodiments, the patient treated with daily administrations of ripretinib may have significant progression free survival (e.g., about 3 months progression free survival or more, e.g., about 6 months progression free survival, as compared to a second line daily administration of 50 mg sunitinib for four weeks followed by two weeks without daily administrations on a 42-day cycle, wherein the patient's tumor has progressed from, or the patient was intolerant to, the previous first line administration of imatinib.

[00070] Contemplated treatments with ripretinib may treat a broad spectrum of KIT and PDGFRA mutations. For example, a patient's tumor may have a KIT exon 9 mutation, a PDGFRA exon 18 mutation, a PDGFRA exon 12 mutation or a PDGFRA exon 18 activation loop mutation. For example, the patient's tumor mutation is a PDGFRA D842V mutation.

[00071] In some embodiments, a patient's tumor has an imatinib resistant mutation selected from the group consisting of a KIT exon 17 activation loop mutation, a KIT exon 18 activation loop mutation, a KIT exon 13 mutation, a KIT exon 14 mutation, a KIT exon 18 mutation, a PDGFRA exon 12 mutation, a PDGFRA exon 14 mutation, a PDGRFA exon 15 mutation, and a PDGFRA exon 18 activation loop mutation. For example, the imatinib resistant mutation is a PDGFRA D842V mutation.

[00072] In some embodiments, the patient's tumor has an imatinib resistant mutation selected from the group consisting of KIT exon 13 or 14 mutation, PDGFRA exon 14 or 15 mutation, a KIT 17 or 18 activation loop mutation, and a PDGFRA 18 activation loop mutation. For example, the patient's tumor has an imatinib resistant KIT exon 17 mutation.

[00073] Also described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg or more, e.g., up to about 600 mg, e.g. up to about 250 mg, e.g., 100 mg or 150 mg, of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first

line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib. Contemplated methods of treatment include orally administering 100 mg, 150 mg or more of ripretinib daily without administering sunitinib on a 42-day cycle. In some embodiments, the method comprises administering to the patient 110 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 120 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 130 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 140 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 150 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 200 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 250 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 300 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 350 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 400 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 450 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 500 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 550 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 600 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 650 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 700 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 750 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 800 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 850 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 900 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 950 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 1000 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 150 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 200 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 250 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 300 mg of

ripretinib once daily. In some embodiments, the method comprises administering to the patient 350 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 400 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 450 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 500 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 550 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 600 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 650 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 700 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 750 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 800 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 850 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 900 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 950 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 1000 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 150 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 200 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 250 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 300 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 350 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 400 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 450 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 500 mg of ripretinib twice daily.

[00074] In some embodiments, a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg or more of ripretinib daily, e.g., up to about 600 mg, e.g., 100 mg to 250 mg, e.g., 100 mg to 500 mg, e.g., 100 mg to 250 mg, e.g., 150 mg, wherein the patient was previously administered at least two tyrosine kinase inhibitors, is contemplated. Contemplated methods of treatment include orally administering 100 mg, 150 mg or more of ripretinib daily without

administering sunitinib on a 42-day cycle. In some embodiments, the method comprises administering to the patient 110 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 120 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 130 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 140 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 150 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 200 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 250 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 300 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 350 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 400 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 450 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 500 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 550 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 600 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 650 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 700 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 750 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 800 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 850 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 900 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 950 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 1000 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 100 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 150 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 200 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 250 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 300 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 350 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 400 mg of ripretinib once

daily. In some embodiments, the method comprises administering to the patient 450 mg of ripretinib daily. In some embodiments, the method comprises administering to the patient 500 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 550 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 600 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 650 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 700 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 750 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 800 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 850 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 900 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 950 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 1000 mg of ripretinib once daily. In some embodiments, the method comprises administering to the patient 150 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 200 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 250 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 300 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 350 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 400 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 450 mg of ripretinib twice daily. In some embodiments, the method comprises administering to the patient 500 mg of ripretinib twice daily. In some embodiments, the patient has previously been administered two separate tyrosine kinase inhibitors, each selected from the group consisting of imatinib, sunitinib, regorafenib, lapatinib, gefitinib, erlotinib, vatalanib, crenolanib, and pharmaceutically acceptable salts thereof. In some embodiments, each of the tyrosine kinase inhibitors is independently selected from the group consisting of imatinib, sunitinib, and regorafenib. In some embodiments, each of the tyrosine kinase inhibitors is independently selected from the group consisting of imatinib mesylate, sunitinib malate, and regorafenib.

[00075] In some embodiments of the methods described herein, the patient is orally administered one or more tablets comprising ripretinib. For example, the disclosed methods

include a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient one or more tablets comprising ripretinib, e.g., tablets each comprising 50 mg to 100 mg of ripretinib, daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib. In some embodiments, the patient is administered one tablet comprising ripretinib. In some embodiments, the patient is administered one tablet comprising 50 mg of ripretinib. In some embodiments, the patient is administered one tablet comprising 50 mg of ripretinib once daily. In some embodiments, the patient is administered two tablets each comprising 50 mg of ripretinib. In some embodiments, the patient is administered two tablets each comprising 50 mg of ripretinib once daily. In some embodiments, the patient is administered three tablets each comprising 50 mg of ripretinib. In some embodiments, the patient is administered three tablets each comprising 50 mg of ripretinib once daily. In some embodiments, the patient is administered four tablets each comprising 50 mg of ripretinib. In some embodiments, the patient is administered four tablets each comprising 50 mg of ripretinib once daily. In some embodiments, the patient is administered five tablets each comprising 50 mg of ripretinib. In some embodiments, the patient is administered five tablets each comprising 50 mg of ripretinib once daily. In some embodiments, the patient is administered six tablets each comprising 50 mg of ripretinib. In some embodiments, the patient is administered six tablets each comprising 50 mg of ripretinib once daily.

[00076] Additionally, the disclosed methods include a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient, on a daily basis, one or more tablets each comprising ripretinib, e.g., tablets each comprising 50 mg to 100 mg of ripretinib, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib. In some embodiments, the patient is administered one tablet comprising ripretinib. In some embodiments, the patient is administered one tablet comprising 50 mg of ripretinib. In some embodiments, the patient is administered one tablet comprising 50 mg of ripretinib once daily. In some embodiments, the patient is administered two tablets each comprising 50 mg of ripretinib. In some embodiments, the patient is administered, once daily, two tablets each comprising 50 mg of ripretinib. In some embodiments, the patient is administered three

tablets each comprising 50 mg of ripretinib. In some embodiments, the patient is administered, once daily, three tablets each comprising 50 mg of ripretinib once daily.

[00077] In some embodiments, provided is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient, on a daily basis, one or more tablets each comprising ripretinib, e.g., tablets each comprising 50 mg to 100 mg of ripretinib, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib. In some embodiments, the patient is administered one tablet comprising ripretinib. In some embodiments, the patient is administered one tablet comprising 50 mg of ripretinib. In some embodiments, the patient is administered one tablet comprising 50 mg of ripretinib once daily. In some embodiments, the patient is administered two tablets each comprising 50 mg of ripretinib. In some embodiments, the patient is administered, once daily, two tablets each comprising 50 mg of ripretinib. In some embodiments, the patient is administered three tablets each comprising 50 mg of ripretinib. In some embodiments, the patient is administered, once daily, three tablets each comprising 50 mg of ripretinib. In some embodiments, the patient has previously been administered two separate tyrosine kinase inhibitors, each selected from the group consisting of imatinib, sunitinib, regorafenib, lapatinib, gefitinib, erlotinib, vatalanib, crenolanib, and pharmaceutically acceptable salts thereof. In some embodiments, each of the tyrosine kinase inhibitors is independently selected from the group consisting of imatinib, sunitinib, and regorafenib. In some embodiments, each of the tyrosine kinase inhibitors is independently selected from the group consisting of imatinib mesylate, sunitinib malate, and regorafenib.

[00078] In another embodiment, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg of ripretinib once daily, wherein the patient was previously administered three or more kinase inhibitors before administration of the ripretinib. In some embodiments, after at least 4 weeks of the daily ripretinib administration, the patient has at least a 5-month progression-free survival as measured using mRECIST v1.1. In some embodiments, orally administering to the patient 150 mg of ripretinib once daily comprises administering to the patient three tablets each tablet comprising 50 mg of ripretinib. In some embodiments, one of the three or more kinase inhibitors is imatinib. In some embodiments, the patient was previously administered imatinib, sunitinib and regorafenib.

[00079] In some embodiments, if the patient suffers from a Grade 3 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises a) withholding administration of ripretinib for at least 7 days or until the patient

has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily (e.g., 100 mg once daily) ripretinib for at least 28 days.

[00080] In some embodiments, if the patient suffers from a Grade 2 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises: a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythorysesthia syndrome within 7 days of withholding administration, then administering to the patient 150 mg daily ripretinib or c) if the patient has not recovered, then administering to the patient 100mg daily ripretinib for at least 28 days.

[00081] In another embodiment, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg daily ripretinib, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib.

[00082] In some embodiments, if the patient suffers from a Grade 3 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises a) withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily (e.g., 100 mg once daily) ripretinib for at least 28 days.

[00083] In some embodiments, if the patient suffers from a Grade 2 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises: a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythorysesthia syndrome within 7 days of withholding administration, then administering to the patient 150 mg daily ripretinib or c) if the patient has not recovered, then administering to the patient 100mg daily ripretinib for at least 28 days.

[00084] In another embodiment, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg of ripretinib once or twice daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of

imatinib. In some embodiments, if the patient suffers from Grade 3 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises a) withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily (e.g., 100 mg once daily) ripretinib for at least 28 days. In some embodiments, if the patient suffers from Grade 3 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises a) withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily (e.g., 100 mg once daily) ripretinib for at least 28 days. In some embodiments, if the patient suffers from Grade 2 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises: a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythorysesthia syndrome within 7 days of withholding administration, then administering to the patient 150 mg daily ripretinib or c) if the patient has not recovered, then administering to the patient 100mg daily ripretinib for at least 28 days. In some embodiments, if the patient suffers from a Grade 3 adverse disorder selected from arthralgia or myalgia upon administration of the ripretinib, the method further comprises: a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 adverse disorder, then administering to the patient 100 mg daily (e.g., 100 mg once daily) ripretinib for at least 28 days. In some embodiments, if the patient suffers from Grade 3 hypertension upon administration of the ripretinib, the method further comprises withholding administration of ripretinib until the patient's blood pressure is controlled, and if the patient has less than or equal to Grade 1 blood pressure is, administering to the patient 150 mg daily ripretinib, or if the patient has more than Grade 1 blood pressure, administering 100 mg daily (e.g., 100 mg once daily) ripretinib.

[00085] In another embodiment, described herein is a method for achieving at least 5 months of progression free survival as determined by mRECIST 1.1 in a patient having an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100, 150 200, or 300 mg of ripretinib daily or twice daily for at least 28 days. In some embodiments, the patient has been administered at least one previous kinase inhibitor. In some embodiments, the patient has been administered at least three previous kinase inhibitors. In some embodiments, the at least one previous kinase inhibitor is imatinib. In

some embodiments, comprising orally administering to the patient 100, 150 or 200 mg of ripretinib daily or twice daily for at least 4 months.

[00086] In another embodiment, described herein is a method for achieving at least 5 months of progression free survival as determined by mRECIST 1.1 in a patient having an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100, 150, or 200 mg of ripretinib daily or twice daily for at least 28 days. In some embodiments, the patient has been administered at least one previous kinase inhibitor. In some embodiments, the patient has been administered at least three previous kinase inhibitors. In some embodiments, the at least one previous kinase inhibitor is imatinib. In some embodiments, comprising orally administering to the patient 100, 150, or 200 mg of ripretinib daily or twice daily for at least 4 months.

[00087] In another embodiment, descried herein is a method of treating a patient suffering from Grade 3 palmer-plantar erythrodysesthia syndrome while being administered 150 mg ripretinib daily or twice daily, comprising withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily (e.g., 100 mg once daily) ripretinib for at least 28 days.

[00088] In another embodiment, descried herein is a method of treating a patient suffering from Grade 2 palmer-plantar erythrodysesthia syndrome upon administration of 150 mg ripretinib daily or twice daily, comprising a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythorysesthia syndrome within 7 days of withholding administration, then administering to the patient 150 mg daily ripretinib or c) if the patient has not recovered, then administering to the patient 100mg daily ripretinib for at least 28 days.

[00089] In another embodiment, described herein is a method of treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a CYP3A4 inhibitor, the method comprising: orally administering to the patient 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, once or twice daily, and wherein upon administration of the ripretinib and the CYP3A4 inhibitor, provides an increased ripretinib area under the plasma concentration curve ($AUC_{0\text{-}inf}$) of 80% or more in the patient as compared to administration of ripretinib without concurrent treatment of the CYP3A4 inhibitor, and therefore the patient is at higher risk of an adverse event; and monitoring the patient more frequently, as compared to a patient not being treated with a

CYP3A4 inhibitor, for the adverse event. In some embodiments, if the patient suffers from a Grade 3 palmer-plantar erythrodysesthia syndrome adverse event, the method further comprises a) withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily ripretinib for at least 28 days. In some embodiments, if the patient suffers from Grade 2 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises: a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythorysesthia syndrome within 7 days of withholding administration, then administering to the patient 150 mg daily ripretinib or c) if the patient has not recovered, then administering to the patient 100mg daily ripretinib for at least 28 days. In some embodiments, the CYP3A4 inhibitor is selected from the group consisting of itraconazole, ketoconazole, clarithromycin, and indinavir. In some embodiments, the CYP3A4 inhibitor is itraconazole. In some embodiments, the patient has previously been administered one or more tyrosine kinase inhibitors, each selected from the group consisting of imatinib, sunitinib, regorafenib, lapatinib, gefitinib, erlotinib, vatalanib, crenolanib, and pharmaceutically acceptable salts thereof.

[00090] In another embodiment, described herein is a method of treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a proton pump inhibitor, the method comprising: orally administering to the patient 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, once or twice daily, and wherein administration of the ripretinib and proton pump inhibitor to the patient provides no clinically significant difference in the plasma exposure of ripretinib in the patient as compared to administration of ripretinib without concurrent treatment of the proton pump inhibitor. In some embodiments, the proton pump inhibitor is selected from the group consisting of pantoprazole, omeprazole, lansoprazole, rabeprazole, esomeprazole, and dexlansoprazole. In some embodiments, the proton pump inhibitor is pantoprazole. In some embodiments, the patient is being treated concurrently with 40 mg of the proton pump inhibitor once daily.

[00091] In another embodiment, described herein is a method of treating a gastrointestinal stromal tumor in a patient in need thereof, the method comprising orally administering to the

patient 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, once or twice daily, wherein the ripretinib is administered to the patient with food or without food. In some embodiments, the food comprises a high-fat meal (*e.g.,* a high-fat meal described herein).

[00092] In some embodiments, the therapeutic efficacy of ripretinib is determined by the progression-free survival of the patient after independent radiologic review using Response Evaluation Criteria in Solid Tumors (RECIST). In some embodiments, the therapeutic efficacy of ripretinib is determined by the progression-free survival of the patient after independent radiologic review using modified Response Evaluation Criteria in Solid Tumors (mRECIST). In some embodiments, the therapeutic efficacy of ripretinib is determined by the Objective Response Rate (ORR), Time to Tumor Progression (TTP) or Overall Survival (OS) of the patient after independent radiologic review using mRECIST. In some embodiments, the therapeutic efficacy of ripretinib is determined by the progression-free survival of the patient based on investigator assessment. In some embodiments, the therapeutic efficacy of ripretinib is determined by the quality of life of the patient in accordance with European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item (EORTC-QLQ-C30) and the EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaires. In some embodiments, the therapeutic efficacy of ripretinib is determined by the disease control rate of the patient. In some embodiments, the therapeutic efficacy of ripretinib is determined by the duration of response of the patient.

[00093] After at least one month, two months, e.g., 42 days or more of treatment with ripretinib, the patient may have a progression-free survival as measured using mRECIST v1.1. As another example, the patient may have a least a 5 or 6 month progression-free survival as compared to placebo after at least 4 weeks of daily administration of ripretinib, and/or for example, after 4 weeks of daily administration of ripretinib, significantly reduced the risk of disease progression or death by 85%.

[00094] In some embodiments, the patient has at least one measurable tumor lesion according to modified RECIST Version 1.1 within 21 days prior to the first dose of ripretinib. In some embodiments, the patient has a non-nodal tumor lesion of greater than or equal to 1.0 cm in the long axis or greater than or equal to double the slide thickness in the long axis, within 21 days prior to the first dose of ripretinib.

[00095] In some embodiments, the patient's tumor has a KIT exon 9 mutation, a PDGFRA exon 18 mutation, a PDGFRA exon 12 mutation or a PDGFRA exon 18 activation loop mutation. For example, the patient's tumor mutation is a PDGFRA D842V mutation.

[00096] In some embodiments, the patient's tumor has an imatinib resistant, sunitinib resistant, and/or regorafenib resistant mutation selected from the group consisting of a KIT exon 17 activation loop mutation, a KIT exon 18 activation loop mutation, a KIT exon 13 mutation, a KIT exon 14 mutation, a KIT exon 18 mutation, a PDGFRA exon 12 mutation, a PDGFRA exon 14 mutation, a PDGRFA exon 15 mutation, and a PDGFRA exon 18 activation loop mutation. For example, the resistant mutation is a PDGFRA D842V mutation.

[00097] In some embodiments, the patient's tumor has a drug resistant mutation selected from the group consisting of KIT exon 13 or 14 mutation, PDGFRA exon 14 or 15 mutation, a KIT 17 or 18 activation loop mutation, and a PDGFRA 18 activation loop mutation. For example, the tumor has a drug resistant KIT exon 17 mutation.

Dose Modifications

[00098] Dose modifications may be made in the methods of administering ripretinib described herein as a result of adverse events experienced by the patient. In some embodiments, the dose modification is a dose interruption. In some embodiments, the dose modification is a permanent discontinuation in dosing. In some embodiments, the dose modification is a dose reduction. In some embodiments, the dose of ripretinib administered to the patient is reduced from 150 mg once daily, e.g., three tablets each comprising 50 mg of ripretinib, to 100 mg once daily, e.g., two tablets each comprising 50 mg of ripretinib. In some embodiments, the dose of ripretinib administered to the patient is reduced from 150 mg once daily, e.g., three tablets each comprising 50 mg of ripretinib, to 50 mg once daily, e.g., one tablet comprising 50 mg of ripretinib. In some embodiments, the adverse reaction is selected from the group consisting of a hand-foot skin reaction (e.g., palmar-plantar erthrodysesthesia syndrome), hypertension, arthralgia, and myalgia.

[00099] In some embodiments, the adverse event is graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 (*e.g.*, baseline, Grade 1, Grade 2, Grade 3, or Grade 4). In some embodiments, the dose modification is a dose interruption (*e.g.*, a dose interruption of at least 7 days) as a result of a

Grade 2 adverse event. In some embodiments, dosing resumes at the same dose level before the dose interruption if the adverse event is lowered to Grade 1 or baseline within a first time period (*e.g.*, within 7 days). In some embodiments, dosing resumes at a reduced dose level before the dose interruption if the adverse event is lowered to Grade 1 or baseline after a first time period (*e.g.*, after 7 days). In some embodiments, the reduced dose level is re-escalated to the dose level prior to the dose interruption if the adverse event is lowered to Grade 1 or baseline after a first time period but is maintained as a Grade 1 or baseline adverse event after a second time period (*e.g.*, after 28 days). In some embodiments, the dose modification is a dose interruption (*e.g.*, a dose interruption of at least 7 days up to a maximum of 28 days) as a result of a Grade 3 adverse event. In some embodiments, dosing is continued at a reduced level after the dose interruption. In some embodiments, the dose modification is a permanent discontinuation in dosing as a result of a Grade 4 adverse event (e.g., Grade 4 hypertension).

[000100] A patient can be administered an additional treatment in response to an adverse event or to prevent an adverse event from occurring. In some embodiments, a patient suffering from an adverse dermatologic reaction, e.g., a hand-foot skin reaction, e.g., palmar-plantar erthrodysesthesia syndrome, is administered a topical composition (e.g., an emollient) to treat the adverse dermatologic reaction. In some embodiments, the patient is administered the topical composition (e.g., an emollient) based on the severity of the adverse dermatologic reaction, e.g., a Grade 2, Grade 3 adverse dermatologic reaction, e.g., a Grade 1, Grade 2, or Grade 3 hand-foot skin reaction, e.g., a Grade 1, Grade 2 or Grade 3 palmar-plantar erthrodysesthesia syndrome. In some embodiments, the topical composition (e.g., an emollient) is administered to the patient during a dose interruption of ripretinib. In some embodiments, the topical composition (e.g., an emollient) is administered to the patient contemporaneously with a dose of ripretinib, e.g., a reduced dose of ripretinib.

[000101] A patient can also be administered an additional treatment prior to, or during administration of ripretinib in accordance with the methods described herein to prevent or ameliorate an adverse event. In some embodiments, the patient is administered a topical composition (e.g., an emollient) before and/or during ripretinib administration to prevent or ameliorate the onset of an adverse dermatologic reaction, e.g., a hand-foot skin reaction, e.g., palmar-plantar erthrodysesthesia syndrome.

EXAMPLES

Example 1. An open-label, randomized study to compare the efficacy of ripretinib versus sunitinib in patients with advanced GIST with prior imatinib therapy.

[000102] **Study Design.** Approximately 358 eligible patients will be randomized into two cohorts in a 1:1 ratio in which one cohort undergoes continuous 42-day cycles of receiving ripretinib dosed at 150 mg daily (179 patients) and the other cohort receives sunitinib dosed at 50 mg daily for 4 weeks and then 2 weeks off on 42-day cycles (179 patients).

[000103] Given the mutation-driven natural history of GIST and the well-described relationship between secondary mutations and emergence of resistance to first- and second-line TKIs, the results of this study will evaluate ripretinib compared with sunitinib as second-line therapy in patients with GIST following imatinib therapy.

[000104] The primary end point of the study is to assess the progression-free survival (PFS) of ripretinib by blinded independent central review (BICR) using modified Response Evaluation Criteria in Solid Tumors version 1.1 (mRECIST v1.1). The key secondary efficacy end points include the assessment of ORR by BICR using mRECIST v1.1 and OS.

