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Ripretinib in patients with advanced gastrointestinal stromal tumor (GIST): a randomized, double-blind, placebo-controlled phase 3 study (INVICTUS)

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Summary

Background: Resistance to approved inhibitors of KIT proto-oncogene, receptor tyrosine kinase (KIT) and platelet-derived growth factor receptor alpha (PDGFRA) remains a clinical challenge in advanced gastrointestinal stromal tumor (GIST). We compared the efficacy and safety of ripretinib, a switch-control tyrosine kinase inhibitor (TKI) active against a broad spectrum of *KIT* and *PDGFRA* mutations, with placebo in advanced GIST patients.

Methods: This phase 3, randomized, placebo-controlled, double-blind study enrolled adult patients in 12 countries at 29 unique sites. Patients aged ≥ 18 years with advanced GIST with progression on at least imatinib, sunitinib, and regorafenib or documented intolerance to any of these treatments despite dose modifications, and ECOG performance status (PS) of 0–2 were randomized (2:1) to either oral ripretinib 150 mg once daily (QD) or placebo. Randomization was done via an interactive response system using randomly permuted block sizes of six and stratified according to number of prior therapies (3 vs ≥ 4) and ECOG PS (0 vs 1 or 2). Patients, investigators, research staff, and sponsor study team were masked to a patient's treatment allocation until the blinded independent central review (BICR) showed progressive disease for the patient. The primary endpoint was progression-free survival (PFS) assessed by BICR. The primary analysis was done in the intent-to-treat population and safety was assessed in patients who received at least 1 dose of study drug. PFS results are described for the double-blind period. An open-label period followed disease progression by BICR in which patients randomized to ripretinib could discontinue ripretinib, continue at the same dose of ripretinib, or increase to 150 mg twice daily; patients randomized to placebo could discontinue the study or crossover to open-label ripretinib 150 mg QD. The INVICTUS study is registered with ClinicalTrials.gov (NCT03353753) and as a randomized controlled trial with the World Health Organization International Clinical Trials Registry Platform (EUCTR2017-002446-76-ES) and follow-up is continuing.

Findings: Between February 27, 2018 and November 16, 2018, 129 patients were randomized to ripretinib (n=85) or placebo (n=44). At data cutoff (May 31, 2019), there had been 88 PFS events, with 51 in the ripretinib group and 37 in the placebo group. In the double-blind period, ripretinib improved PFS over placebo (median 6·3 vs 1·0 months, respectively; HR 0·15, 95% CI 0·09–0·25; p<0·0001). PFS rates at 6 months were estimated to be 51% (95% CI 39·4–61·4) and 3·2% (95% CI 0·2–13·8) in the ripretinib and placebo groups, respectively. Ripretinib was associated with a favorable safety profile. The most common (>2%) grade 3 or 4 treatment-related TEAEs in the ripretinib group (n=85) included lipase increased (4 [4·7%]), hypertension (3 [3·5%]), fatigue (2 [2·4%]), and hypophosphatemia (2 [2·4%]); in the placebo group (n=43), anemia (3 [7·0%]), fatigue (1 [2·3%]), diarrhea (1 [2·3%]), decreased appetite (1 [2·3%]), dehydration (1 [2·3%]), hyperkalemia (1 [2·3%]), acute kidney injury (1 [2·3%]), and pulmonary edema (1 [2·3%]) were reported. Treatment-related serious adverse events (SAEs) were reported in 8 (9·4%) of 85 patients receiving ripretinib and 3 (7·0%) of 43 patients receiving placebo. Treatment-related deaths occurred in 1 patient in the placebo group (septic shock and pulmonary edema) and 1 patient in the ripretinib group (death, the patient died during sleep, the reason unknown).

Interpretation: Ripretinib significantly improved median PFS over placebo in advanced GIST resistant to currently approved treatments with a favorable safety profile. Ripretinib may represent a new standard of care for advanced GIST patients previously treated with ≥3 prior TKIs, a patient population with no currently approved broad-spectrum options.

Funding: Deciphera Pharmaceuticals, LLC.