[000105] **Statistical Analysis.** PFS is defined as the time from randomization to the date of the first documented progression of disease or death due to any cause and is based on BICR assessment of the primary end point. OS is defined as the time from randomization to the date of death due to any cause. OS and PFS with 95% CI will be summarized using Kaplan-Meier methodology; point estimates of hazard ratios will be obtained from a Cox regression model. Objective response is defined as a CR or PR by BICR assessment using mRECIST v1.1.

Example 2. A randomized, double-blind, placebo-controlled, international, multicenter study to evaluate the safety, tolerability, and efficacy of ripretinib compared to placebo in patients with advanced GIST whose previous therapies have included imatinib, sunitinib, and regorafenib.

[000106] This study was a randomized (2:1), double-blind, placebo-controlled, international, multicenter study to evaluate the safety, tolerability, and efficacy of ripretinib compared to placebo in 129 patients with advanced GIST whose previous therapies have included at least imatinib, sunitinib, and regorafenib. Patients were randomized 2:1 to either 150 mg of ripretinib or placebo once daily. The primary efficacy endpoint is progression-free survival (PFS) as determined by independent radiologic review using modified Response Evaluation Criteria in Solid Tumors (RECIST). Secondary endpoints as determined by

independent radiologic review using modified RECIST include Objective Response Rate (ORR), Time to Tumor Progression (TTP) and Overall Survival (OS).

[000107] **Results.** This study achieved its primary endpoint of improved PFS as determined by blinded independent central radiologic review using modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

[000108] Ripretinib demonstrated a median PFS of 6.3 months (27.6 weeks) compared to 1.0 month (4.1 weeks) in the placebo arm and significantly reduced the risk of disease progression or death by 85% (HR of 0.15, $p<0.0001$) compared to placebo. PFS rates at 6 months were 51% (95%CI: 39.4,61.4) for ripretinib and 3.2% (95%CI: 0.2,13.8) for placebo. Plots of survival probability with respect to PFS for patients on ripretinib and patients on placebo are shown in **FIG. 1**.

[000109] For the key secondary endpoint of objective response rate (ORR), as determined by blinded independent central radiologic review using modified RECIST version 1.1, ripretinib demonstrated an ORR of 9.4% compared with 0% for placebo (p-value=0.0504), which was not statistically significant. Ripretinib in this study also showed a clinically meaningful improvement over placebo in terms of the secondary endpoint overall survival (OS) (median OS 15.1 months vs. 6.6 months, HR = 0.36, nominal p-value=0.0004; OS rates at 12 months were 65.4% (95%CI: 51.6,76.1) for ripretinib and 25.9% (95%CI: 7.2,49.9) for placebo); however, because statistical significance was not achieved for ORR, the hypothesis testing of OS was not formally performed. Plots of survival probability with respect to OS of patients on ripretinib and patients on placebo are shown in **FIG. 2**. According to the pre-specified hierarchical testing procedure of the endpoints, the hypothesis testing of OS cannot be formally conducted unless the test of ORR is statistically significant. The OS data for the placebo arm includes patients taking placebo who, following progression, were crossed-over to ripretinib treatment. Plots illustrating survival probability with respect to OS in patients on ripretinib, crossed over from placebo to ripretinib, and patients without cross-over are shown in **FIG. 3**. Plots and additional data illustrating survival probability with respect to PFS in patients on ripretinib, crossed over from placebo to ripretinib, and patients without cross-over are shown in **FIG. 13**. Additionally, more patients receiving ripretinib had stable disease (SD) for 12 weeks (40 [47·1%] vs 2 [4·5%], respectively) and less PD (16 [18·8%] vs 28 [63·6%], respectively) than patients on placebo. The large percentage of patients receiving ripretinib with stable disease (SD) is notable as the absence of progression is considered an important marker of therapeutic benefit in GIST. Unlike many other advanced solid tumors,

the absence of progression (whether a partial response (PR) or SD) is predictive of PFS and OS benefit in patients with advanced GIST.

[000110] Patients that successfully crossed over from placebo had smaller tumors vs those that did not crossover (median sum of longest diameter of target lesions 119.4 mm vs 183.3 mm). In addition, the median age of those who crossed over was higher than those who did not cross over (68.0 vs 58.0 years) and none had a baseline Eastern Cooperative Oncology Group (ECOG) score of 2, while 3 patients in the group that did not cross over had an ECOG score of 2. Patients that crossed over had a median PFS of 20.0 weeks [95% CI, 8.0–NE] vs 27.6 weeks seen in the initial ripretinib arm and 4.1 weeks seen in the initial placebo arm, respectively. Median OS in patients who crossed over was 11.6 months, vs. 15.1 months in patients initially randomized to ripretinib and 1.8 months in patients on placebo who did not crossover. TEAEs during the crossover period suggest no safety concerns when compared to the safety profile of patients initially assigned to ripretinib.

[000111] Ripretinib was generally well tolerated and the adverse event results were consistent with data from previously presented Phase 1 study results. Grade 3 or 4 treatment-emergent adverse events (TEAEs) occurred in 42 (49%) patients on the ripretinib arm compared to 19 (44%) on the placebo arm. Grade 3 or 4 TEAEs >5% of patients in the ripretinib arm were anemia (9%; n=8), abdominal pain (7%; n=6) and hypertension (7%; n=6). Grade 3 or 4 TEAEs >5% of patients in the placebo arm were anemia (14%; n=6). Table 1 lists TEAEs >15% in the ripretinib arm compared to placebo.

Table 1. Treatment-emergent adverse events for patients administered with either ripretinib or placebo.

Treatment Emergent Adverse Event	**Placebo (N=43)[1]**	**Ripretinib 150 mg Daily (N=85)[1]**
Any event	42 (98%)	84 (99%)
Alopecia	2 (5%)	44 (52%)
Fatigue	10 (23%)	36 (42%)
Nausea	5 (12%)	33 (39%)
Abdominal pain	13 (30%)	31 (36%)
Constipation	8 (19%)	29 (34%)
Myalgia	5 (12%)	27 (32%)
Diarrhea	6 (14%)	24 (28%)
Decreased appetite	9 (21%)	23 (27%)

Palmar-plantar erythrodysaesthesia syndrome	0	18 (21%)
Vomiting	3 (7%)	18 (21%)
Headache	2 (5%)	16 (19%)
Weight decreased	5 (12%)	16 (19%)
Arthralgia	2 (5%)	15 (18%)
Blood bilirubin increased	0	14 (16%)
Oedema peripheral	3 (7%)	14 (16%)
Muscle spasms	2 (5%)	13 (15%)

[000112] In table 1, (1) indicates that the safety population includes 128 patients. One patient was randomized to placebo but did not receive study drug.

Patient Reported Outcomes

[000113] Patient reported outcomes were assessed by EQ-5D-5L, which provides a visual analogue scale (VAS), and EORTC QLQ-C30, which provides physical function and role function scales. The EQ-5D-5L VAS (or EQ-VAS) records the respondent's overall current health on a vertical visual analogue scale and provides a quantitative measure of the patient's perception of overall health. These patient outcomes were reported across 28-day cycles of receiving 150 mg QD ripretinib or placebo.

[000114] **FIG. 5** depicts patient report outcome by EQ-VAS showing the visual scale used to assess scores (**FIG. 5A**), score changes from baseline (**FIG. 5B**) and corresponding patient percentage distributions (**FIG. 5C**). The EQ-VAS score improved on average 3.7 from baseline to Cycle 2, Day 1 (C2D1) among patients taking ripretinib in contrast to placebo patients who saw on average, a decline from baseline to C2D1 of 8.9 ($p=0.004$). 70 patients were receiving ripretinib and 32 were receiving placebo.

[000115] The EORTC QLQ-C30 is an assessment of function and symptoms of therapy by cancer patient, and is not specific to any cancer. The EORTC QLQ-C30 is a 30-question plus one global health status, including 5 functional scales, 3 symptom scales and a global health status.

[000116] **FIG. 6** depicts EORTC QLQ-C30 physical function questions (**FIG. 6A**), patient score changes from baseline in response (**FIG. 6B**) and corresponding patient percentage distributions (**FIG. 6C**). Physical function scores improved on average 1.6 from baseline to C2D1 among patients taking ripretinib in contrast to placebo patients who saw on average, a decline from baseline to C2D1 of 8.9 ($p=0.004$). 71 patients were receiving ripretinib and 32 were receiving placebo.

[000117] **FIG. 7** depicts EORTC QLQ-C30 role function questions (**FIG. 7A**) and patient score changes from baseline in response (**FIG. 7B**) and corresponding patient percentage distributions (**FIG. 7C**). Role function score improved on average 3.5 from baseline to C2D1 among patients taking ripretinib in contrast to placebo patients who saw on average, a decline from baseline to C2D1 of 17.1 (p=0.001). 70 patients were receiving ripretinib and 32 were receiving placebo.

[000118] **FIG. 8** depicts patient score changes from baseline (**FIG. 8A**) and corresponding patient percentage distributions (**FIG. 8B**) in response to Question C29 of EORTC QLQ-C30 ("How would you rate your overall health during the past week?") from a scale of 1 ("Very poor") to 7 ("Excellent"). There was a 0.20 improvement in C29 score in the ripretinib group compared to a 0.78 decrease in the placebo group (p=0.001). 70 patients were receiving ripretinib and 32 were receiving placebo.

[000119] **FIG. 9** depicts patient score changes from baseline (**FIG. 9A**) and corresponding patient percentage distributions (**FIG. 9B**) in response to Question C30 of EORTC QLQ-C30 ("How would you rate your overall quality of life during the past week?") from a scale of 1 ("Very poor") to 7 ("Excellent"). There was a 0.28 improvement in score in the ripretinib group compared to a 0.76 decrease in the placebo group (p=0.001). 70 patients were receiving ripretinib and 32 were receiving placebo.

[000120] **FIG. 10** depicts mean changes in baseline scores in EQ-VAS across various time points, from Cycle 1, Day 15 up to Cycle 15, Day 1 of the intention-to-treat population. **FIG. 11A** and **FIG. 11B** depict mean changes in baseline scores in EORTC QLQ-C30 role function and EORTC QLQ-C30 physical function, respectively, across various time points, from Cycle 1, Day 15 up to Cycle 15, Day 1 of the intention-to-treat population. **FIG. 12A** and **FIG. 12B** depict mean changes in baseline scores in EORTC QLQ-C30 question C29 response and EORTC QLQ-C30 question C30 response, respectively, across various time points, from Cycle 1, Day 15 up to Cycle 15, Day 1 of the intention-to-treat population.

Open-label phase and Dose escalation

[000121] Patients whose disease progressed during the double blind phase of the study were escalated to 150 mg BID ripretinib, continued at the 150 mg QD dose, or discontinued in an open label-phase of the study. **Table 8** shows a comparison of patients that received 150 mg QD ripretinib at the data cutoff time point of the double blind phase and the data cutoff time point of of the open-label phase. The data in **Table 8** suggest that data cut 9 months after the primary double-blind analysis has shown improvement in mOS and a similar mPFS in the ripretinib arm.

[000122] In the study, at least 31 patients dose escalated to 150 mg BID ripretinib in an open-label phase upon disease progression. PFS studies in the double-blind and open-label periods for these patients are depicted in **FIG. 14A** and **FIG. 14B**, respectively, with **FIG. 14C** depicting median PFS data.

Wild Type (KIT and PDGFRA) Mutations

[000123] PFS data among patients with wild-type KIT or PDGFRA mutations were further evaluated at 150 mg ripretinib QD. PFS data of patients with these wild-type KIT and PDGFRA mutations are shown in **FIG. 15**.

Additional Mutational Analyses

[000124] Progression free survival PFS and overall survival (OS) data based on patients with a primary Exon 11 mutation or patients with a non-Exon 11 mutation are shown in **FIGS. 16A** (PFS) and **16B** (OS) at 150 mg ripretinib QD. The data show that, regardless of primary mutation, whether a primary Exon 11 or a non-Exon 11 primary mutation, GIST patients derive similar benefit from ripretinib over placebo.

[000125] Progression free survival PFS and overall survival (OS) data based on patients with a primary Exon 11 mutation or those with a primary Exon 9 mutation are shown in **FIGS. 17A** (PFS) and **17B** (OS) at 150 mg ripretinib QD. The data show that, Regardless of primary mutation, both Exon 11 and Exon 9 GIST patients derive a benefit from ripretinib over placebo.

[000126] Furthermore, progression free survival PFS and overall survival (OS) data based on patients with a primary Exon 11 mutation, or a primary Exon 9 mutation, or other mutations, and wild type (KIT and PDGFRA) are shown in **FIGS. 18A** (PFS) and **19B** (OS) at 150 mg ripretinib QD.

[000127] PFS studies for patients with certain primary mutations (Exon 9 or Exon 11) who dose escalated to 150 mg BID ripretinib are shown in **FIGS. 19A and 19B** for the double-blind and open-label periods, respectively.

[000128] Additionally, **FIG. 20** shows exemplary progression free survival data for patients with other KIT mutations and PGDFR mutations in the study of Example 2 at 150 mg ripretinib QD.

[000129] **FIGS. 26A-D** depicts an exemplary comparison of PFS of patient subgroups with Exon 9 (**FIG. 26A**), Exon 11 (**FIG. 26B**), Exon 13 (**FIG. 26C**), or Exon 17 (**FIG. 26D**) KIT

mutations. This exemplary data show that ripretinib showed PFS benefit in all assessed patient subgroups compared to placebo.

Example 3. Results for a clinical study of ripretinib in patients with second-line through fourth-line plus GIST.

[000130] Results. Data from 178 GIST patients receiving ripretinib at doses of ≥100mg daily are noted in Table 2. The table includes investigator-assessed objective response rate (ORR) by best response, disease control rate (DCR) and median progression free survival (mPFS), all of which were determined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Table 2. Results/clinical study of ripretinib

Line of Therapy(1)	Objective Response Rate by Best Response Includes Unconfirmed (Confirmed Only)	Disease Control Rate at 3 Months	Median Progression Free Survival (mPFS)	Censored Patients for mPFS	Mean Treatment Duration(2)(3)
Second-Line (n=37)	30% (22%)	81%	42 weeks	38%	43 weeks
Third-Line (n=31)	23% (13%)	80%	40 weeks	32%	48 weeks
Fourth-Line (n=60)	15% (8%)	73%	30 weeks	30%	49 weeks
≥Fourth-Line (n=110)(4)	11% (7%)	66%	24 weeks	22%	41 weeks

[000131] In Table 2, (1) indicates overall number of patients (n=178) remains the same as prior data presented at ESMO 2018; based on additional data cleaning, one patient from each of 2nd line and 4th/≥4th line were reclassified as 3rd line patients; (2) refers to median treatment durations were: 2nd line = 44 weeks, 3rd line = 48 weeks, 4th line = 46 weeks and ≥4th line = 29 weeks; (3) refers to including 60 patients who elected for intra-patient dose escalation from 150 mg QD to 150 mg BID; and (4) refers to the number of patients including 60 patients from 4th line.

[000132] Ripretinib was generally well tolerated and the updated adverse events were consistent with previously presented Phase 1 data in patients with GIST. Grade 3 or 4 treatment-emergent adverse events (TEAEs) in >5% of patients were lipase increased (18%; n=33), anemia (11%; n=20), hypertension (7%; n=13) and abdominal pain (6%; n=11). 13% of patients (n=24) experienced TEAEs leading to study treatment discontinuation, 17% of

patients (n=31) experienced TEAEs leading to dose reduction and 49% of patients (n=88) had TEAEs leading to study drug interruption. Table 3 lists TEAEs >10% for GIST patients treated with ≥100mg of ripretinib daily.

Table 3. Treatment-emergent adverse events for patients administered with 100 mg of ripretinib daily.

GIST PATIENTS @ ≥ 100 MG DAILY Treatment Emergent Adverse Events (TEAEs) >10%			
Alopecia	102 (57%)	0 (0%)	102 (57%)
Fatigue	94 (53%)	4 (2%)	98 (55%)
Myalgia	79 (44%)	0 (0%)	79 (44%)
Nausea	77 (43%)	1 (1%)	78 (44%)
Palmar-plantar erythrodysaesthesia syndrome	71 (40%)	1 (1%)	72 (40%)
Constipation	67 (37%)	0 (0%)	67 (37%)
Decreased appetite	60 (34%)	2 (1%)	62 (35%)
Diarrhea	50 (28%)	3 (2%)	53 (30%)
Weight decreased	51 (29%)	1 (1%)	52 (29%)
Lipase increased	18 (10%)	33 (18%)	51 (29%)
Muscle spasms	47 (26%)	0 (0%)	47 (26%)
Abdominal pain	33 (18%)	11 (6%)	44 (25%)
Vomiting	42 (24%)	2 (1%)	44 (25%)
Arthralgia	40 (22%)	0 (0%)	40 (22%)
Anemia	18 (10%)	20 (11%)	38 (21%)
Hypertension	25 (14%)	13 (7%)	38 (21%)
Cough	37 (21%)	0 (0%)	37 (21%)
Dry skin	37 (21%)	0 (0%)	37 (21%)
Dyspnea	32 (18%)	4 (2%)	36 (20%)
Headache	33 (18%)	1 (1%)	34 (19%)
Back Pain	30 (17%)	2 (1%)	32 (18%)
Dizziness	29 (16%)	0 (0%)	29 (16%)
Rash	27 (15%)	0 (0%)	27 (15%)
Hypokalaemia	21 (12%)	5 (3%)	26 (15%)
Hypophosphataemia	17 (10%)	8 (5%)	25 (14%)
Actinic keratosis	25 (14%)	0 (0%)	25 (14%)
Blood bilirubin increase	16 (9%)	5 (3%)	21 (12%)
Amylase increased	19 (11%)	2 (1%)	21 (12%)
Insomnia	21 (12%)	0 (0%)	21 (12%)
Seborrhoeic keratosis[(2)]	21 (12%)	0 (0%)	21 (12%)
Urinary tract infection	16 (9%)	4 (2%)	20 (11%)

Dysgeusia	20 (11%)	0 (0%)	20 (11%)
Pain in extremity	18 (10%)	1 (1%)	19 (11%)
Blood creatine phosphokinase increased	13 (7%)	5 (3%)	18 (10%)
Upper respiratory tract infection	18 (10%)	0 (0%)	18 (10%)
Rash maculo-papular	18 (10%)	0 (0%)	18 (10%)
Hypomagnesaemia	18 (10%)	0 (0%)	18 (10%)
Pruritus	18 (10%)	0 (0%)	18 (10%)
Skin papilloma[(2)]	17 (10%)	0 (0%)	17 (10%)
Vision blurred	17 (10%)	0 (0%)	17 (10%)

[000133] In table 3, (1) refers to including one patient that only participated in the food effect portion of the Phase 1 study; and (2) indicates that dermatology skin exams were implemented to better evaluate skin lesions.

Example 4. Results for a clinical study of 150 mg QD ripretinib administered to patients with second-line through fourth-line plus GIST.

[000134] Efficacy and safety results from the escalation and expansion phases of a phase 1 study for patients with GIST treated at ripretinib 150 mg QD as the starting dose in 28-day cycles are presented. Local, investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST 1.1) response assessments were performed every 2 cycles, and patients in the expansion cohorts who progressed per RECIST 1.1 were allowed to dose escalate to 150 mg BID.

[000135] 142 patients with GIST in the escalation and expansion phases were treated at 150 mg QD dose. Number of patients by line of therapy were as follows: 31 2nd line, 28 3rd line, and 83 ≥4th line patients. 135 patients (95.1%) had KIT-mutant GIST, and 7 patients (4.9%) had PDGFRA-mutant GIST.

[000136] Results on the efficacy by line of therapy in patients with GIST receiving ripretinib 150 mg QD are presented in Table 4. For example, the confirmed-only complete response (CR), partial response (PR), stable disease, and progressive disease are presented in Table 4. The objective response rate data in Table 4 relates to the proportion of patients with CR + PR. The median PFS data in Table 4 refers to progression-free survival per investigator assessment, by line of therapy. PFS plots by line of therapy are also shown in **FIG. 4**.

Table 4: Efficacy by line of therapy in patients with GIST receiving ripretinib 150 mg QD.

Parameters	2nd Line (n=31)	3rd Line (n=28)	≥4th Line (n=83)
Best response (confirmed only), n (%)			
CR	0	0	0
PR	6 (19.4)	4 (14.3)	6 (7.2)
Stable disease	21 (67.7)	18 (64.3)	49 (59.0)
Progressive disease	4 (12.9)	6 (21.4)	22 (26.5)
Not evaluable	0	0	1 (1.2)
No response assessment	0	0	5 (6.0)
ORR, n (95% CI)	19.4 (7.5, 37.5)	14.3 (4.0, 32.7)	7.2 (2.7, 15.1)
Duration of treatment[a]			
Mean, weeks (SD)	56.1 (34.24)	57.5 (32.95)	44.9 (36.58)
Median, weeks	64	51	29
Min, Max	4, 132	8, 124	0.1, 140
Duration of response			
n	6	4	6
Number of events	3	1	3
Median, weeks	80	NE	76.1
95% CI	24.7, 80.0	52.1, NE	24.1, NE
PFS			
Number of censored patients	8	6	12
Median, weeks	46.4	36.3	23.9
95% CI	24.0, 60.0	23.9, 48.4	15.9, 24.3

In Table 4: [a]64 subjects escalated to 150 mg BID among patients with GIST in the 150 mg QD dose group. CI, confidence interval; CR, complete response; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, standard deviation. Local (investigator) response assessment.

[000137] In subjects dose escalated to 150 mg BID, PFS before (PFS1) and after (PFS2) dose escalation was evaluated and is shown in **FIGS. 25A** and **25B**, respectively. The data support that, regardless of line of therapy, patients received additional clinical benefit by investigator assessment after dose escalation to 150 mg BID.

Mutational Analysis

[000138] **FIG. 27** shows PFS data of exemplary second and third-line patients with Exons 9, 11, 13, or 17 KIT mutations. The data show that, in second and third line populations, patients with such various KIT mutations have comparable PFS.

Example 5. Protocol for dose modification of ripretinib as a result of adverse reactions.

[000139] If dose modifications of ripretinib are required due to adverse reactions, the following protocol will be applied: reduce the dose in 50 mg (one tablet) increments; the lowest recommended dose of ripretinib is 50 mg once daily. Ripretinib dosage reductions for adverse reactions are summarized in Table 5.

Table 5: Recommended Dose Reduction for Adverse Reactions

Dose Level	Dose
Recommended starting dose	150 mg once daily
First dose reduction	Reduce to 100 mg once daily
Second dose reduction (lowest recommended dose)	Reduce to 50 mg once daily

[000140] Dosing will be reduced, interrupted, or discontinued for certain toxicities. See Table 6 for dose modification guidelines.

Table 6: Recommended Dose Modifications for ripretinib

Adverse Reaction	Severity[a]	Dosage Modifications
Hand-foot skin reaction (HFSR) [palmar-plantar erythrodysesthesia syndrome (PPES)]	Grade 2	• Interrupt ripretinib for at least 7 days. • If the event returns to Grade 1 or baseline within 7 days, resume ripretinib at the same dose level.

Adverse Reaction	Severity[a]	Dosage Modifications
		• If the event returns to Grade 1 or baseline after 7 days, resume ripretinib at a reduced dose level (see Table 5). • If after a dose reduction, the event is maintained at Grade 1 or baseline for at least 28 days, consider re-escalating ripretinib by 1 dose level (see Table 5). • If this is a recurrence, after event returns to Grade 1 or baseline, resume ripretinib at a reduced dose level (see Table 5) regardless of time to improvement.
	Grade 3	• Interrupt ripretinib for at least 7 days or until the event returns to Grade 1 or baseline (maximum 28 days). Resume ripretinib at a reduced dose level (see Table 5). • If after a dose reduction the event is maintained at Grade 1 or baseline for at least 28 days of dosing, consider re-escalating ripretinib by 1 dose level (see Table 5).
Hypertension	Grade 3	• Medically manage hypertension to achieve normal blood pressure . • If symptomatic hypertension, withhold ripretinib and treat hypertension. Resume ripretinib at the same dose level after symptoms have resolved. • If blood pressure is not controlled with medical management, reduce ripretinib to the next dose level (see Table 5). • If Grade 3 hypertension recurs despite ripretinib dose reduction and medical management, reduce ripretinib to the lowest recommended dose of 50 mg once daily.
	Grade 4 Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	• Discontinue ripretinib permanently.
Arthralgia/Myalgia	Grade 2	• Interrupt ripretinib for at least 7 days.

Adverse Reaction	Severity[a]	Dosage Modifications
		• If the event returns to Grade 1 or baseline within 7 days, resume ripretinib at the same dose level. • If the event returns to Grade 1 or baseline after 7 days, resume ripretinib at a reduced dose level (see Table 5) . • If after a dose reduction, the event is maintained at Grade 1 or baseline for at least 28 days of dosing, consider re-escalating ripretinib by 1 dose level (see Table 5). • If this is a recurrence, after event returns to Grade 1 or baseline, resume ripretinib at a reduced dose level (see Table 5) regardless of time to improvement.
	Grade 3	• Interrupt ripretinib for at least 7 days or until the event returns to Grade 1 or baseline (maximum 28 days). Resume ripretinib at a reduced dose level (see Table 5). • If after a dose reduction the event is maintained at Grade 1 or baseline for at least 28 days of dosing, consider re-escalating ripretinib by 1 dose level (see Table 5).
Other adverse reactions	Grade 3 or higher toxicity considered related to treatment	• Interrupt ripretinib until toxicity resolves to Grade 1 or baseline (maximum 28 days). • If the event returns to Grade 1 or baseline, resume ripretinib at a reduced dose level (see Table 5). • If the reduced dose is tolerated without recurrence of the event for at least 28 days, consider re-escalating ripretinib to the prior dose level (see Table 5). • If Grade 3 or higher toxicity recurs, discontinue ripretinib.
BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure [a] Graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03		

Example 6. Safety of ripretinib and impact of alopecia and palmar-plantar erythrodysesthesia (PPES) on patient-reported outcomes.

[000141] The safety of ripretinib and the impact of alopecia and palmar-plantar erythrodysesthesia (PPES) on patient-reported outcomes (PROs) of patients treated in the

study described in Example 2 herein are described. Ripretinib had a favorable overall safety and tolerability profile in the trial of Example 2. When stratified by alopecia and PPES, patient reported assessments of function, overall health, and overall quality of life were maintained over time. For both alopecia and PPES, onset and maximum severity occurred almost simultaneously, indicating that these events generally did not progressively worsen. Overall, these results suggest that alopecia and PPES are manageable and that ripretinib treatment offsets any negative impact associated with these AEs.

[000142] Patient reported outcomes (PROs) were assessed with questions from the EuroQol 5D (EQ 5D 5L) and the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C30).

[000143] Generalized estimating equation (GEE) models were used in statistical analyses in which: Repeated measures models across visits where the outcome was 1 of the 5 PROs; models were built only for ripretinib patients; for alopecia patients, cycles 1 and 2 were excluded to account for median time of alopecia onset; covariates were sex, alopecia/PPES (yes/no), and Eastern Cooperative Oncology Group (ECOG) score at baseline; and when there was no end date for the AE, it was coded conservatively as having extended to the last visit of the double blind period.

[000144] In the ripretinib arm, the most common treatment-emergent adverse event (TEAE) was alopecia (51.8%) and the most common grade 3/4 TEAE was anemia (9.4%). The highest severity classification for alopecia is grade 2; therefore, no patients in either arm had grade 3/4 alopecia. Alopecia was slightly more common in femalesvs males in the ripretinib arm (56.8% vs 43.2%). In the ripretinib arm, 21.2% of patients reported PPES; no patients had grade 3 PPES (grade 3 is the highest severity classification for PPES). There were no serious adverse events of alopecia or PPES reported. Within the ripretinib arm, 7.1%, 23.5%, and 5.9% of patients experienced a TEAE leading to dose reduction, dose interruption, or death, respectively, compared with 2.3%, 20.9%, and 23.3% in the placebo arm. In patients receiving ripretinib, the median worst grade of alopecia occurred very shortly after the median first appearance (**FIG. 21**). The median first appearance and worst grade of PPES occurred simultaneously in patients receiving ripretinib (**FIG. 21**).

[000145] **Table 7** shows a GEE analysis summary of the association between alopecia and PPES with the 5 PRO measures in patients taking ripretinib. In a repeated measures analysis, there was a trend toward an improvement of the 5 PROs among patients with alopecia (**Table 7**). The presence of alopecia was associated with better self-reported overall quality of life (**Table 7**). This was statistically significant at $P < 0.01$, but did not exceed the threshold for

meaningful change. There was no association between PPES and the 5 PRO measures (**Table 7**).

Table 7. GEE analysis summary of the association between alopecia and PPES with the 5 PRO measures in patients taking ripretinib.

	Mean Estimate	**Mean Confidence Limit**	**P-value from ChiSq**
Alopecia			
EORTC-QLQ-C30			
Overall health	0.17	(−0.10, 0.44)	0.2222
Overall quality of life	0.35	(0.03, 0.67)	0.0313
Physical function	3.17	(−0.29, 6.64)	0.0729
Role function	4.50	(−2.87, 11.87)	0.2310
EQ-5D-5L			
VAS	3.01	(−0.64, 6.67)	0.1062
PPES			
EORTC-QLQ-C30			
Overall health	0.06	(−0.29, 0.41)	0.7457
Overall quality of life	0.12	(−0.26, 0.50)	0.5368
Physical function	3.03	(−0.92, 6.99)	0.1325
Role function	2.83	(−5.52, 11.17)	0.5070
EQ-5D-5L			
VAS	1.65	(−2.11, 5.41)	0.3903

[000146] Longitudinal graphs out to Cycle 10, Day 1 demonstrate similar trends in mean change from baseline for the 5 PROs for patients receiving ripretinib that developed alopecia or PPES and those that did not (**FIGS. 22A, 22B, 22C, 22D, 23A, 23B, 23C, 23D, 24A, and 24B**).

Table 8. Comparison of double blind and open label data cut time periods.

	Ripretinib (N=85) Double-blind cut	Ripretinib (N=85) Open-label cut
Progression-Free Survival by BICR		
Number of events (%)	51 (60)	64 (75)
Progressive disease	46 (54)	58 (68)
Deaths	5 (6)	6(7)
Median PFS (months) (95% CI)	6.3 (4.6, 6.9)	6.3 (4.6, 8.1)

Hazard ratio (95% CI)	0.15 (0.09, 0.25)	0.16 (0.10, 0.27)
p-value	< 0.0001	< 0.0001*
Overall Response Rate by BICR		
Overall Response Rate (%)	9	12
(95% CI)	(4.2, 18)	(5.8 , 20.6)
p-value	0.0504	0.0156*
Overall Survival		
Number of deaths (%)	26 (31)	38 (45)
Median OS (months) (95% CI)	15 (12, 15)	Not Reached (13, NE)
Hazard ratio (95% CI) / p-value	0.36 (0.21, 0.62) / 0.0004*	0.43 (0.26, 0.69) / 0.0014*
Exposure		
Mean in the double blind period (months)	5.6	7.6

Example 7. Studies of ripretinib and Compound A with strong CYP3A inhibitors.

[000147] Coadministration of 150 mg QD ripretinib with a strong CYP3A inhibitor increased the exposure of ripretinib and its active metabolite (Compound A), which may increase the risk of adverse reactions. Coadministration of ripretinib with itraconazole (a strong CYP3A inhibitor and also a P-gp inhibitor) increased ripretinib C_{max} by 36% and $AUC_{0\text{-}inf}$ by 99% and also increased Compound A $AUC_{0\text{-}inf}$ by 99% with no change in its C_{max}.

Example 8. Studies of ripretinib with a proton-pump inhibitor.

[000148] The effect of a proton-pump inhibitor on the exposure of ripretinib was evaluated. No clinically significant differences in the plasma exposure to ripretinib and Compound A were observed when ripretinib was coadministered with pantoprazole, a proton-pump inhibitor. Although ripretinib has pH-dependent solubility, concomitant administration of 40 mg QD pantoprazole with 150 mg QD ripretinib did not affect ripretinib exposure.

Example 9. Studies of food effect on ripretinib and Compound A exposure.

[000149] The effect of a high-fat breakfast on ripretinib and Compound A exposure was evaluated. A high fat meal consisted of approximately 150, 250, and 500-600 calories from

protein, carbohydrate, and fat, respectively. Following administration of ripretinib with a high-fat meal at a 150 mg dose, ripretinib $AUC_{0\text{-}24h}$ and C_{max} were higher by 30% and 22%, respectively. For the metabolite Compound A, $AUC_{0\text{-}24h}$ and C_{max} were higher by 47% and 66%, respectively. The food effect is not considered to be clinically significant based on exposure-response analysis. Therefore, ripretinib may be taken with or without food at approximately same time each day.

EQUIVALENTS

[000150] Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific embodiments described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

What is claimed is:

1. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 300 mg of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

2. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 600 mg of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

3. The method of claim 1 or 2, wherein the patient is administered 150 mg of ripretinib daily.

4. The method of claim 2, wherein the patient is administered 500 mg of ripretinib daily.

5. The method of claim 1 or 2, wherein the patient is administered 150 mg of ripretinib once daily.

6. The method of claim 2, wherein the patient is administered 150 mg of ripretinib twice daily.

7. The method of claim 2, wherein the patient is administered 250 mg of ripretinib twice daily.

8. The method of any one of claims 1-7, wherein the patient was only previously treated with the first line administration of imatinib.

9. The method of claim 8, wherein the patient was not previously given a second line administration of sunitinib therapy and/or a third-line administration of regorafenib therapy.

10. The method of any one of claims 1-9, wherein the patient has a non-nodal tumor lesion greater than or equal to 1.0 cm in the long axis or greater than or equal to double the slide thickness in the long axis, within 21 days prior to the first dose of ripretinib.

11. The method of any one of claims 1-10, wherein administering ripretinib is a 42-day cycle comprising daily administration of ripretinib without administering sunitinib.

12. The method of claim 11, wherein, after at least one 42-day cycle, the patient has a progression-free survival as measured using mRECIST v1.1.

13. The method of claim 11 or 12, wherein the patient has a significant progression free survival as compared to a second-line daily administration of 50 mg sunitinib for four weeks followed by two weeks without daily administrations on a 42-day cycle, wherein the patient's tumor has progressed from, or the patient was intolerant to, the previous first line administration of imatinib.

14. The method of any one of claims 1-13, wherein the tumor has, a KIT exon 9 mutation, a PDGFRA exon 18 mutation, a PDGFRA exon 12 mutation, or a PDGFRA exon 18 activation loop mutation.

15. The method of claim 14, wherein the mutation is a PDGFRA D842V mutation.

16. The method of any one of claims 1-15, wherein the tumor has an imatinib resistant mutation selected from the group consisting of a KIT exon 17 activation loop mutation, a KIT exon 18 activation loop mutation, a KIT exon 13 mutation, a KIT exon 14 mutation, a KIT exon 18 mutation, a PDGFRA exon 12 mutation, a PDGFRA exon 14 mutation, a PDGRFA exon 15 mutation, and a PDGFRA exon 18 activation loop mutation.

17. The method of claim 16, wherein the imatinib resistant mutation is a PDGFRA D842V mutation.

18. The method of claim 16 or 17, wherein the tumor has an imatinib resistant mutation selected from the group consisting of KIT exon 13 or 14 mutation, PDGFRA exon 14 or 15 mutation, a KIT 17 or 18 activation loop mutation, and a PDGFRA 18 activation loop mutation.

19. The method of any one of claims 15-18, wherein the tumor has an imatinib resistant KIT exon 17 mutation.

20. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 250 mg of ripretinib daily,

wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib, or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

21. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 600 mg of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib, or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

22. The method of claim 20 or 21, wherein the patient is administered 150 mg of ripretinib daily.

23. The method of claim 21, wherein the patient is administered 500 mg of ripretinib daily.

24. The method of claim 20 or 21, wherein the patient is administered 150 mg of ripretinib once daily.

25. The method of claim 21, wherein the patient is administered 150 mg of ripretinib twice daily.

26. The method of claim 21, wherein the patient is administered 250 mg of ripretinib twice daily.

27. The method of any one of claims 20-26, wherein the patient has at least one measurable tumor lesion according to modified RECIST Version 1.1 within 21 days prior to the first dose of ripretinib.

28. The method of any one of claims 20-27, wherein the patient has a non-nodal tumor lesion of greater than or equal to 1.0 cm in the long axis or greater than or equal to double the slide thickness in the long axis, within 21 days prior to the first dose of ripretinib.

29. The method of any one of claims 20-28, wherein the tumor has, a KIT exon 9 mutation, a PDGFRA exon 18 mutation, a PDGFRA exon 12 mutation or a PDGFRA exon 18 activation loop mutation.

30. The method of claim 29, wherein the mutation is a PDGFRA D842V mutation.

31. The method of any one of claims 20-30, wherein the tumor has an imatinib resistant, sunitinib resistant, and/or regorafenib resistant mutation selected from the group consisting of a KIT exon 17 activation loop mutation, a KIT exon 18 activation loop mutation, a KIT exon 13 mutation, a KIT exon 14 mutation, a KIT exon 18 mutation, a PDGFRA exon 12 mutation, a PDGFRA exon 14 mutation, a PDGRFA exon 15 mutation and a PDGFRA exon 18 activation loop mutation.

32. The method of claim 31, wherein the resistant mutation is a PDGFRA D842V mutation.

33. The method of claim 31 or 32, wherein the tumor has a drug resistant mutation selected from the group consisting of KIT exon 13 or 14 mutation, PDGFRA exon 14 or 15 mutation, a KIT 17 or 18 activation loop mutation, and a PDGFRA 18 activation loop mutation.

34. The method of any one of claims 20-33, wherein the tumor has a drug resistant KIT exon 17 mutation.

35. The method of any one of claims 20-34, wherein administering ripretinib is a 42-day cycle comprising daily administration of ripretinib without administering sunitinib.

36. The method of claim 35, wherein, after at least one 42-day cycle, the patient has a progression-free survival as measured using mRECIST v1.1.

37. The method of any one of claims 20-36, wherein the patient has at least a 5 or 6 month progression-free survival as compared to placebo after at least 4 weeks of daily administration of ripretinib.

38. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient one or more tablets comprising

ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

39. The method of claim 38, wherein the patient is administered three tablets each comprising 50 mg of ripretinib once daily.

40. The method of claim 38, wherein the patient is administered two tablets each comprising 50 mg of ripretinib once daily.

41. The method of claim 38, wherein the patient is administered one tablet comprising 50 mg of ripretinib once daily.

42. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient to the patient one or more tablets comprising ripretinib, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

43. The method of claim 42, wherein the patient is administered, once daily, three tablets each comprising 50 mg of ripretinib.

44. The method of claim 42, wherein the patient is administered, once daily two tablets each comprising 50 mg of ripretinib.

45. The method of claim 42, wherein the patient is administered one tablet comprising 50 mg of ripretinib once daily.

46. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 600 mg of ripretinib daily, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib.

47. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg of ripretinib once daily, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib.

48. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient, on a daily basis, one or more tablets each comprising ripretinib, e.g., tablets each comprising 50 mg to 100 mg of ripretinib, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib.

49. The method of claim 48, wherein the patient is administered, once daily, three tablets each comprising 50 mg of ripretinib.

50. The method of any one of claims 46-49, wherein the patient has previously been administered two separate tyrosine kinase inhibitors, each selected from the group consisting of imatinib, sunitinib, regorafenib, lapatinib, gefitinib, erlotinib, vatalanib, crenolanib, and pharmaceutically acceptable salts thereof.

51. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg of ripretinib once daily, wherein the patient was previously administered three or more kinase inhibitors before administration of the ripretinib.

52. The method of claim 51, wherein after at least 4 weeks of the daily ripretinib administration, the patient has at least a 5-month progression-free survival as measured using mRECIST v1.1.

53. The method of claim 51 or 52, wherein orally administering to the patient 150 mg of ripretinib once daily comprises administering to the patient three tablets each tablet comprising 50 mg of ripretinib.

54. The method of any one of claims 51-53, wherein one of the three or more kinase inhibitors is imatinib.

55. The method of any one of claims 51-54, wherein the patient was previously administered imatinib, sunitinib and regorafenib.

56. The method of any one of claims 51-55, wherein if the patient suffers from a Grade 3 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises a) withholding administration of ripretinib for at least 7 days or

until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily ripretinib for at least 28 days.

57. The method of any one of claims 51-55, wherein if the patient suffers from a Grade 2 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises: a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythorysesthia syndrome within 7 days of withholding administration, then administering to the patient 150 mg daily ripretinib or c) if the patient has not recovered, then administering to the patient 100mg daily ripretinib for at least 28 days.

58. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg daily ripretinib, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib.

59. The method of claim 58, wherein if the patient suffers from a Grade 3 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises a) withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily ripretinib for at least 28 days.

60. The method of claim 58, wherein if the patient suffers from a Grade 2 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises: a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythorysesthia syndrome within 7 days of withholding administration, then administering to the patient 150 mg daily ripretinib or c) if the patient has not recovered, then administering to the patient 100mg daily ripretinib for at least 28 days.

61. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg of ripretinib once or twice

daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

62. The method of 61, wherein if the patient suffers from Grade 3 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises a) withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily ripretinib for at least 28 days.

63. The method of any one of claims 3-20, wherein if the patient suffers from Grade 3 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises a) withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily ripretinib for at least 28 days.

64. The method of any one of claims 3-20, wherein if the patient suffers from Grade 2 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises: a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythorysesthia syndrome within 7 days of withholding administration, then administering to the patient 150 mg daily ripretinib or c) if the patient has not recovered, then administering to the patient 100mg daily ripretinib for at least 28 days.

65. The method of any one of claims 3-20, wherein if the patient suffers from a Grade 3 adverse disorder selected from arthralgia or myalgia upon administration of the ripretinib, the method further comprises: a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 adverse disorder, then administering to the patient 100 mg daily ripretinib for at least 28 days.

66. The method of any one of claims 3-20, wherein if the patient suffers from Grade 3 hypertension upon administration of the ripretinib, the method further comprises withholding administration of ripretinib until the patient's blood pressure is controlled, and if the patient has less than or equal to Grade 1 blood pressure is, administering to the patient 150 mg daily ripretinib, or if the patient has more than Grade 1 blood pressure, administering 100 mg daily ripretinib.

67. A method for achieving at least 5 months of progression free survival as determined by mRECIST 1.1 in a patient having an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100, 150, 200, or 300 mg of ripretinib daily or twice daily for at least 28 days.

68. The method of claim 67, wherein the patient has been administered at least one previous kinase inhibitor.

69. The method of claim 67-68, wherein the patient has been administered at least three previous kinase inhibitors.

70. The method of claim 68 or 69, wherein the at least one previous kinase inhibitor is imatinib.

71. The method of any one of claims 67-70, comprising orally administering to the patient 100, 150 or 200 mg of ripretinib daily or twice daily for at least 4 months.

72. A method of treating a patient suffering from Grade 3 palmer-plantar erythrodysesthia syndrome while being administered 150 mg ripretinib daily or twice daily, comprising withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily ripretinib for at least 28 days.

73. A method of treating a patient suffering from Grade 2 palmer-plantar erythrodysesthia syndrome upon administration of 150 mg ripretinib daily or twice daily, comprising a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythorysesthia syndrome within 7 days of withholding administration, then administering to the patient 150 mg daily ripretinib or c) if the patient has not recovered, then administering to the patient 100mg daily ripretinib for at least 28 days.

74. A method of treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a CYP3A4 inhibitor, the method comprising:

orally administering to the patient 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, once or twice daily, and wherein upon administration of the ripretinib and the CYP3A4 inhibitor, provides an increased ripretinib area under the plasma concentration curve ($AUC_{0\text{-}inf}$) of 80% or more in the patient as compared to administration of ripretinib without concurrent treatment of the CYP3A4 inhibitor, and therefore the patient is at higher risk of an adverse event; and

monitoring the patient more frequently, as compared to a patient not being treated with a CYP3A4 inhibitor, for the adverse event.

75. The method of claim 74, wherein if the patient suffers from a Grade 3 palmer-plantar erythrodysesthia syndrome adverse event, the method further comprises a) withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily ripretinib for at least 28 days.

76. The method of claim 75, wherein if the patient suffers from Grade 2 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further comprises: a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythorysesthia syndrome within 7 days of withholding administration, then administering to the patient 150 mg daily ripretinib or c) if the patient has not recovered, then administering to the patient 100mg daily ripretinib for at least 28 days.

77. The method of any one of claims 74-76, wherein the CYP3A4 inhibitor is selected from the group consisting of itraconazole, ketoconazole, clarithromycin, and indinavir.