Keywords: receptor tyrosine kinase; tyrosine kinase inhibitor; KIT; PDGFRA; DCC-2618; gastrointestinal stromal tumor; Phase 3 trial; targeted therapy; ripretinib; sarcoma

Research in context

Evidence before this study

Activating genomic alterations in *KIT proto-oncogene, receptor tyrosine kinase (KIT)* and/or *platelet-derived growth factor receptor alpha (PDGFRA)* drive cellular growth in gastrointestinal stromal tumors (GISTs). Standard treatment of advanced GIST includes tyrosine kinase inhibitors (TKIs) including imatinib as first-line therapy followed by sunitinib and regorafenib as second- and third-line therapies, respectively. Following treatment with imatinib, secondary resistance mutations in *KIT* and *PDGFRA* can arise and disrupt TKI binding and shift the kinase into an activated conformation. Our PubMed search for articles published between January 2005 and January 2020, using the terms “gastrointestinal stromal tumor” or “GIST” combined with “*KIT*” or “*PDGFRA*”, limited to English, provided data from studies showing that currently approved TKIs do not fully cover these secondary resistance mutations, leading to suboptimal efficacy results for progression-free survival and overall survival with second- and third-line therapies. Patients that have progressed on approved TKIs (imatinib, sunitinib, regorafenib, or avapritinib [the latter only approved for GIST with *PDGFRA* exon 18 mutations]) have no other approved treatment options, which creates a high unmet clinical need.

Ripretinib is a switch-control tyrosine kinase inhibitor designed to broadly inhibit *KIT* and *PDGFRA* kinase signaling through a dual mechanism of action that locks the kinase in the inactive state, preventing downstream signaling and cell proliferation.

Added value of this study

We report the efficacy and safety outcomes of the INVICTUS study (NCT03353753), a randomized, double-blind, placebo-controlled, phase 3 study of ripretinib as \geq fourth-line therapy in advanced GIST patients, a stage of the disease where no other approved broad-spectrum treatment option is

available. Our study results showed efficacy of ripretinib as \geq fourth-line therapy in advanced GIST with a statistically significant improvement in median progression-free survival (mPFS) compared with placebo. mPFS and ORR reported with ripretinib as \geq fourth-line therapy in GIST patients exceed that reported in the pivotal studies of second-line sunitinib and third-line regorafenib, as well as pazopanib and imatinib also tested in this setting. In this study, overall survival rate was more than doubled in patients receiving ripretinib compared with placebo in spite of crossover, an effect, that to our knowledge, has not been reported before in this patient population. However, the patients in our study were heavily pretreated and those receiving placebo experienced a rapid decline and approximately one-third of patients did not cross over to receive ripretinib, primarily due to death during the first cycle of placebo or disease progression. Patients receiving ripretinib reported stable overall health and physical and role functioning outcomes, whereas a clinically meaningful worsening of these outcomes was reported in the placebo group. These results highlight the need for new treatments in patients with advanced disease and may limit the future use of placebo controls in studies evaluating \geq fourth-line therapies in GIST. Importantly, as a new TKI with a novel mechanism of action, ripretinib was associated with a generally well-tolerated safety profile.

Implications of all the available evidence

Our study results showed clinical activity of ripretinib as \geq fourth-line therapy in advanced GIST patients, an area of unmet medical need with no currently approved broad-spectrum treatment options. Ripretinib, a TKI whose activity is not restricted to a specific GIST mutation, may represent a new standard of care for the general advanced GIST patient population who have received treatment with at least imatinib, sunitinib, and regorafenib.