78. The method of any one of claims 74-77, wherein the CYP3A4 inhibitor is itraconazole.

79. The method of any one of claims 74-78, wherein the patient has previously been administered one or more tyrosine kinase inhibitors, each selected from the group consisting of imatinib, sunitinib, regorafenib, lapatinib, gefitinib, erlotinib, vatalanib, crenolanib, and pharmaceutically acceptable salts thereof.

80. A method of treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a proton pump inhibitor, the method comprising: orally administering to the patient 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, once or twice daily, and wherein upon administration of the ripretinib and proton pump inhibitor, provides no clinically significant difference in the plasma exposure of ripretinib in the patient as compared to administration of ripretinib without concurrent treatment of the proton pump inhibitor.

81. The method of claim 80, wherein the proton pump inhibitor is selected from the group consisting of pantoprazole, omeprazole, lansoprazole, rabeprazole, esomeprazole, and dexlansoprazole.

82. The method of claim 80 or 81, wherein the proton pump inhibitor is pantoprazole.

83. The method of any one of claims 80-82, wherein the patient is being treated concurrently with 40 mg of the proton pump inhibitor once daily.

84. A method of treating a gastrointestinal stromal tumor in a patient in need thereof, the method comprising orally administering to the patient 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, once or twice daily, wherein the ripretinib is administered to the patient with food or without food.

85. The method of claim 83, wherein the food comprises a high-fat meal.

FIG. 1

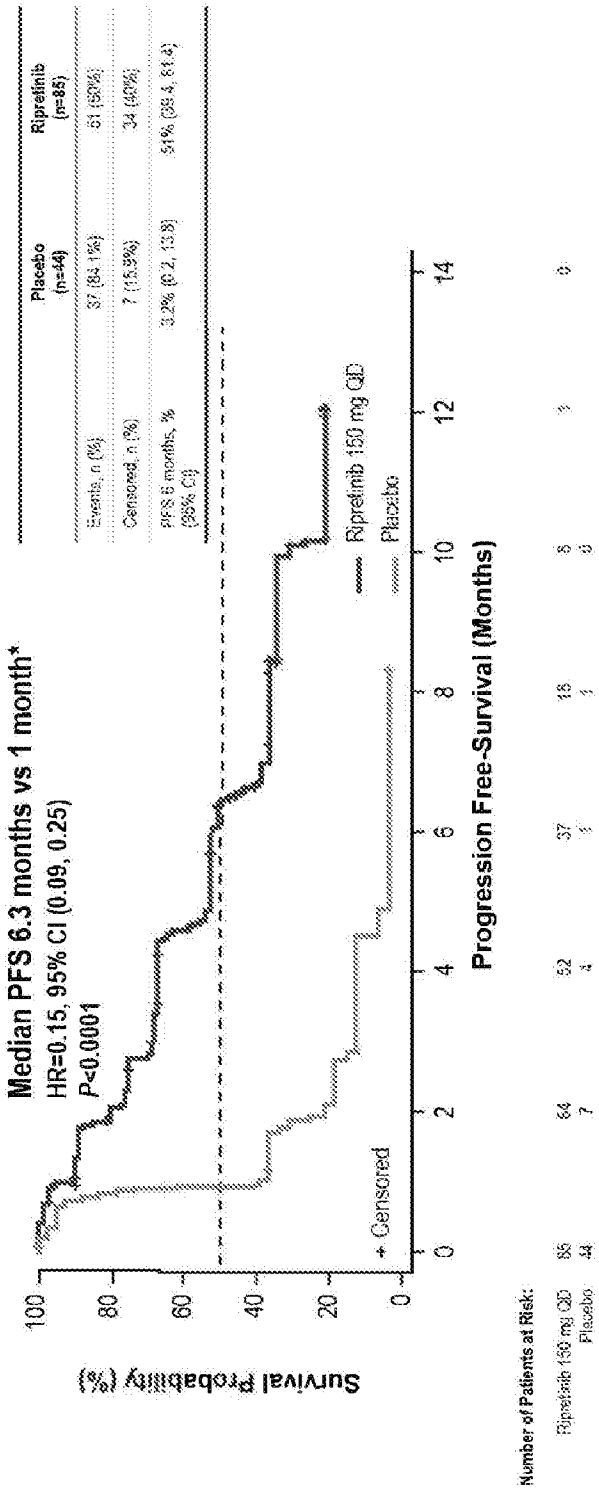
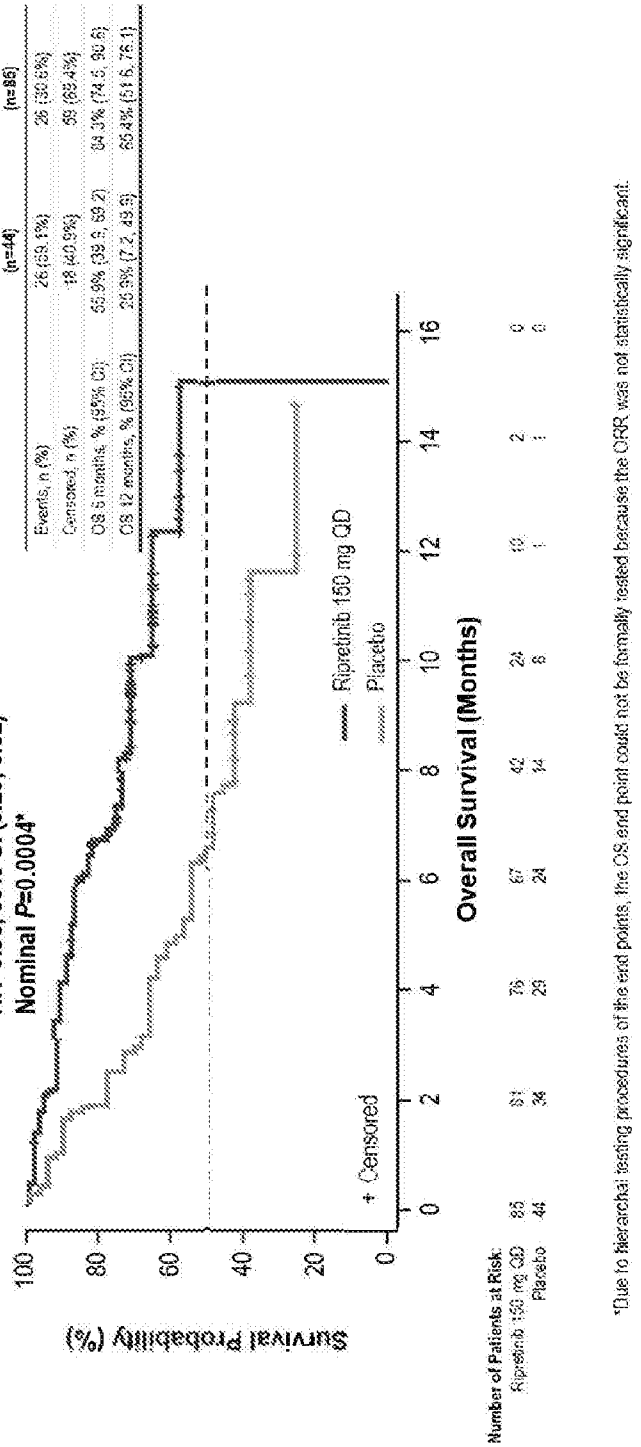

Median PFS 6.3 months vs 1 month*
HR=0.15, 95% CI (0.09, 0.25)
P<0.0001
Placebo (n=44)
Ripretinib (n=85)
Events, n (%) 37 (84.1%) 51 (60%)
Censored, n (%) 7 (15.9%) 34 (40%)
PFS 6 months, % (95% CI) 3.2% (0.2, 13.8) 51% (38.4, 61.4)
Survival Probability (%)
100
80
60
40
20
0
+ Censored
Ripretinib 160 mg QD
Placebo
0 2 4 6 8 10 12 14
Progression Free-Survival (Months)
Number of Patients at Risk:
Ripretinib 160 mg QD 85 64 52 37 18 8 3 0
Placebo 44 7 4 1 1 0
*Double-blind period

FIG. 2



*Due to hierarchal testing procedures of the end points, the OS end point could not be formally tested because the ORR was not statistically significant.

FIG. 3

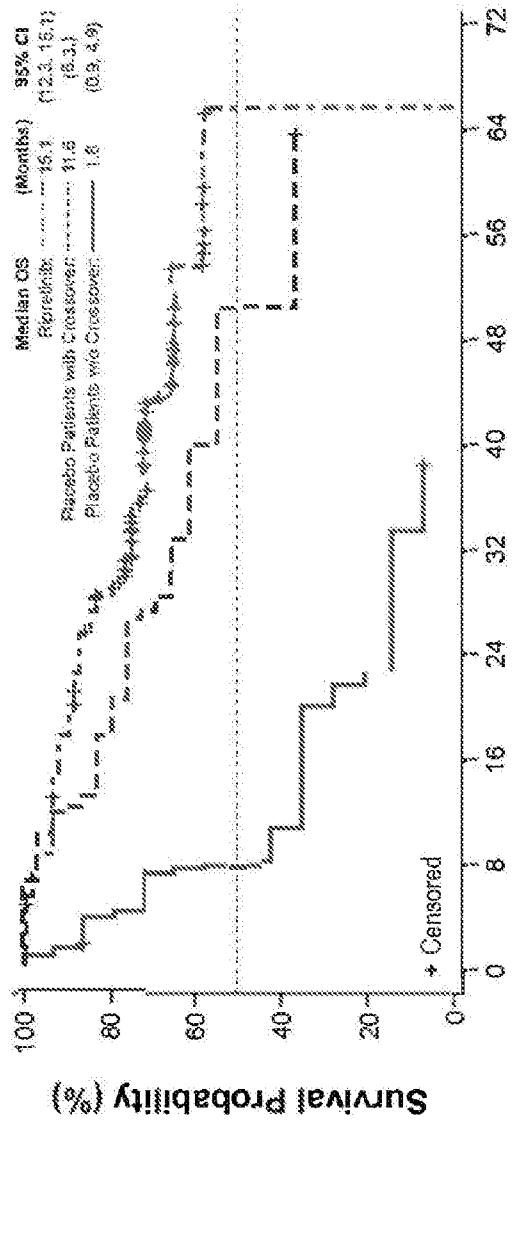

Median OS (Months) 95% CI
Ripretinib 15.1 (12.3, 19.1)
Placebo Patients with Crossover 11.2 (8.3,)
Placebo Patients w/o Crossover 1.8 (0.9, 4.9)
Survival Probability (%)
100
80
60
40
20
0
+ Censored
0 8 16 24 32 40 48 56 64 72
Overall Survival (Months)
Number of Patients at Risk
Ripretinib 85 81 76 70 57 35 14 5 2 0
Placebo Patients with Crossover 29 28 24 22 15 10 8 1 0 0
Placebo Patients w/o Crossover 15 6 5 2 2 0 0 0 0 0

FIG. 4

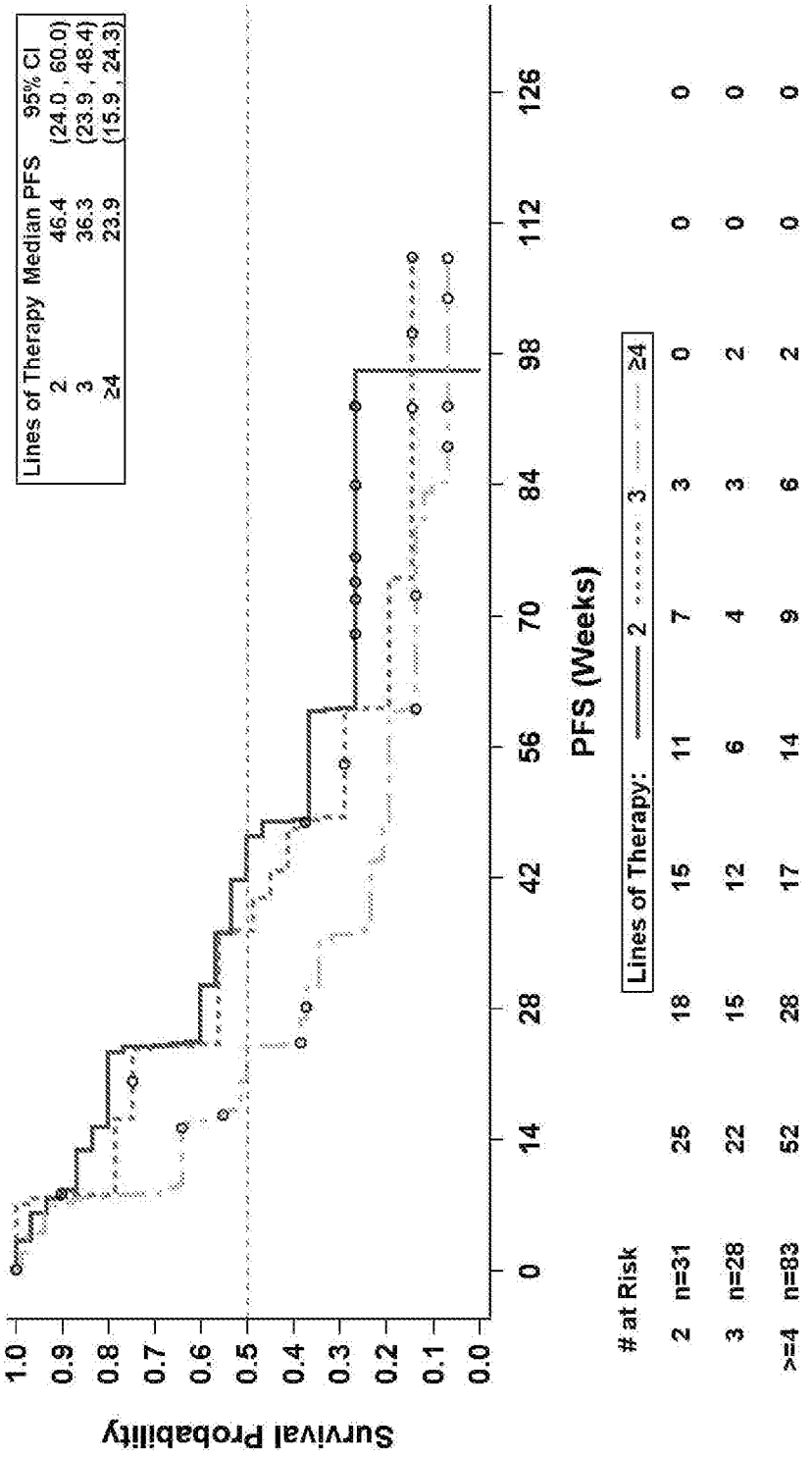

Lines of Therapy Median PFS 95% CI
2 46.4 (24.0 , 60.0)
3 36.3 (23.9 , 48.4)
≥4 23.9 (15.9 , 24.3)
Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 14 28 42 56 70 84 98 112 126
PFS (Weeks)
Lines of Therapy: 2 3 ≥4
at Risk
2 n=31 25 18 15 11 7 3 0 0 0 0
3 n=28 22 15 12 6 4 3 2 0 0 0
>=4 n=83 52 28 17 14 9 6 2 0 0 0

FIG. 5

5A

We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100.

100 means the best health you can imagine.
0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = 77

5B

5C

Treatment	Change from Baseline	Percentage of Patients
Ripretinib	Improvement and No Change	67
	Deterioration > MCID	33
Placebo	Improvement and No Change	41
	Deterioration > MCID	59

FIG. 6

Treatment	Change from Baseline	Percentage of Patients
Ripretinib	Improvement and No Change	68
	Deterioration > MCID	32
Placebo	Improvement and No Change	44
	Deterioration > MCID	56

Role Function Questions

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4

These scores are converted to a scale ranging from 0 to 100. A larger value is good and a lower value is bad

FIG. 7A

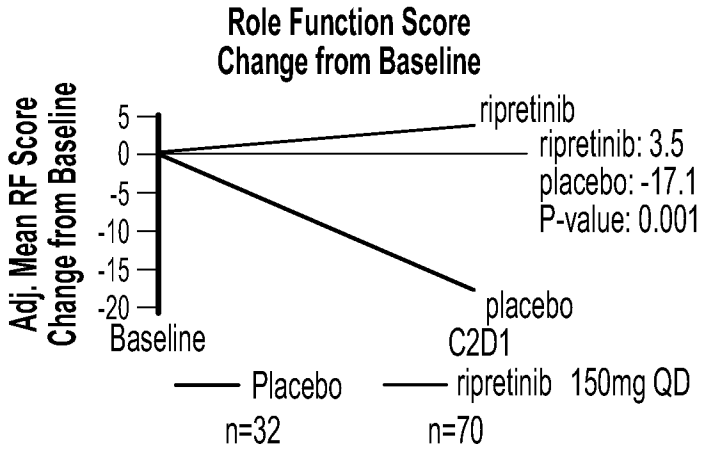


FIG. 7B

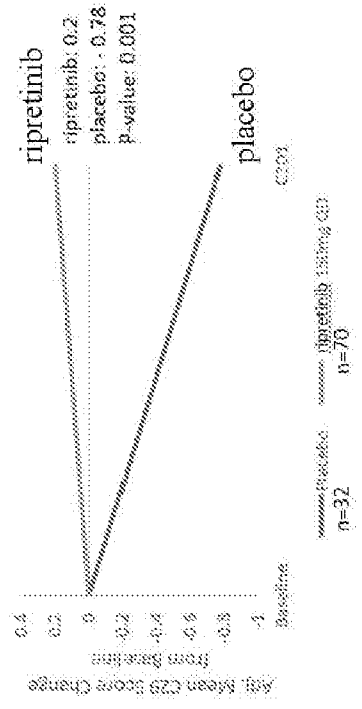
Treatment	Change from Baseline	Percentage of Patients
Ripretinib	Improvement and No Change	77
	Deterioration > MCID	23
Placebo	Improvement and No Change	50
	Deterioration > MCID	50

FIG. 7C

SUBSTITUTE SHEET (RULE 26)

FIG. 8

8A

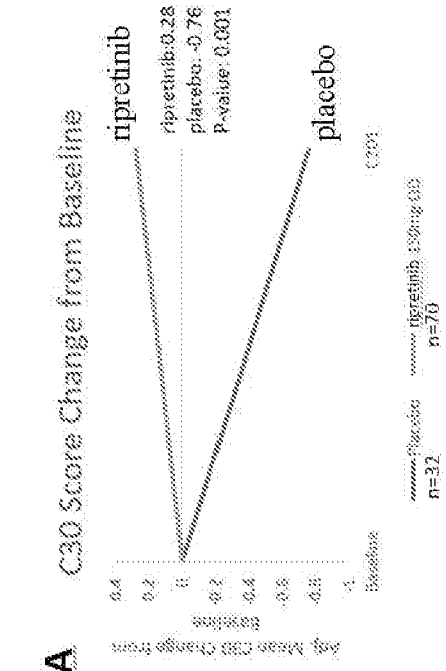


8B

Treatment	Change from Baseline	Percentage of Patients
Ripretinib	Improvement and No Change	74
	Deterioration > MCID	26
Placebo	Improvement and No Change	47
	Deterioration > MCID	53

FIG. 9

9A



9B

Treatment	Change from Baseline	Percentage of Patients
Ripretinib	Improvement and No Change	79
	Deterioration > MCID	21
Placebo	Improvement and No Change	59
	Deterioration > MCID	41

FIG. 10

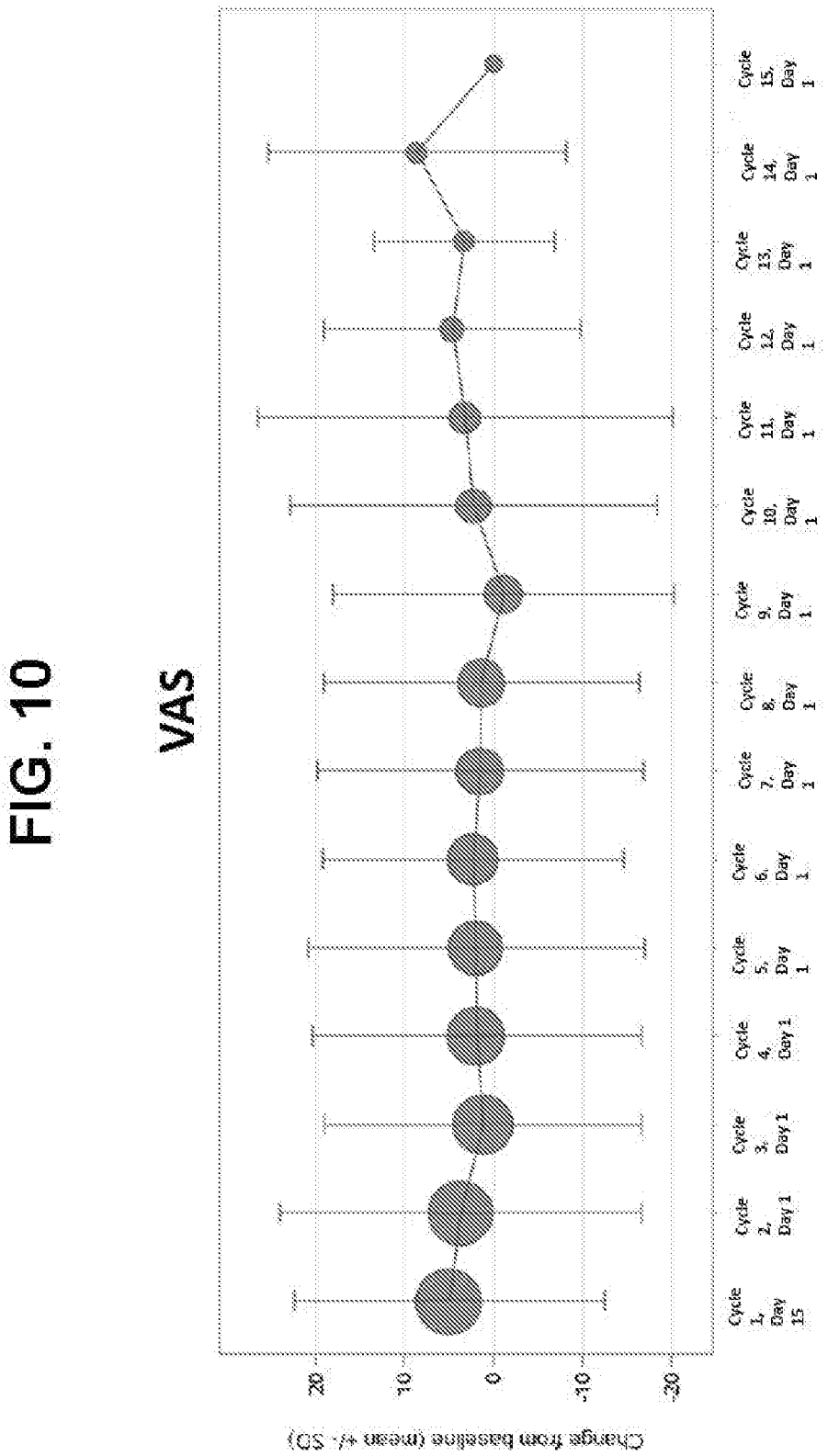
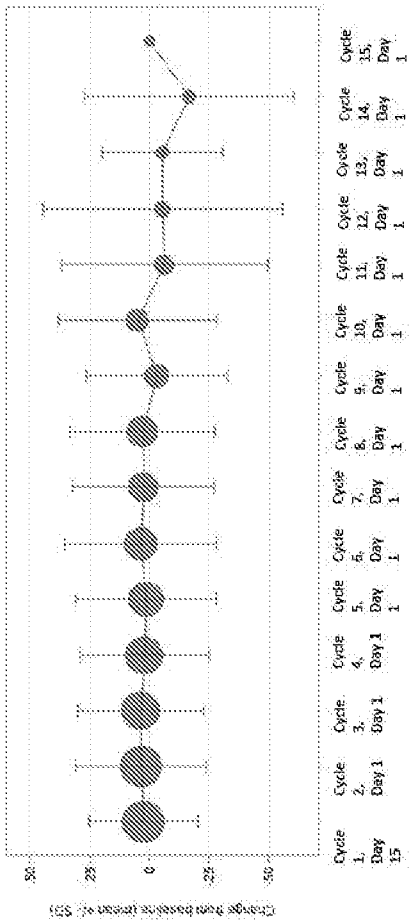