Introduction

Gastrointestinal stromal tumors (GISTs) most often harbor oncogenic mutations in *KIT proto-oncogene, receptor tyrosine kinase (KIT)* or platelet-derived growth factor receptor alpha (*PDGFRA*).^{1,2} Standard treatment for patients with locally advanced metastatic GIST are KIT/PDGFRA-directed tyrosine kinase inhibitors (TKIs).³⁻⁵ First-line treatment with imatinib in advanced GIST results in response or tumor control in >80% of patients. However, imatinib does not provide a cure, as approximately 50% of patients experience progressive disease (PD) by 24 months and estimated 10-year progression-free survival (PFS) rates are 9.2% to 9.5%.^{3,6,7} Progressing metastases often harbor secondary mutations within the ATP-binding domain or activation loop of KIT, which represent the major mechanism of resistance to current TKIs.⁸⁻¹⁰ Both sunitinib and regorafenib, approved for second- and third-line treatment, respectively, inhibit some of these resistance mutations^{11,12}, but neither drug covers the full spectrum of possible mutations^{13,13}, yielding mPFS of 5.6 and 4.8 months, respectively.^{4,14-16} Avapritinib is only approved in GIST with *PDGFRA* exon 18 mutations which account for approximately 6% of the overall GIST population.¹⁷⁻¹⁹ No approved broad-spectrum treatment options are available beyond third-line and consequently, a high unmet need exists for treatments that are effective against secondary mutations leading to TKI-resistant GIST.

Ripretinib (DCC-2618) is a switch-control TKI that broadly inhibits KIT and PDGFRA kinase signaling through a dual mechanism of action.²⁰ Ripretinib is designed to precisely and durably bind to both the switch pocket and the activation loop to lock the kinase in the inactive state, preventing downstream signaling and cell proliferation. This dual mechanism of action provides broad inhibition of KIT and PDGFRA kinase activity, including *KIT/PDGFRA* wild-type as well as multiple primary and secondary mutations associated with drug resistant GIST. Amongst other kinases, ripretinib also inhibits platelet-derived growth factor receptor beta (PDGFRB), angiopoietin-1 receptor (TIE2), vascular endothelial

growth factor receptor 2 (VEGFR2), and serine/threonine-protein kinase B-raf (BRAF) based on *in vitro* enzyme assay data.²⁰

A first-in-human phase 1 study in GIST and other advanced solid tumors (NCT02571036) determined the recommended phase 2 dose of ripretinib as 150 mg once daily (QD) which was associated with a favorable tolerability profile and was active in advanced GIST refractory to multiple prior TKIs. Notably, doses of ripretinib 150 mg twice daily (BID) were tolerated without clinically meaningful dose-limiting side effects.²¹

Here we report the results of the phase 3 study, INVICTUS, which evaluated the safety and efficacy of ripretinib as \geq fourth-line therapy vs placebo in advanced GIST patients.

Methods

Study design and participants

INVICTUS is a phase 3, randomized, placebo-controlled, double-blind study conducted in 12 countries at 29 different medical centers (Appendix, pp 1).

Key inclusion criteria included patients \geq 18 years of age with a diagnosis of GIST with \geq 1 measurable lesion according to modified Response Evaluation Criteria in Solid Tumors version 1.1 (mRECIST v1.1). The mRECIST modifications followed those described by Demetri et al¹⁵ and included: a) lymph nodes were not chosen as target lesions; enlarged lymph nodes were followed as nontarget lesions; b) bone lesions were not chosen as target lesions; and c) positron emission tomography was not acceptable for radiologic evaluation. A progressively growing new tumor nodule within a preexisting tumor mass had to meet the following criteria to be considered as unequivocal evidence of progression according to the mRECIST v1.1: a) the lesion was at least 2 cm in size and definitively a new active GIST lesion (eg, enhancing with contrast or other criteria to rule out artifact) or b) the lesion had to be expanding on at

least 2 sequential imaging studies. Patients provided an archival tumor tissue sample if no anticancer therapy had been administered after sample collection; otherwise, a fresh tumor tissue sample was required before the first dose of study drug. Patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2, had adequate organ function and bone marrow reserve, and had progressed on at least imatinib, sunitinib, and regorafenib or had documented intolerance to any of these treatments despite dose modifications; progression or intolerance was determined by the investigator. Key exclusion criteria included anticancer therapy received within 14 days or 5 times the half-life (whichever was longer) before the first dose of study drug. After study commencement, our eligibility criteria was expanded to include patients with *KIT* or *PDGFRA* wild-type GIST. Complete inclusion and exclusion criteria are available in the study protocol. The study protocol is available online at <http://link.deciphera.com/INVsp>.

This study was conducted in accordance with the Declaration of Helsinki and the International council for Harmonisation Guidelines for Good Clinical Practice. Patients provided written informed consent to participate in this study. The protocol, protocol amendments, and informed-consent documents were approved by the institutional review board or ethics committee at each site before the start of the study.

Randomisation and masking

Enrolled patients were randomized 2:1 to either ripretinib or placebo. The 2:1 allocation ratio design was chosen to provide more exposure to ripretinib, which was more ethical in a placebo-controlled study, and provided a greater safety exposure group for ripretinib. Randomization was done via an interactive response technology (IRT) system using randomly permuted block sizes of six and stratified according to number of prior therapies (3 vs ≥ 4) and ECOG PS (0 vs 1 or 2); enrolled patients who had received ≥ 4 therapies were limited to <40%. Treatment allocation sequence was generated using a

computer system and the IRT concealed the allocation. Ripretinib tablets and matching placebo tablets were manufactured for Deciphera Pharmaceuticals, LLC. Patients, investigators, research staff, and the sponsor study team were masked to a patient's treatment allocation until the blinded independent central review (BICR) confirmed PD for the patient.

At the time of PD by BICR per mRECIST version 1.1, patients were unblinded and provided the option to continue or crossover to ripretinib open-label therapy.

Procedures

Patients were assigned to receive oral ripretinib 150 mg QD + best supportive care (BSC) or placebo + BSC daily for 28-day cycles (Appendix, pp 2). Patients were treated on their assigned group until they developed PD, experienced unacceptable toxicity, or withdrew consent. At the time of PD, those receiving ripretinib were permitted to dose escalate to ripretinib 150 mg BID, continue ripretinib 150 mg QD if demonstrating clinical benefit, or discontinue ripretinib; patients receiving placebo were permitted to cross over to ripretinib 150 mg QD or discontinue the study. Patients who crossed over to ripretinib from placebo and had further PD by investigator assessment were permitted to dose escalate to ripretinib 150 mg BID, continue ripretinib 150 mg QD if demonstrating clinical benefit, or discontinue study therapy. Study drug dose interruptions or modifications were permitted at the discretion of the investigator. In the double-blind period, the first dose reduction was to 100 mg QD and the second reduction was to 50 mg QD. Patients requiring a dose lower than 50 mg QD were discontinued from the study.

Tumor assessments using computed tomography scans (magnetic resonance imaging scans were permitted for patients allergic to contrast media) were made at screening, then every cycle through Cycle 4. After Cycle 4 (or if unblinded and found to be on ripretinib) assessments were performed every other cycle. If a patient crossed over from placebo to ripretinib, tumor assessments were performed

every other cycle, and at end of treatment. During the double-blind period, tumor assessments were based on BICR. An initial indication of a partial response (PR) or complete response (CR) based on BICR was confirmed ≥ 4 weeks later. During the open-label period, overall response based on investigator assessments was used to guide treatment options. An initial indication of a PR or CR based on investigator assessment was confirmed ≥ 4 weeks later. Patients were contacted every 3 months by phone call to collect long-term overall survival (OS) data.

Select quality of life (QOL) assessments that were pre-specified in the statistical analysis plan were made on Cycle 1 Day 1 (baseline), Cycle 1 Day 15, Cycle ≥ 2 Day 1, and at end of treatment using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item (EORTC QLQ-30) questionnaire (physical and role functioning questions only) and the EuroQol 5-Dimension 5-Level (EQ-5D-5L) EuroQol visual analogue scale (EQ-VAS). EORTC QLQ-30 physical function score was calculated from questions which asked if patients had trouble doing strenuous activities like carrying a heavy shopping bag or suitcase, trouble taking a short/long walk, if they needed to stay in bed or a chair during the day and if they needed help with eating, dressing, washing or using the toilet. The role function score was calculated from questions which asked if there were any limitations in daily activities or the pursuit of hobbies or other leisure activities. Patients could score each question on a scale of 1 to 4, where 1 means 'Not at all' and 4 means 'Very much'. The EQ-VAS asks patients to report their overall health on a vertical visual analogue scale, ranging from "Worst Possible" to "Best Possible" health. This score was converted to a number ranging from 0 to 100.