VAS
Change from baseline (mean +/- SD)
20
10
0
-10
-20
Cycle 1, Day 15
Cycle 2, Day 1
Cycle 3, Day 1
Cycle 4, Day 1
Cycle 5, Day 1
Cycle 6, Day 1
Cycle 7, Day 1
Cycle 8, Day 1
Cycle 9, Day 1
Cycle 10, Day 1
Cycle 11, Day 1
Cycle 12, Day 1
Cycle 13, Day 1
Cycle 14, Day 1
Cycle 15, Day 1

FIG. 11

11A



11B

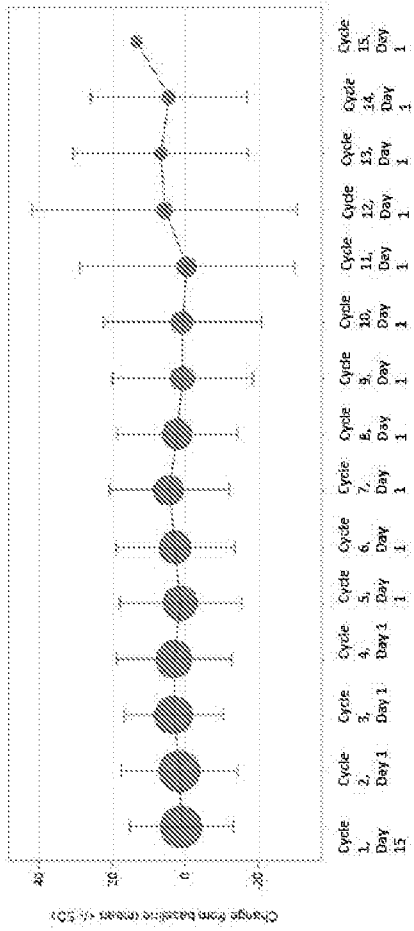
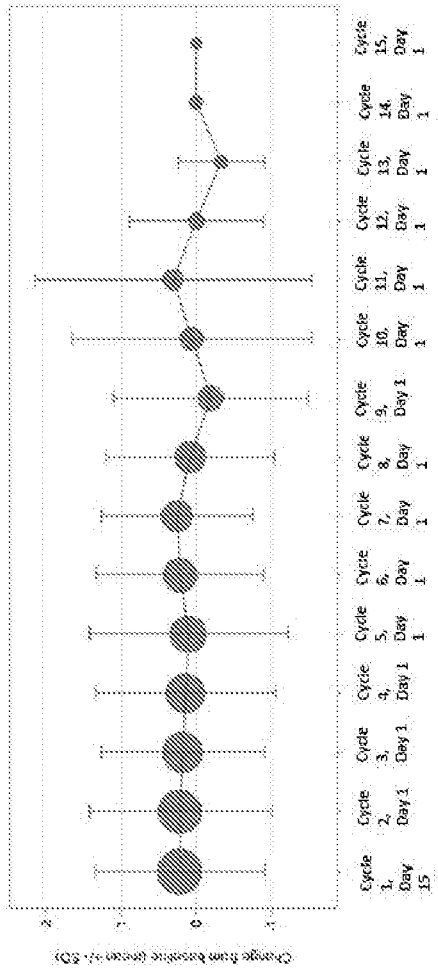


FIG. 12

12A



12B

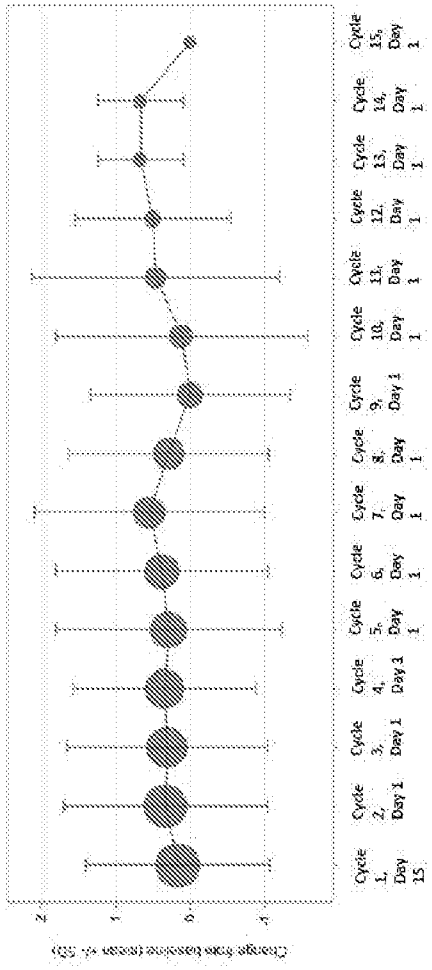


FIG. 13

	Placebo (N=44)	Placebo /Ripretinib (N=29)	Ripretinib (N=85)
Events n (%)	37 (84.1)	13 (44.8)	51 (60.0)
Censored n (%)	7 (15.9)	**16 (55.1)**	34 (40.0)
Median PFS (weeks) % (95% CI)	4.1 (4.0, 7.3)	20.0 (8.0, NE)	27.6 (20.0, 29.9)

*NE = Not Estimable

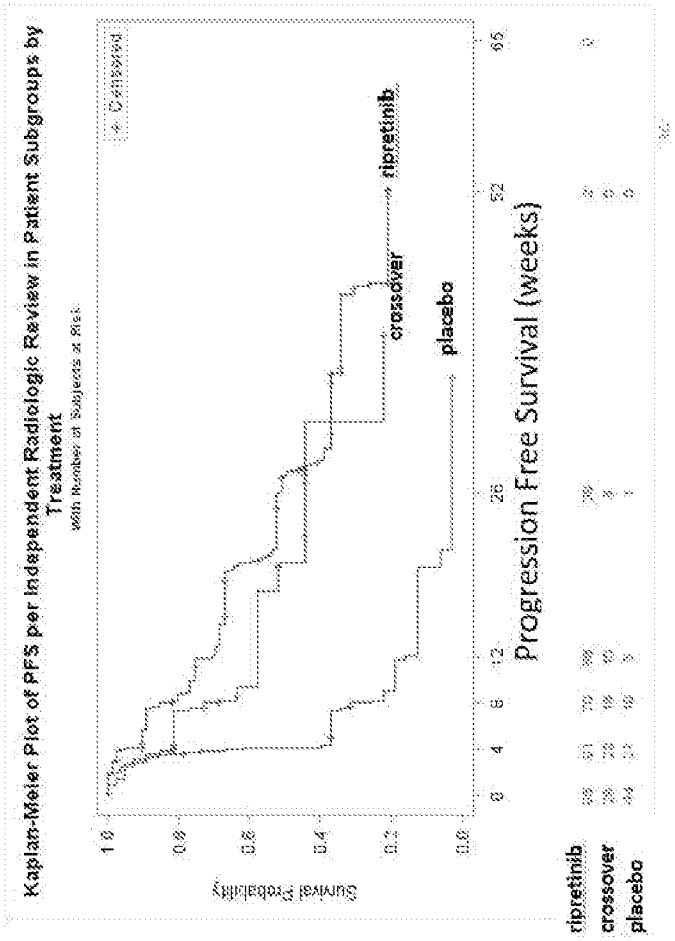
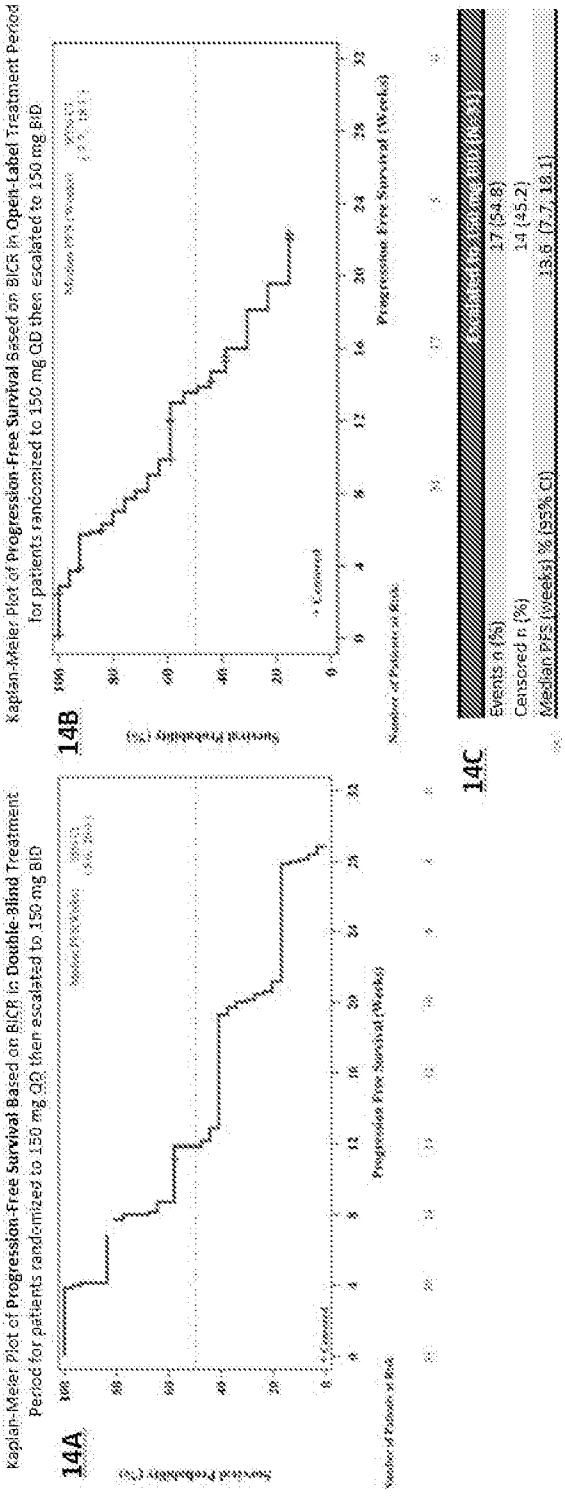


FIG. 14


14A
Kaplan-Meier Plot of Progression-Free Survival Based on BICR in Double-Blind Treatment Period for patients randomized to 150 mg QD then escalated to 150 mg BID
14B
Kaplan-Meier Plot of Progression-Free Survival Based on BICR in Open-Label Treatment Period for patients randomized to 150 mg QD then escalated to 150 mg BID
14C
Events n (%)
17 (54.8)
Censored n (%)
14 (45.2)
Median PFS (weeks) % (95% CI)
13.6 (7.7, 18.1)

Gene	Subj ID	Arm	PFS (Weeks)	Censored?	Mutation
Wild Type	1	DCC-2618 150 mg QD	11.1429	Yes	None
Wild Type	2	DCC-2618 150 mg QD	52.1429	Yes	SDHC/TP53
Wild Type	3	DCC-2618 150 mg QD	24.7143	Yes	None
Wild Type	4	DCC-2618 150 mg QD	8.7143	No	SDHC/ATRX
Wild Type	5	DCC-2618 150 mg QD	36.4286	Yes	KRAS
Wild Type	6	DCC-2618 150 mg QD	8.7143	No	MCL1 Amplification
Wild Type	7	DCC-2618 150 mg QD	26	No	NF1
Wild Type	8	Placebo	4	No	CDKN2A/CDKN28/PTEN I
Wild Type	9	Placebo	36	Yes	SDHA/TP53
Wild Type	10	Placebo	9	No	NF1

FIG. 15

FIG. 16

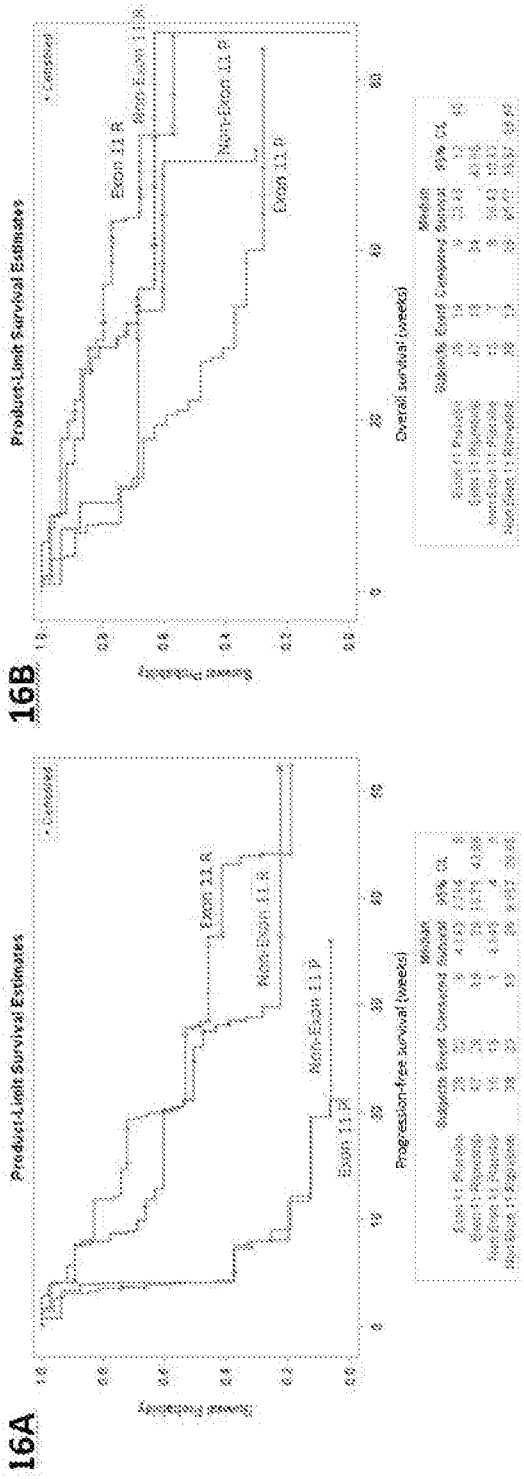

16A
16B
Product-Limit Survival Estimates
Progression-free survival (weeks)
Overall survival (weeks)
Exon 11 R
Non-Exon 11 R
Exon 11 P
Non-Exon 11 P
Censored

FIG. 17

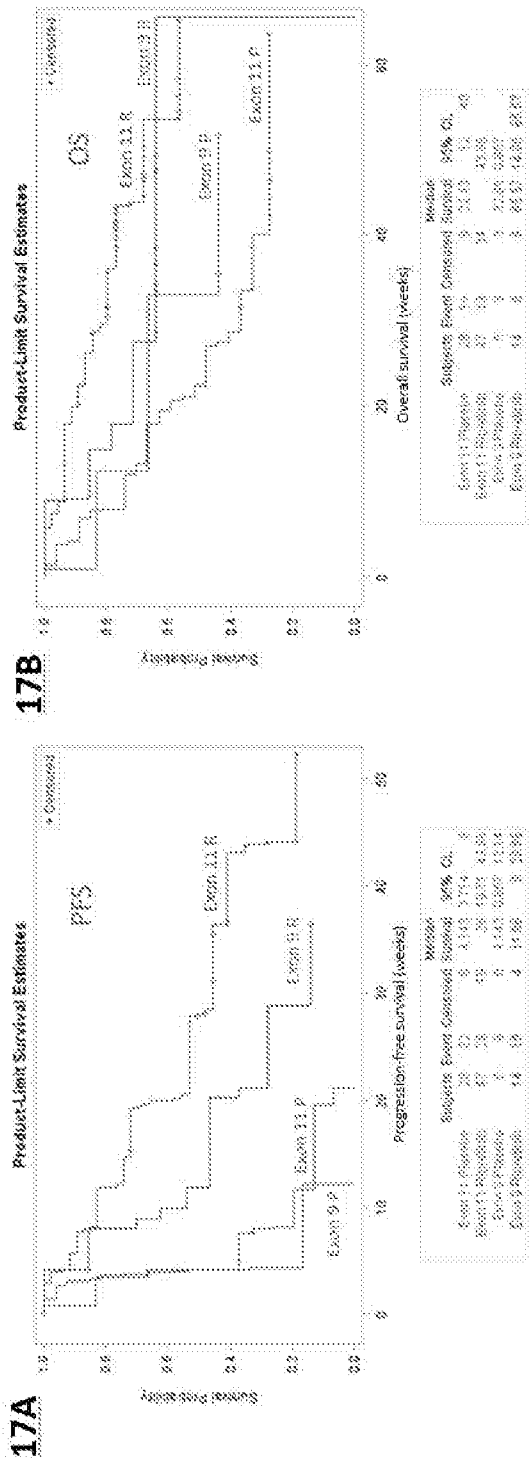

17A
PFS
Product-Limit Survival Estimates
Progression-free survival (weeks)
17B
OS
Product-Limit Survival Estimates
Overall survival (weeks)

FIG. 18

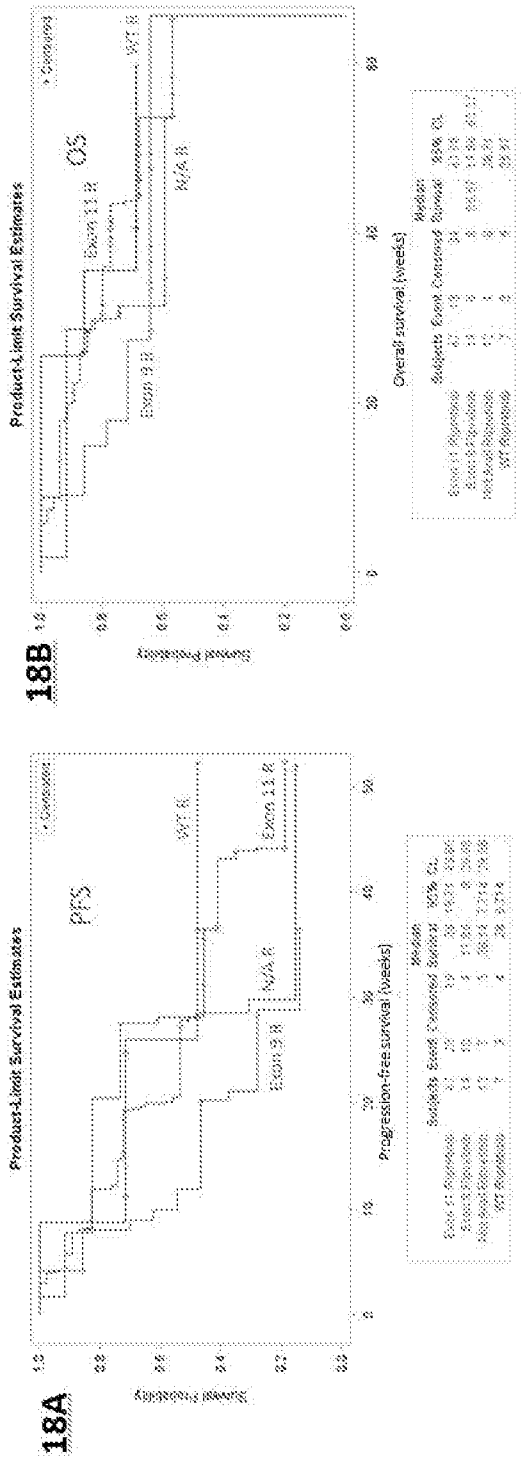
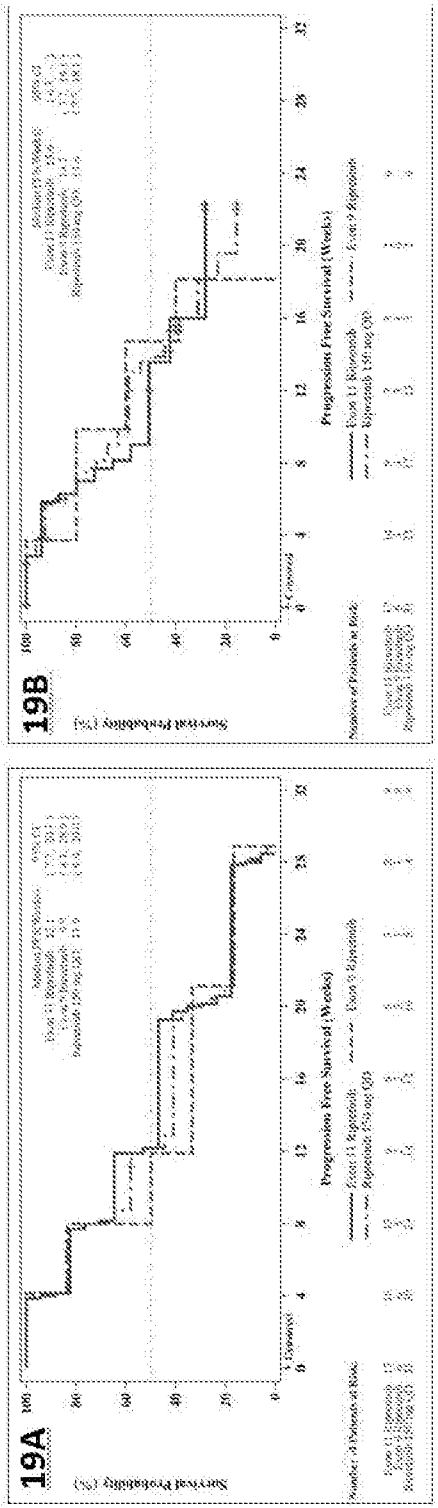

18A
Product-Limit Survival Estimates
PFS
Censored
WT R
Exon 11 R
N/A R
Exon 9 R
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Progression-free survival (weeks)
Median
Subjects Event Censored Survival 95% CL
Exon 11 R 10 10 0 20.14 11.86 NE
Exon 9 R 10 10 0 11.86 5.71 20.29
N/A R 10 9 1 20.29 11.86 NE
WT R 10 4 6 NE 37.14 NE
18B
Product-Limit Survival Estimates
OS
Censored
WT R
Exon 11 R
N/A R
Exon 9 R
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Overall survival (weeks)
Median
Subjects Event Censored Survival 95% CL
Exon 11 R 10 10 0 20.14 11.86 NE
Exon 9 R 10 10 0 11.86 5.71 20.29
N/A R 10 9 1 20.29 11.86 NE
WT R 10 4 6 NE 37.14 NE

FIG. 19



Gene	Subj ID	Arm	PFS (Weeks)	Censored?
KIT Other Exons	11	DCC-2618 150 mg QD	3.0	Yes
KIT Other Exons	12	DCC-2618 150 mg QD	12.9	No
KIT Other Exons	13	Placebo	3.9	No
KIT Other Exons	14	Placebo	7.3	No
PDGFRA	15	DCC-2618 150 mg QD	4.1	No
PDGFRA	16	DCC-2618 150 mg QD	7.6	No
PDGFRA	17	DCC-2618 150 mg QD	28.1	Yes

FIG. 20

FIG. 21

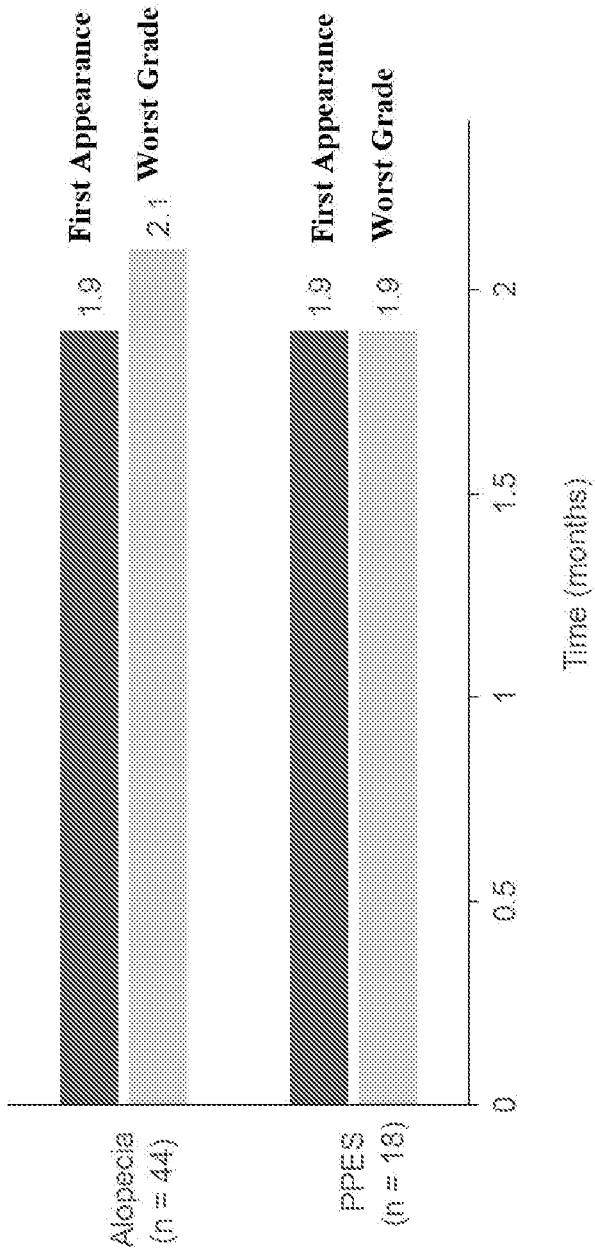

First Appearance
Worst Grade
1.9
2.1
1.9
1.9
Alopecia
(n = 44)
PPES
(n = 18)
0
0.5
1
1.5
2
Time (months)

FIG. 22A

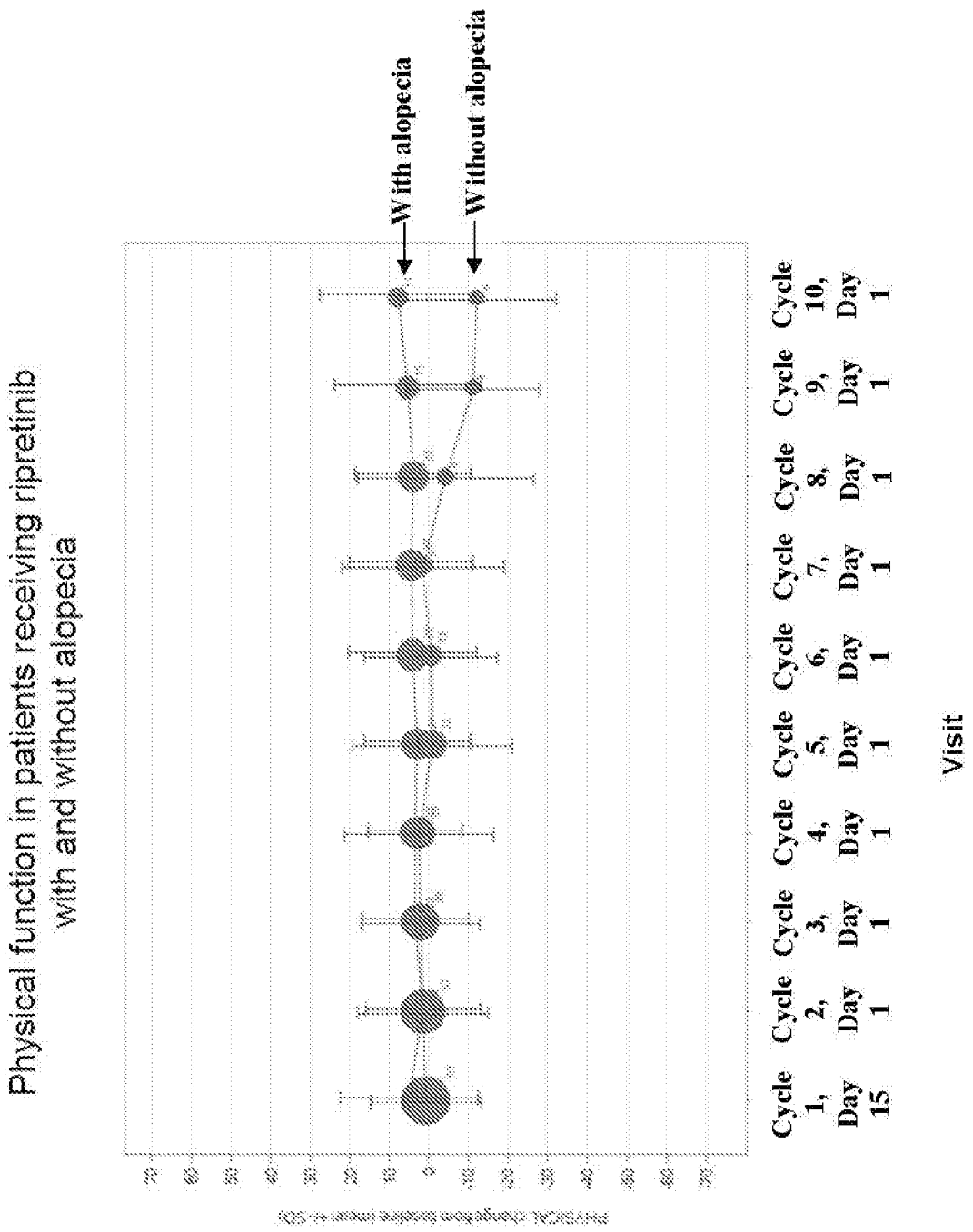

Physical function in patients receiving ripretinib with and without alopecia
With alopecia
Without alopecia
Cycle 1, Day 15
Cycle 2, Day 1
Cycle 3, Day 1
Cycle 4, Day 1
Cycle 5, Day 1
Cycle 6, Day 1
Cycle 7, Day 1
Cycle 8, Day 1
Cycle 9, Day 1
Cycle 10, Day 1
Visit

FIG. 22B

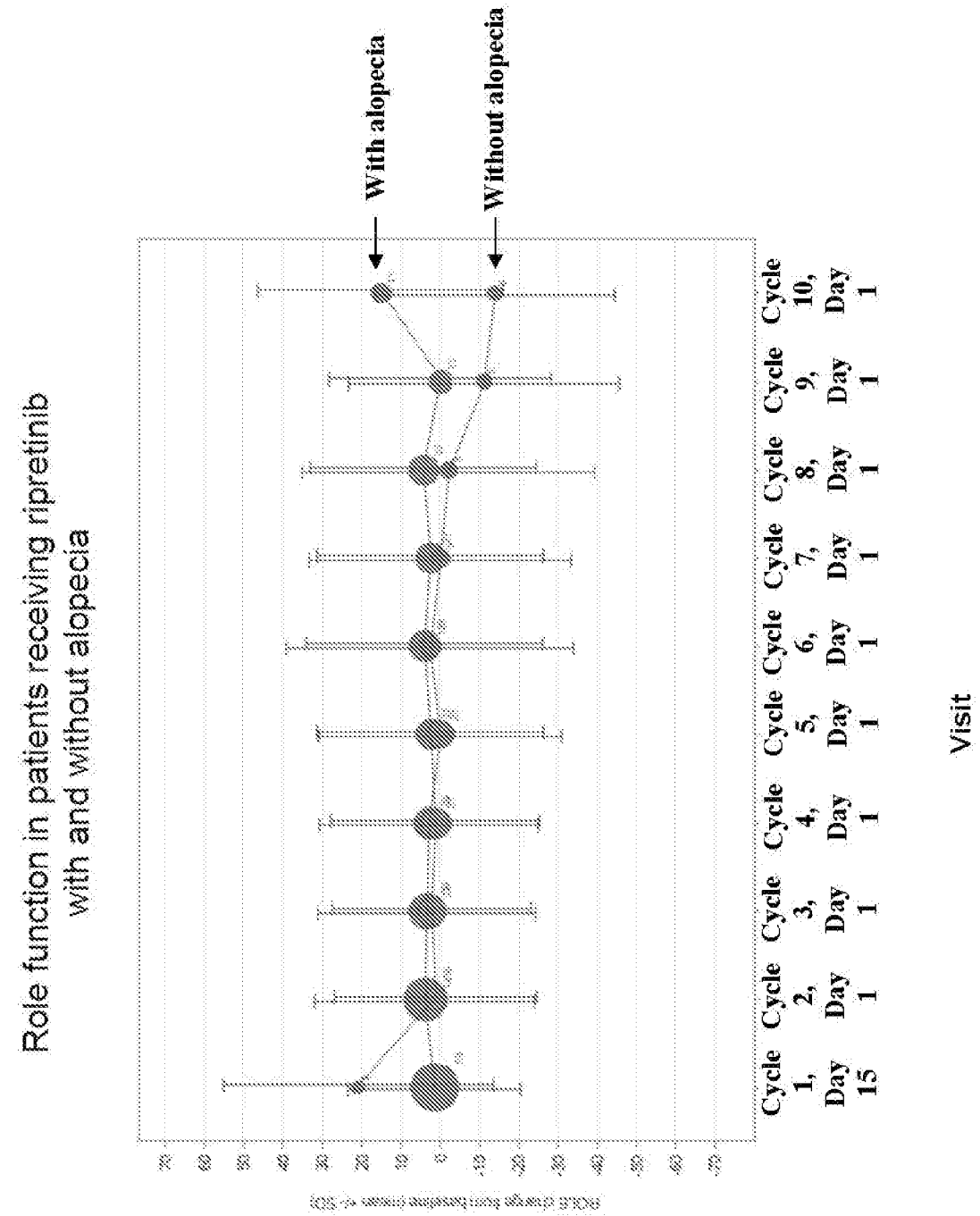

Role function in patients receiving ripretinib with and without alopecia
With alopecia
Without alopecia
Cycle 1, Day 15
Cycle 2, Day 1
Cycle 3, Day 1
Cycle 4, Day 1
Cycle 5, Day 1
Cycle 6, Day 1
Cycle 7, Day 1
Cycle 8, Day 1
Cycle 9, Day 1
Cycle 10, Day 1
Visit

FIG. 22C

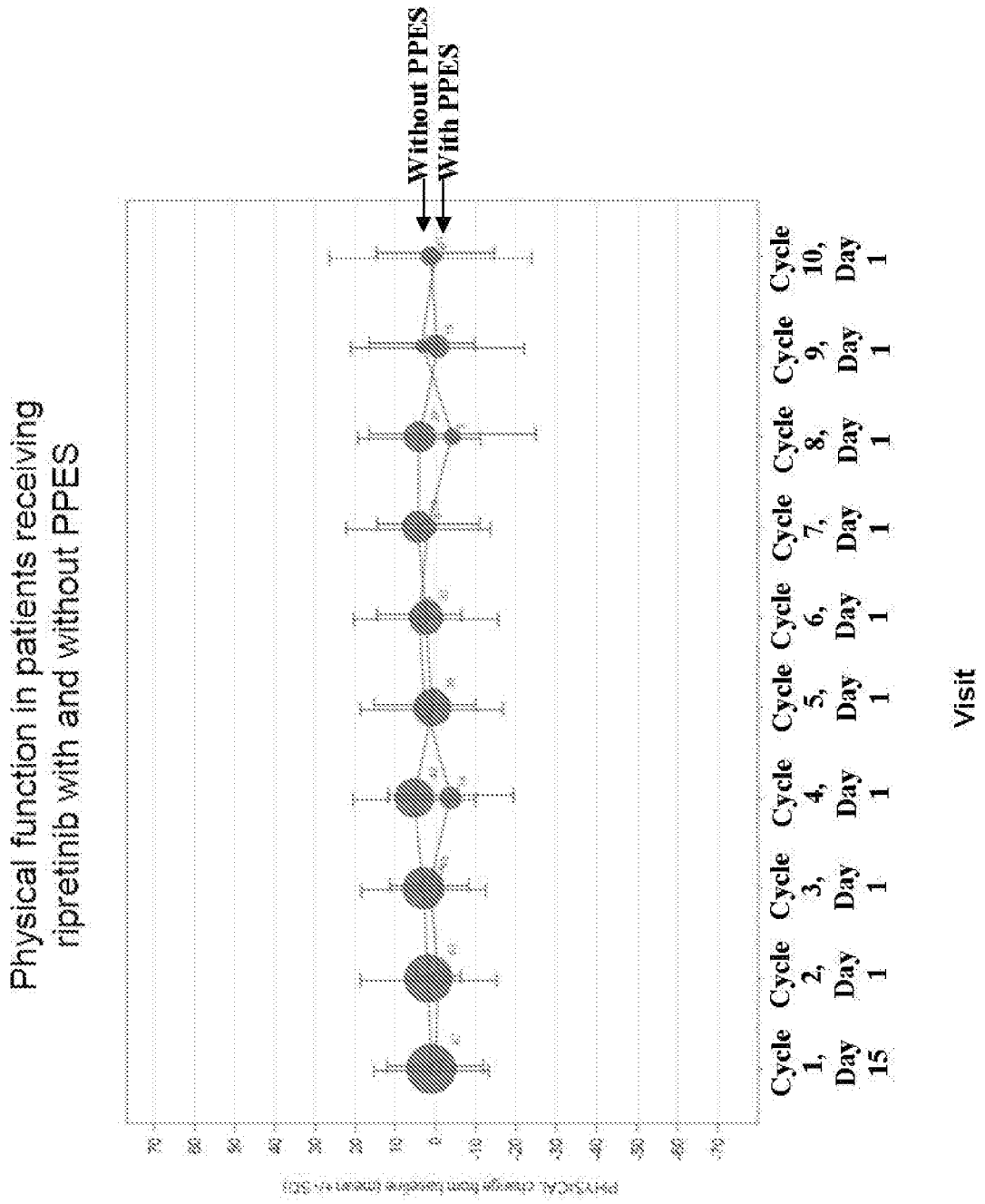

Physical function in patients receiving ripretinib with and without PPES
Without PPES
With PPES
PHYSICAL change from baseline (mean +/- SE)
Cycle 1, Day 15
Cycle 2, Day 1
Cycle 3, Day 1
Cycle 4, Day 1
Cycle 5, Day 1
Cycle 6, Day 1
Cycle 7, Day 1
Cycle 8, Day 1
Cycle 9, Day 1
Cycle 10, Day 1
Visit

FIG. 22D

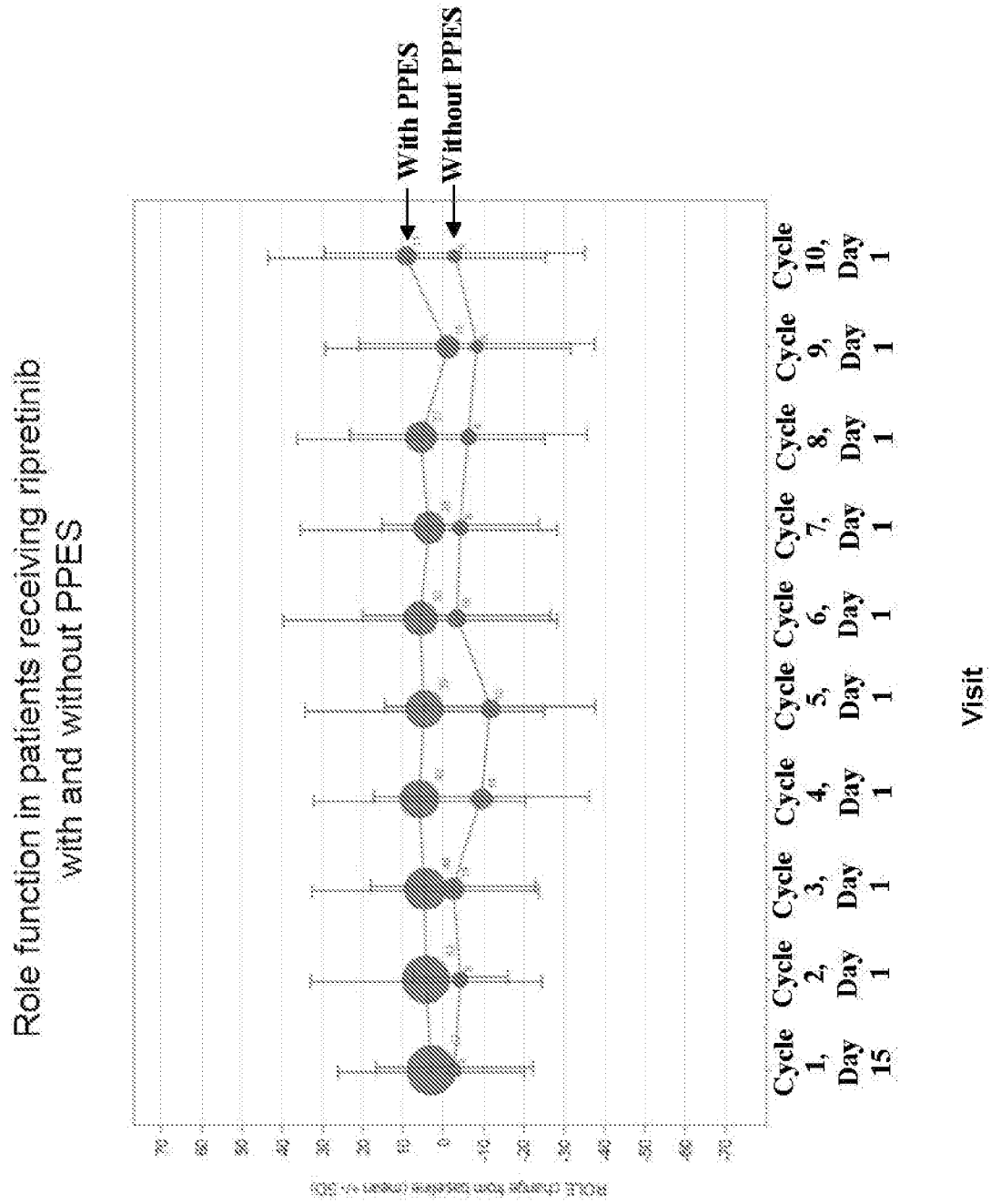

Role function in patients receiving ripretinib with and without PPES
With PPES
Without PPES
Cycle 1, Day 15
Cycle 2, Day 1
Cycle 3, Day 1
Cycle 4, Day 1
Cycle 5, Day 1
Cycle 6, Day 1
Cycle 7, Day 1
Cycle 8, Day 1
Cycle 9, Day 1
Cycle 10, Day 1
Visit