Safety and tolerability were assessed by: analysis of clinical laboratory tests, ECOG PS, changes in vital signs and weight at screening, Cycle 1 Day 1 (baseline), Cycle 1 Day 15, Cycle ≥ 2 Day 1, and at the end of treatment; 12-lead electrocardiogram (ECG) at screening, Cycle 1 Day 1 (baseline), Cycle ≥ 2 Day 1, and at the end of treatment; left ventricular ejection fraction based on echocardiogram/multigated acquisition (MUGA) scan and dermatologic examination by a consulting dermatologist at screening, Cycle 3 Day 1,

every third cycle thereafter, and at the end of treatment; physical examinations at screening and then driven by clinical findings and/or patient complaints; and continuous monitoring adverse events (AEs) from the signing of informed consent to safety follow up (30 days after last dose). Severity of AEs were rated by investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. Safety evaluations included the occurrence of treatment-related treatment-emergent adverse events (TEAEs) and treatment-related serious adverse events (SAEs), as well as treatment-related dose reductions, interruptions, or discontinuations of study drug.

Outcomes

The primary efficacy endpoint was PFS (interval between the date of randomization to the date of documented PD or death due to any cause) per mRECISTv1.1 as assessed by BICR and analyzed according to intent-to-treat (ITT). The key secondary efficacy endpoint was objective response rate (ORR; confirmed CR + PR as assessed by BICR).

Other secondary endpoints reported in this manuscript included OS (interval between the date of randomization and the date of death from any cause), time to progression (TTP) (interval between the date of randomization and the earliest documented evidence of PD based on independent radiologic review), time to best response, PFS by investigator assessment (interval between the date of randomization and the earliest documented evidence of PD based on investigator evaluation or death from any cause), QOL, and safety. Select QOL assessments included the prespecified physical and role functioning scale subsets of the EORTC-QLQ-30 and the EQ-VAS of the EQ-5D-5L. Secondary endpoints not reported in this manuscript included disease-control rate (DCR; CR+PR+stable disease [SD]) at 12 weeks, and pharmacokinetic/pharmacodynamic analyses of ripretinib. DCR was not reported as there is no universally accepted definition and it would not provide additional information beyond the other

reported endpoints. Pharmacokinetic/pharmacodynamic results would be better served in a separate publication.

Results of study endpoints are described herein for the double-blind period with the exception of OS and disposition, which reflect data from both the double-blinded and open-label periods. Subgroup analyses of the outcomes in the open-label period for patients that dose-escalated ripretinib, crossed over to ripretinib, or continued on ripretinib following PD will be reported in a separate manuscript due to the differing natures of the double-blind and open-label periods. The decision to report the double-blind and open-label periods separately was made post-hoc.

Statistical analysis

A sample size of 120 patients (ripretinib, n=80; placebo, n=40), with an assumed 15% patient dropout, and a 2-sided 0.05 significance level in testing the hypothesis of no difference between ripretinib and placebo, was expected to provide >90% power to detect a difference in PFS between ripretinib and placebo. This assumed an mPFS of 4.5 months for ripretinib and 1 month for placebo and ~80% power to detect a 20% difference in ORR, with the assumption of an ORR for ripretinib of 22% and 2% for placebo. To control family-wise type I error, the hypothesis tests for treatment differences were performed at a 2-sided 0.05 level of significance sequentially in the following order: PFS, ORR, OS, QOL as determined by changes from baseline to Cycle 2 Day 1 in physical and role functioning scale subsets of the EORTC-QLQ-C30 (each at 0.025 level of significance). Once a hypothesis test was nonsignificant at $\alpha=0.05$ level, the remaining analyses were reported as descriptive.