FIG. 23A

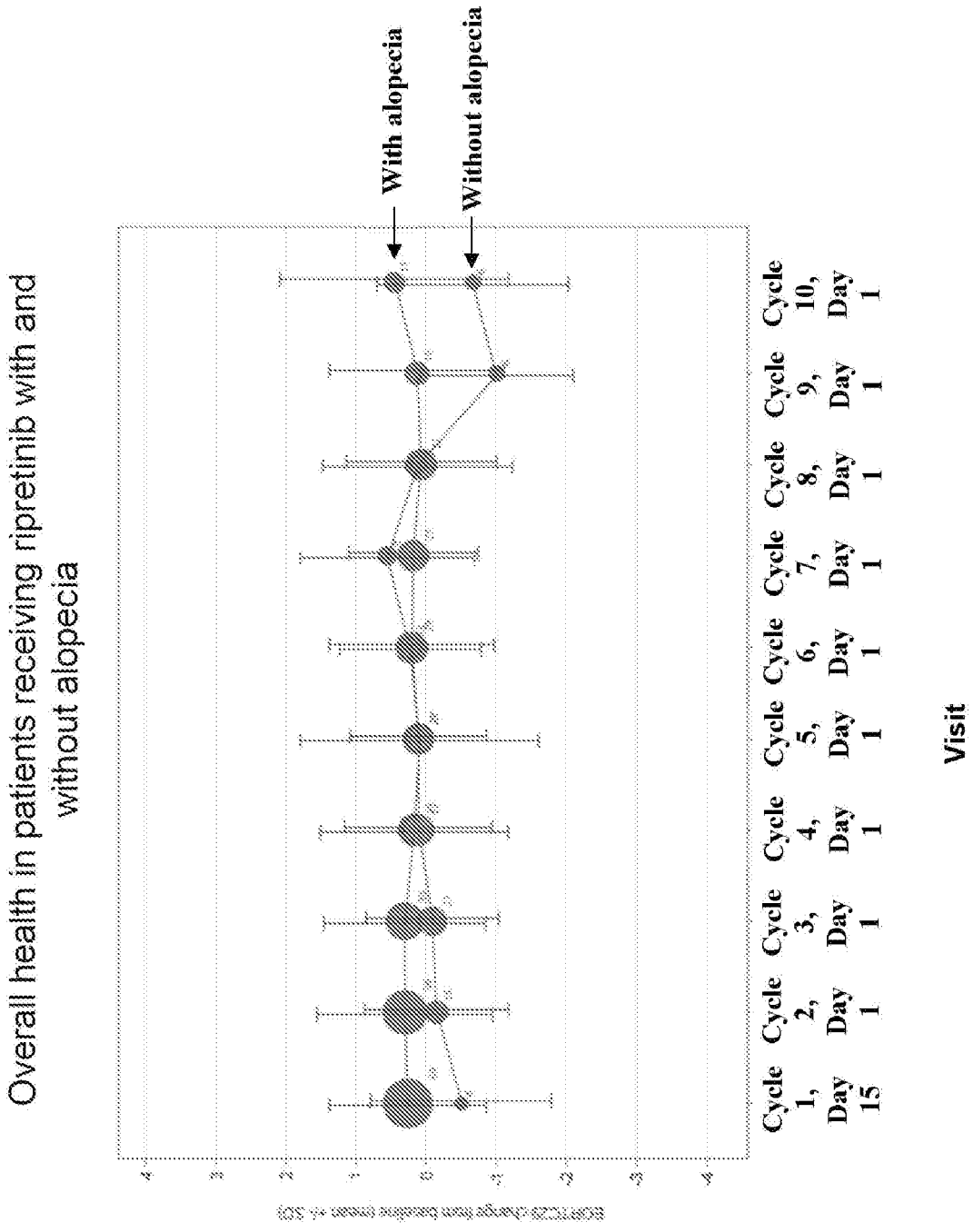

Overall health in patients receiving ripretinib with and without alopecia
With alopecia
Without alopecia
EORTC QLQ change from baseline (mean +/- SD)
4
3
2
1
0
-1
-2
-3
-4
Cycle 1, Day 15
Cycle 2, Day 1
Cycle 3, Day 1
Cycle 4, Day 1
Cycle 5, Day 1
Cycle 6, Day 1
Cycle 7, Day 1
Cycle 8, Day 1
Cycle 9, Day 1
Cycle 10, Day 1
Visit

FIG. 23B

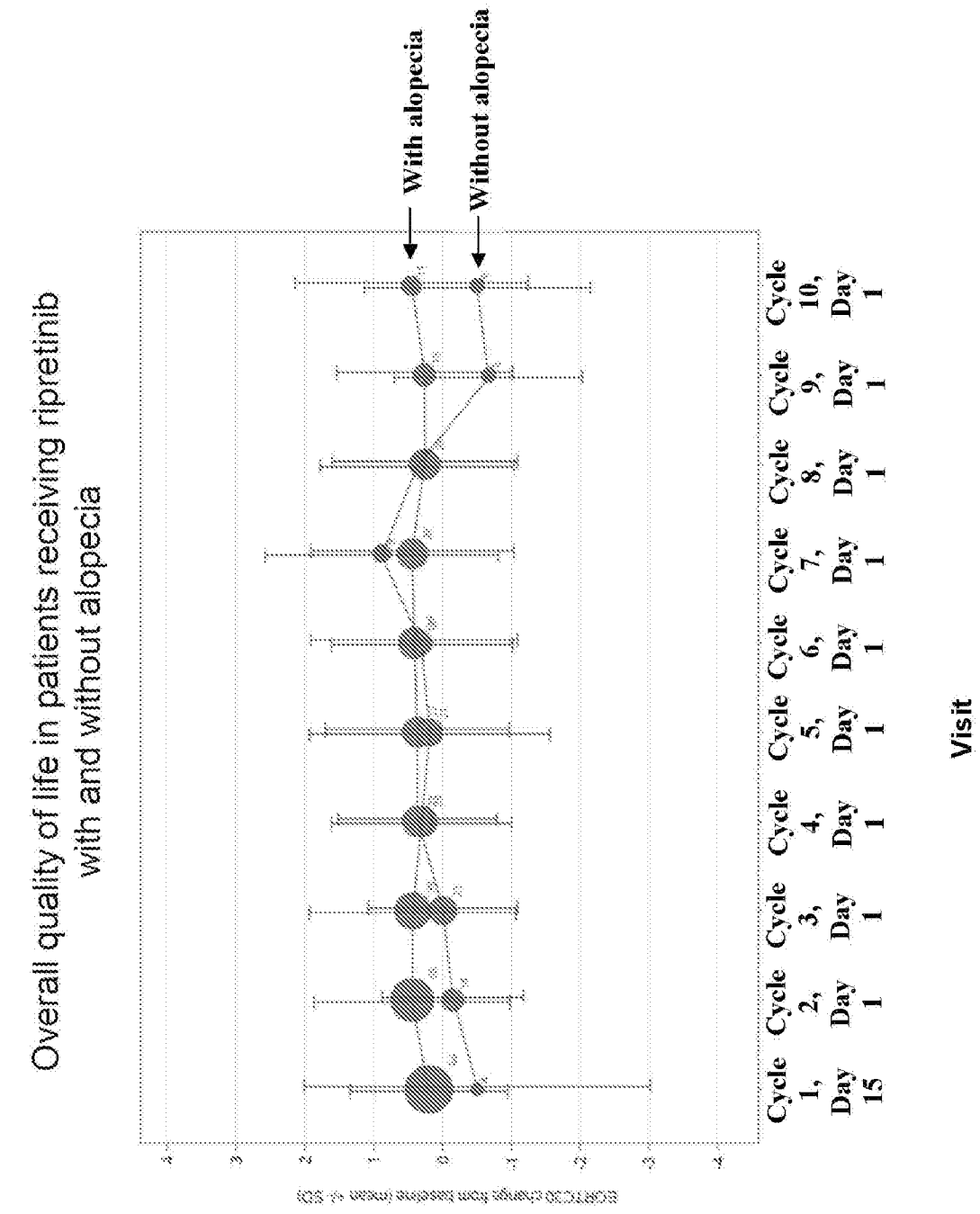

Overall quality of life in patients receiving ripretinib with and without alopecia
With alopecia
Without alopecia
EORTC30 Change from Baseline (mean +/- SD)
4
3
2
1
0
-1
-2
-3
-4
Cycle 1, Day 15
Cycle 2, Day 1
Cycle 3, Day 1
Cycle 4, Day 1
Cycle 5, Day 1
Cycle 6, Day 1
Cycle 7, Day 1
Cycle 8, Day 1
Cycle 9, Day 1
Cycle 10, Day 1
Visit

FIG. 23C

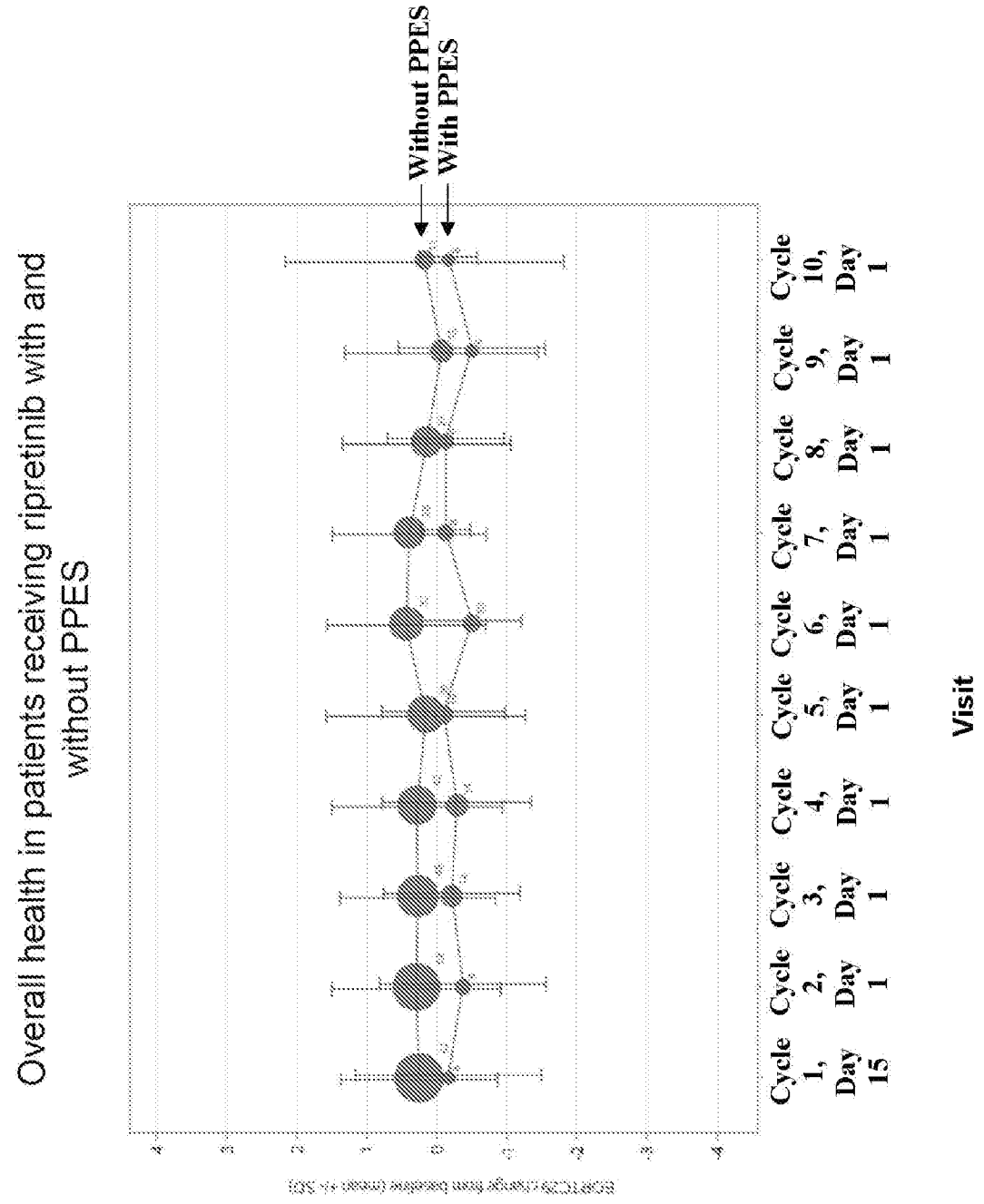

Overall health in patients receiving ripretinib with and without PPES
Without PPES
With PPES
EORTC30 change from baseline (mean +/- SD)
Cycle 1, Day 15
Cycle 2, Day 1
Cycle 3, Day 1
Cycle 4, Day 1
Cycle 5, Day 1
Cycle 6, Day 1
Cycle 7, Day 1
Cycle 8, Day 1
Cycle 9, Day 1
Cycle 10, Day 1
Visit

FIG. 23D

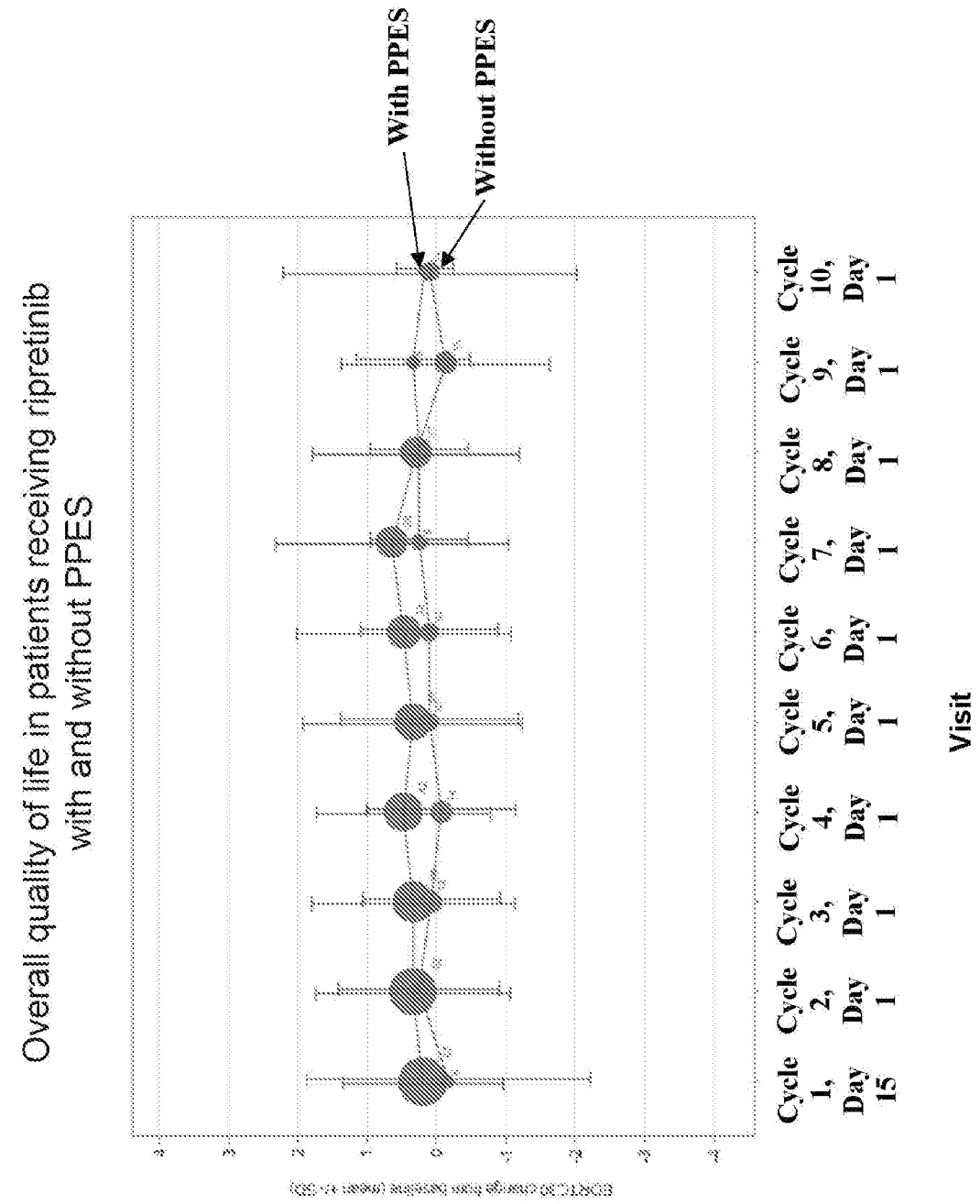

Overall quality of life in patients receiving ripretinib with and without PPES
With PPES
Without PPES
EORTC QLQ-C30 change from baseline (mean +/- SD)
Cycle 1, Day 15
Cycle 2, Day 1
Cycle 3, Day 1
Cycle 4, Day 1
Cycle 5, Day 1
Cycle 6, Day 1
Cycle 7, Day 1
Cycle 8, Day 1
Cycle 9, Day 1
Cycle 10, Day 1
Visit

FIG. 24A

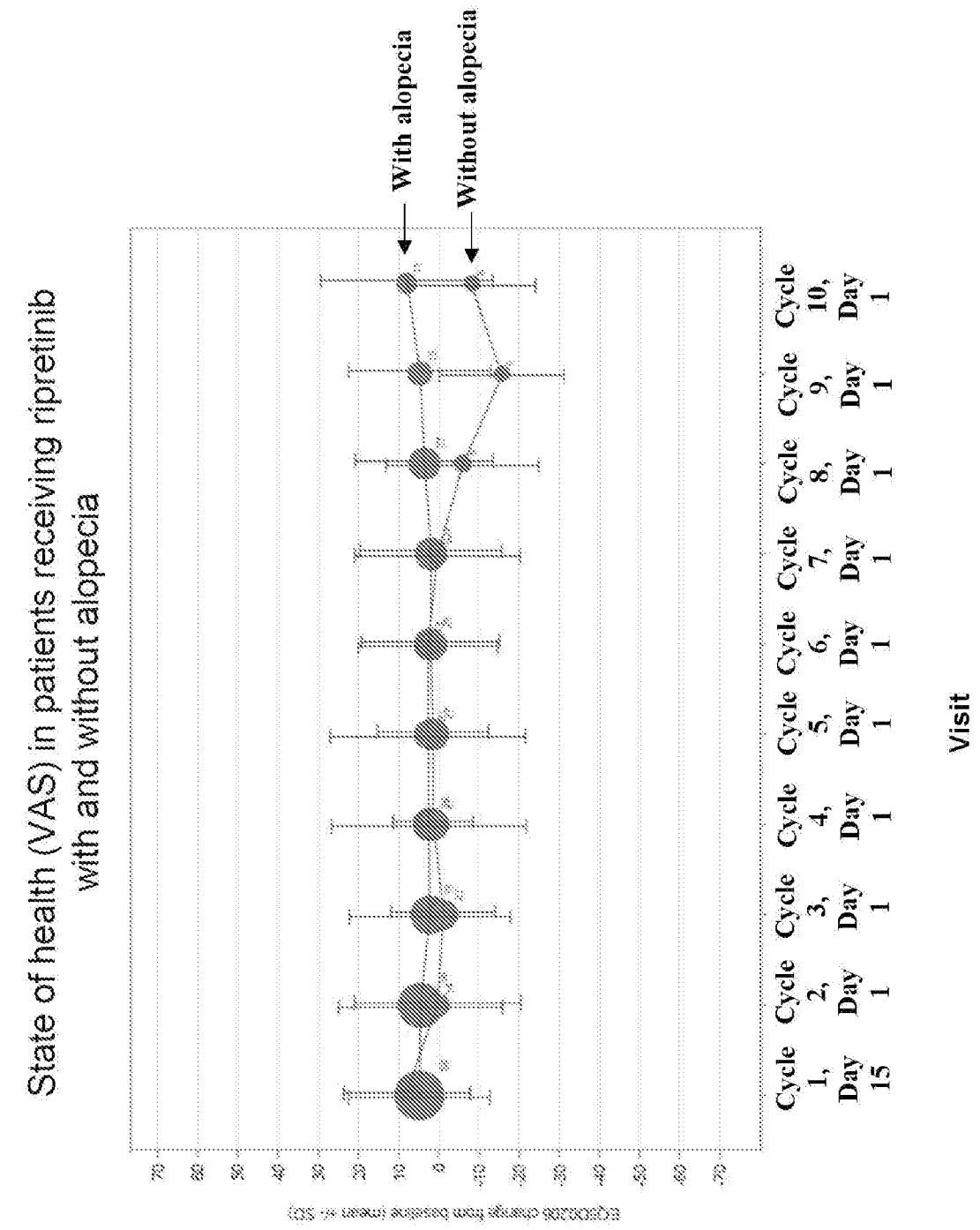

State of health (VAS) in patients receiving ripretinib with and without alopecia
With alopecia
Without alopecia
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
Cycle 1, Day 15
Cycle 2, Day 1
Cycle 3, Day 1
Cycle 4, Day 1
Cycle 5, Day 1
Cycle 6, Day 1
Cycle 7, Day 1
Cycle 8, Day 1
Cycle 9, Day 1
Cycle 10, Day 1
Visit

FIG. 24B

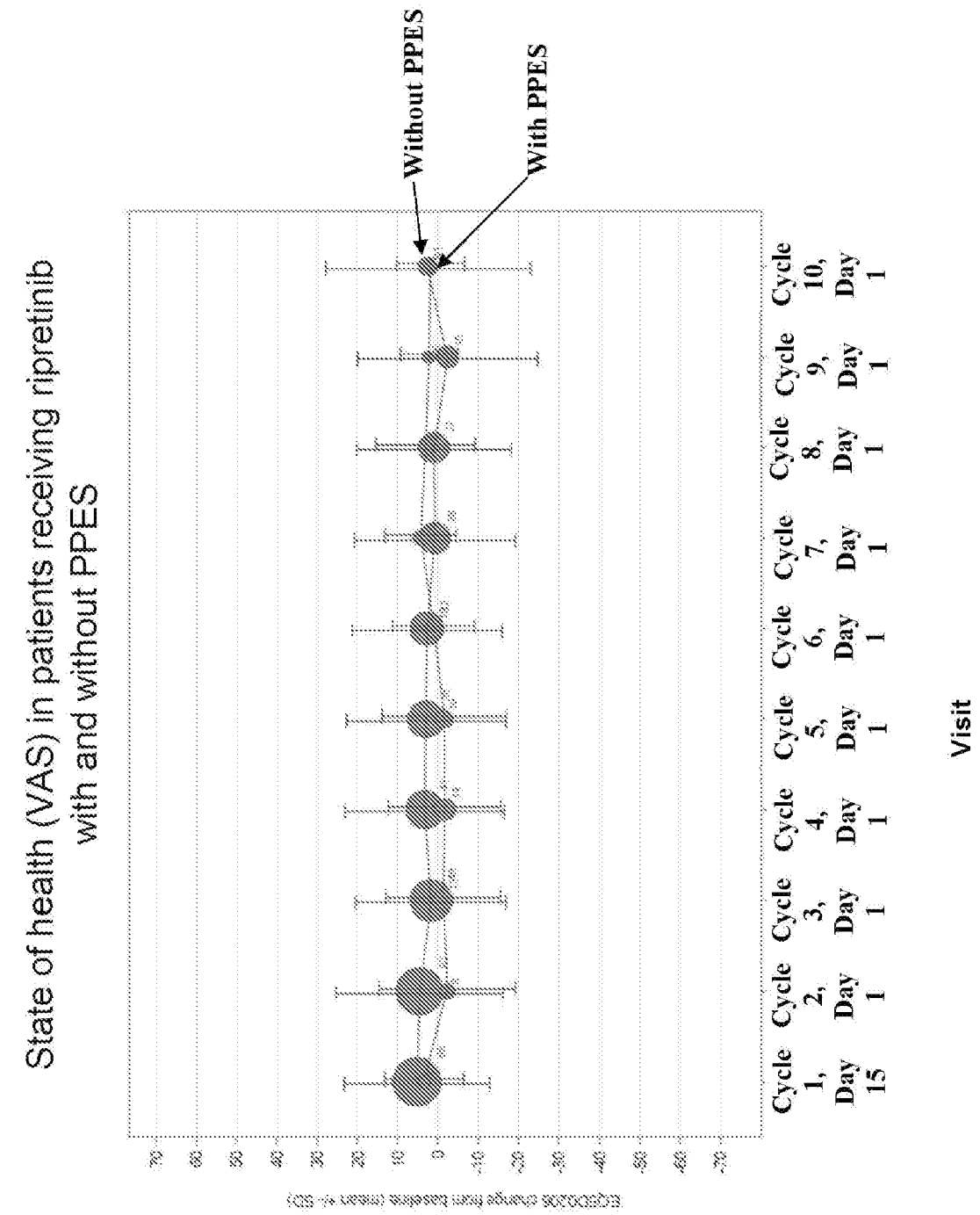

State of health (VAS) in patients receiving ripretinib with and without PPES
Without PPES
With PPES
EQ5D3L change from baseline (mean +/- SD)
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
Cycle 1, Day 15
Cycle 2, Day 1
Cycle 3, Day 1
Cycle 4, Day 1
Cycle 5, Day 1
Cycle 6, Day 1
Cycle 7, Day 1
Cycle 8, Day 1
Cycle 9, Day 1
Cycle 10, Day 1
Visit

FIG. 25A

PFS1

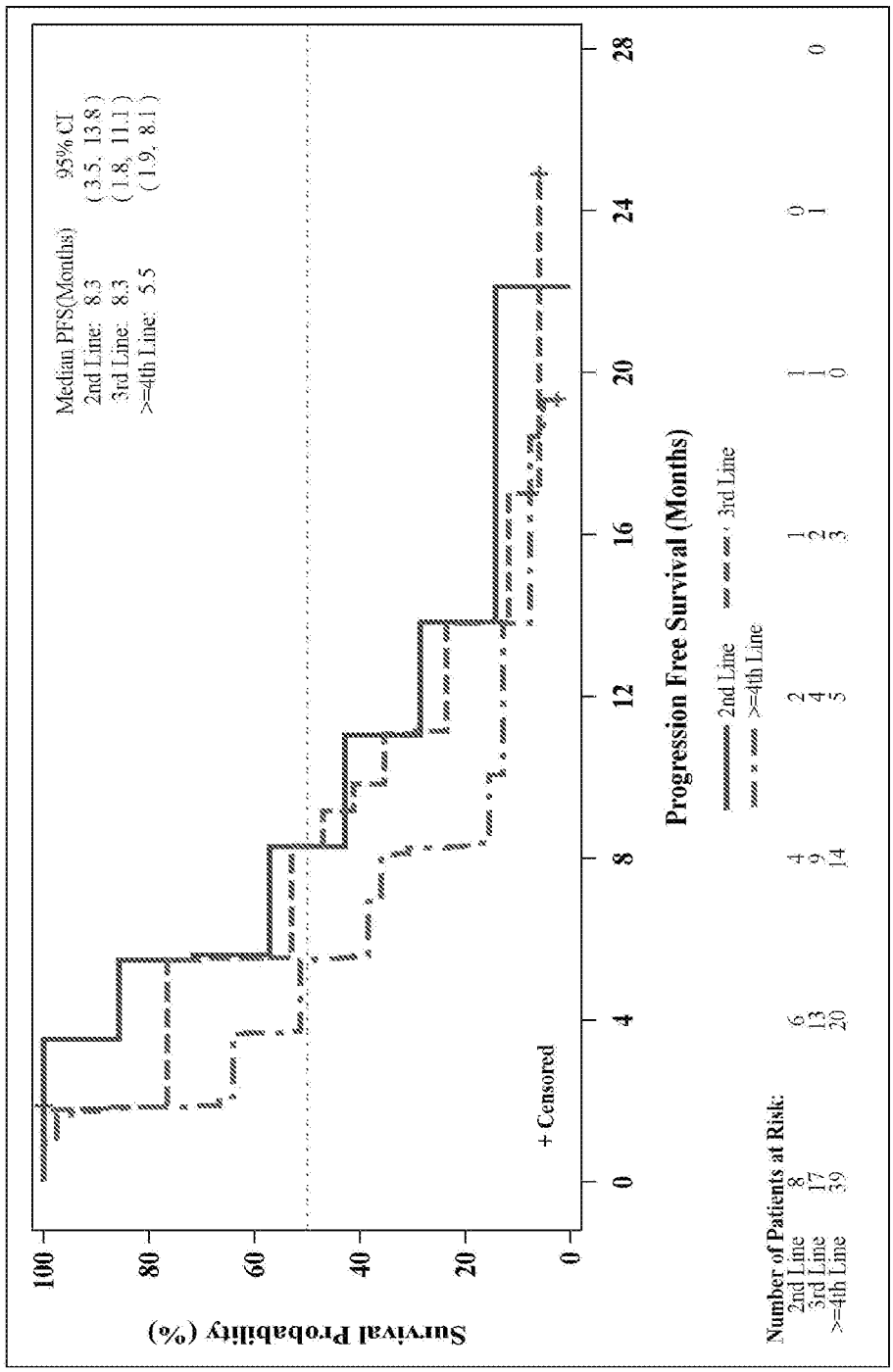

Median PFS(Months) 95% CI
2nd Line: 8.3 (3.5, 13.8)
3rd Line: 8.3 (1.8, 11.1)
>=4th Line: 5.5 (1.9, 8.1)
Survival Probability (%)
100
80
60
40
20
0
+ Censored
0 4 8 12 16 20 24 28
Progression Free Survival (Months)
2nd Line
3rd Line
>=4th Line
Number of Patients at Risk:
2nd Line 8 6 4 2 1 1 0 0
3rd Line 17 13 9 4 2 1 1
>=4th Line 39 20 14 5 3 0

FIG. 25B

PFS2

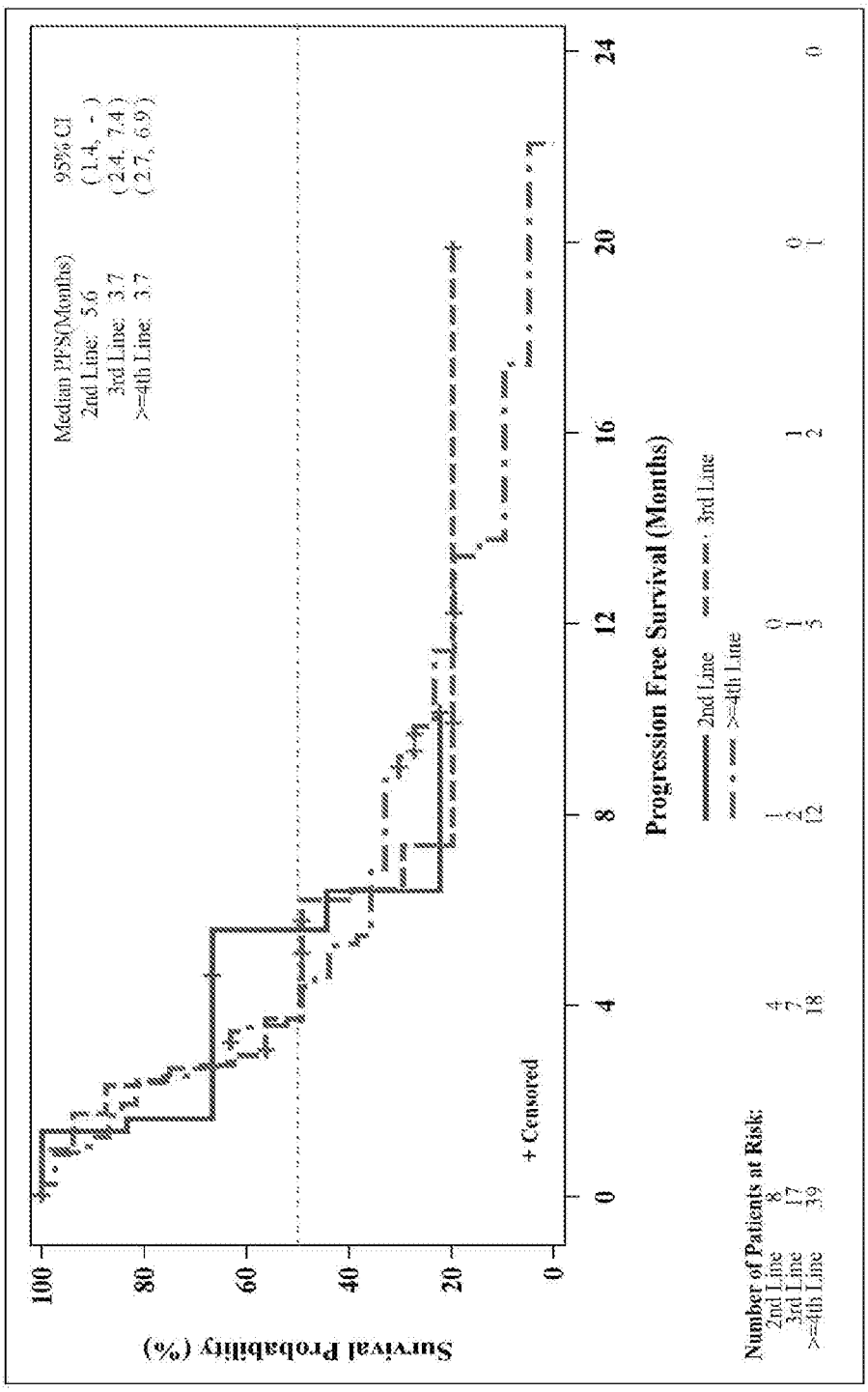
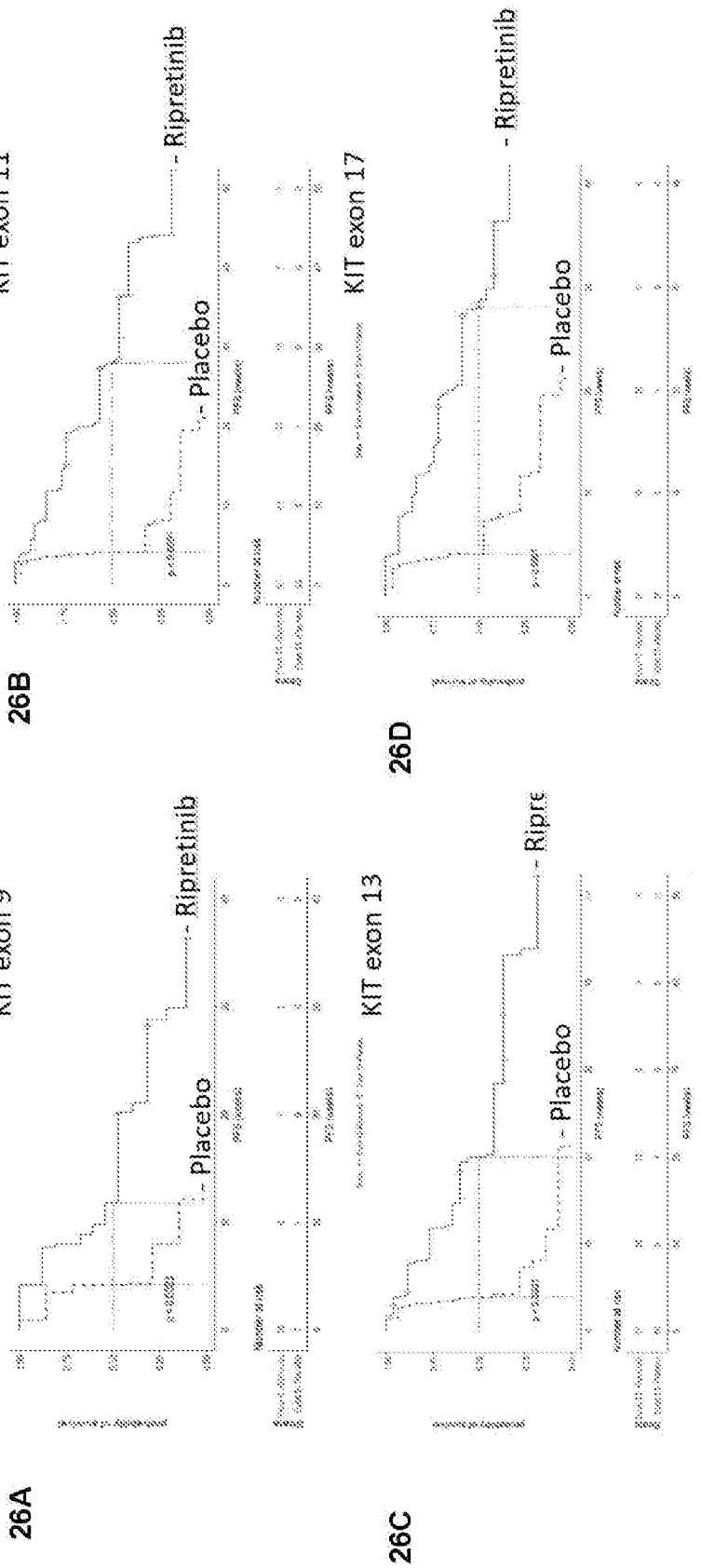
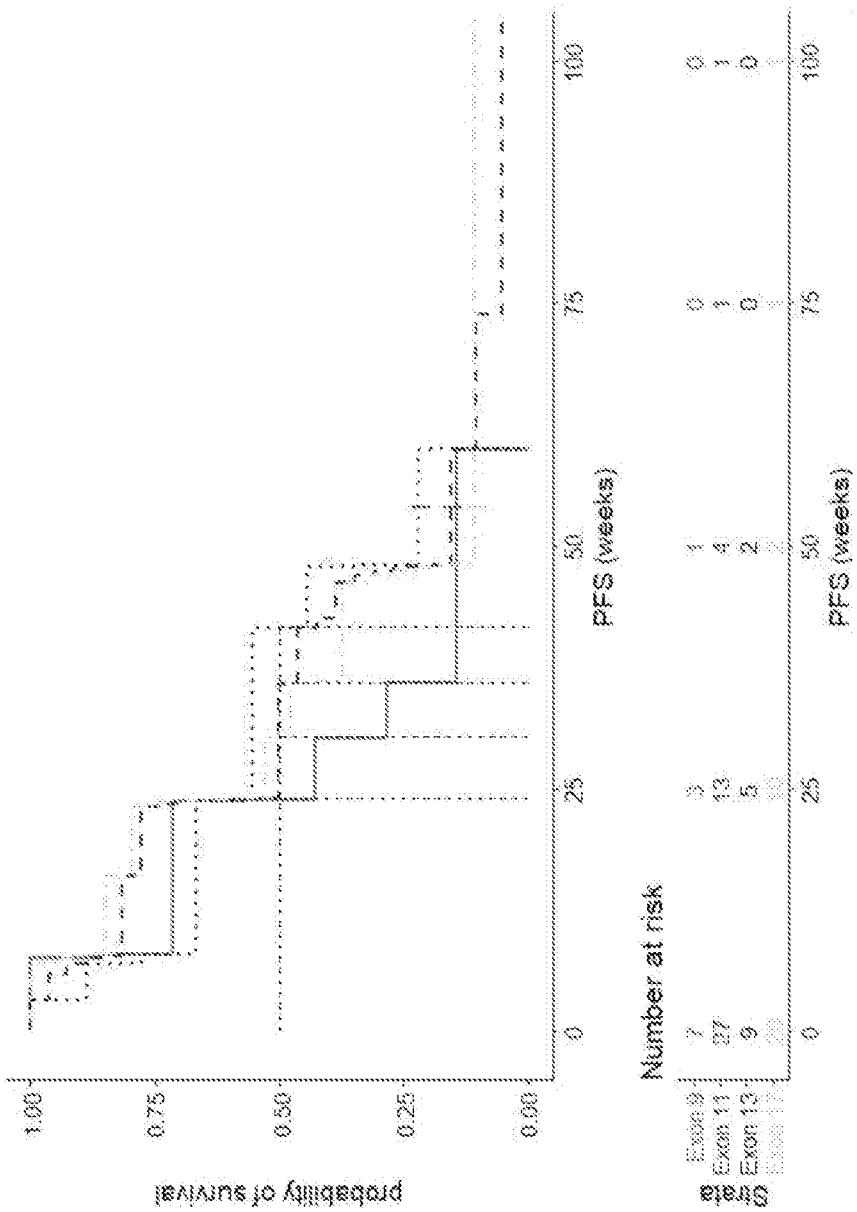

Survival Probability (%)
100
80
60
40
20
0
0
4
8
12
16
20
24
Progression Free Survival (Months)
+ Censored
Median PFS(Months)
2nd Line: 5.6
3rd Line: 3.7
>=4th Line: 3.7
95% CI
(1.4, -)
(2.4, 7.4)
(2.7, 6.9)
2nd Line
3rd Line
>=4th Line
Number of Patients at Risk:
2nd Line 8 4 1 0
3rd Line 17 7 2 1 0
>=4th Line 39 18 12 3 1 0

FIG. 26



26A 26B 26C 26D

FIG. 27


Strata Exon 9 Exon 11 Exon 13 Exon 17
probability of survival
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
PFS (weeks)
Number at risk
Strata
Exon 9 7 3 1 0 0
Exon 11 27 13 4 1 1
Exon 13 9 5 2 0 0
Exon 17 0 0 0 0 0
0
25
50
75
100
PFS (weeks)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/045876

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4375 A61K45/06 A61P35/00
ADD.

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)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S George ET AL: "INITIAL RESULTS OF PHASE 1 STUDY OF DCC-2618, A BROAD-SPECTRUM KIT AND PDGFRalpha INHIBITOR, IN PATIENTS (PTS) WITH GASTROINTESTINAL STROMAL TUMOR (GIST) BY NUMBER OF PRIOR REGIMENS", , 19 October 2018 (2018-10-19), XP055738640, Retrieved from the Internet: URL:https://www.deciphera.com/wp-content/uploads/2018/10/ESMO-2018-George-et-al.-for-submission-to-ESMO-final.pdf [retrieved on 2020-10-12] the whole document ----- -/--	1-79,84, 85

[X] Further documents are listed in the continuation of Box C.

[X] 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	Date of mailing of the international search report
13 October 2020	22/10/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Hoff, Philippe

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BRYAN D. SMITH ET AL: "Ripretinib (DCC-2618) Is a Switch Control Kinase Inhibitor of a Broad Spectrum of Oncogenic and Drug-Resistant KIT and PDGFRA Variants", CANCER CELL, vol. 35, no. 5, 1 May 2019 (2019-05-01), pages 738-751.e9, XP055738739, US ISSN: 1535-6108, DOI: 10.1016/j.ccell.2019.04.006 abstract page 746, left-hand column, last paragraph - right-hand column, paragraph 2 page 748, right-hand column, last paragraph - page 749, left-hand column, paragraph 1	1-79,84, 85
X	WO 2018/222173 A1 (DECIPHERA PHARMACEUTICALS INC [US]) 6 December 2018 (2018-12-06) page 7, paragraph 29; example 10	1-79,84, 85
X	Janku Filip Et Al.: "Abstract CT058: Ripretinib (DCC-2618) pharmacokinetics (PK) in a Phase I study in patients with gastrointestinal stromal tumors (GIST) and other advanced malignancies: A retrospective evaluation of the PK effects of proton pump inhibitors (PPIs) ¦ Cancer Research", , 1 July 2019 (2019-07-01), XP055738840, Retrieved from the Internet: URL:https://cancerres.aacrjournals.org/content/79/13_Supplement/CT058 [retrieved on 2020-10-12] the whole document	80-85
X	Deciphera Pharmaceuticals: "Deciphera Pharmaceuticals Initiates Pivotal Phase 3 Clinical Study of Ripretinib (DCC-2618) in Second-line Patients with Gastrointestinal Stromal Tumors ("INTRIGUE" Study)", , 20 December 2018 (2018-12-20), page 2018, XP055738716, Retrieved from the Internet: URL:https://investors.deciphera.com/node/7316/pdf [retrieved on 2020-10-12] the whole document	1-85

-/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Study Nct03353753: "Phase 3 Study of DCC-2618 vs Placebo in Advanced GIST Patients Who Have Been Treated With Prior Anticance (invictus)", , 21 November 2018 (2018-11-21), XP055738849, Retrieved from the Internet: URL:https://clinicaltrials.gov/ct2/history/NCT03353753?V_34=View#StudyPageTop [retrieved on 2020-10-12] the whole document	1-85
A	PIOTR RUTKOWSKI ET AL: "Gastrointestinal stromal tumours (GIST) - 2018", ONCOLOGY IN CLINICAL PRACTICE, vol. 14, no. 6, 15 March 2019 (2019-03-15), pages 399-407, XP055695536, ISSN: 2450-1654, DOI: 10.5603/OCP.2018.0053 whole document and more particularly Table 6	1-85
X,P	BLAY JEAN-YVES ET AL: "Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial", THE LANCET ONCOLOGY, ELSEVIER, AMSTERDAM, NL, vol. 21, no. 7, 5 June 2020 (2020-06-05), pages 923-934, XP086205221, ISSN: 1470-2045, DOI: 10.1016/S1470-2045(20)30168-6 [retrieved on 2020-06-05] the whole document	1-85
X,P	Deciphera Pharmaceuticals: "Deciphera Pharmaceuticals Announces Positive Top-line Results from INVICTUS Pivotal Phase 3 Clinical Study of Ripretinib in Patients with Advanced Gastrointestinal Stromal Tumors", , 13 August 2019 (2019-08-13), XP055738648, Retrieved from the Internet: URL:https://investors.deciphera.com/node/7706/pdf [retrieved on 2020-10-12] the whole document	1-85

-/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	Deciphera Pharmaceuticals: "HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use QINLOCK safely and effectively. See full prescribing information for", , 1 May 2020 (2020-05-01), XP055739004, Retrieved from the Internet: URL:https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213973s000lbl.pdf [retrieved on 2020-10-12] the whole document -----	1-85

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2020/045876

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018222173 A1	06-12-2018	AU 2017417160 A1	19-12-2019
		BR 112019025346 A2	30-06-2020
		CA 3065365 A1	06-12-2018
		CN 111328283 A	23-06-2020
		EA 201992805 A1	15-05-2020
		EP 3630110 A1	08-04-2020
		JP 2020528875 A	01-10-2020
		KR 20200008598 A	28-01-2020
		US 2020129489 A1	30-04-2020
		WO 2018222173 A1	06-12-2018