Time-to-event data were summarized using the Kaplan-Meier method and associated 2-sided 95% confidence intervals (CI). A 2-sided stratified log-rank test (0.05 significance level) was used to evaluate treatment difference. Hazard ratio (HR) was obtained from a Cox regression model, and the 95% CI was obtained using the Wald method. The proportional hazard assumption was examined by visual

inspection of the log (-log) plot (Appendix, pp 3). ORR was analyzed by an unstratified 2-sided Fisher's Exact test (0.05 significance level) to evaluate treatment difference, and the 95% CI of treatment difference was calculated using the Newcombe method. Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc).

OS and PFS by investigator assessment were evaluated using a manner similar to the primary endpoint. Descriptive statistics were used to summarize safety data and QOL variables.

The ITT population, defined as all patients who signed the informed consent and were randomized, was used for all efficacy analysis. The safety population, defined as all patients who received at least one dose of study drug, was used for all safety analysis. An independent data monitoring committee was used to review safety data periodically throughout the course of this study.

Statistical methods, including methods used to adjust for missing data, are described further in the study protocol.

This study is registered as a randomized clinical trial with ClinicalTrials.gov (NCT03353753) and as a randomized controlled trial with the World Health Organization International Clinical Trials Registry Platform (EUCTR2017-002446-76-ES) and follow-up is continuing.

Role of the funding source

This study was designed by the sponsor, Deciphera Pharmaceuticals, LLC, with input from the investigators. Data collected by the investigators were analyzed by Deciphera Pharmaceuticals, LLC, and interpreted jointly with all the authors. The authors had access to the data to verify the completeness and accuracy of the data reported and for the adherence of the study to the protocol and the statistical analysis plan. The manuscript was written by the authors with medical writing assistance provided by

the sponsor. The corresponding author had access to all of the data presented in this manuscript and the final responsibility to submit for publication.

Results

Between February 27, 2018 and November 16, 2018, 154 patients were screened for eligibility and 25 were deemed ineligible (n=20, did not meet inclusion/exclusion criteria; n=3, withdrew consent; n=2, other reasons). A total of 129 eligible and assessable patients (ripretinib, n=85; placebo, n=44) underwent randomization at 29 centers and were included in the ITT analyses (figure 1). One patient in the placebo group did not receive treatment but was included in the ITT analyses, but not the safety analyses (ripretinib, n=85; placebo, n=43). Baseline factors were generally well balanced and are provided in table 1. At data cutoff (May 31, 2019), the median follow-up time in the double-blind period was 6.3 months (IQR 5.0) for the ripretinib group and 1.6 months (IQR 1.5) for the placebo group. The median relative dose intensity in the double-blind period was 100% (IQR 1.9) for the ripretinib group and 97% (IQR 13.5) for the placebo group. Fifteen patients did not cross over to ripretinib (figure 1) primarily because of death during the first cycle of placebo (n=4), PD by BICR (n=2; 1 no longer able to receive oral medications; 1 transitioned to hospice), clinical progression without PD identified by BICR (n=3; per protocol, patients without BICR PD were unable to cross over), and adverse event (n=2) (figure 1).

Ripretinib significantly improved mPFS compared with placebo, with an mPFS of 6.3 months vs 1 month, respectively (HR 0.15, 95% CI 0.09–0.25; $p < 0.0001$) (figure 2A). Events were reported in 51 (60.0%) of 85 patients receiving ripretinib and 37 (84.%) of 44 patients receiving placebo. Treatment with ripretinib reduced the risk of PD or death by 85% compared with placebo during the double-blind period. PFS rates at 6 months were estimated to be 51% (95% CI 39.4–61.4) for ripretinib and 3.2% (95% CI 0.2–

13.8) for placebo. PFS analyses consistently favored ripretinib across assessed patient subgroups (Appendix, pp 3).

The confirmed ORR assessed by BICR was 9.4% (8 of 85 patients, all PRs; 95% CI 4.2–17.7) for ripretinib vs 0.0% (0 of 44 patients; 95% CI 0.0–8.0) for placebo ($p=0.050$; table 2). Stable disease rates for 12 weeks and PD rates were increased with ripretinib over placebo (table 2). As of data cutoff, the median duration of response had not yet been reached, and only 1 of 8 responders had progressed (figure 3). Median time to best response was 1.9 (IQR 1.8) months. Estimate of median TTP in the ripretinib group was 6.4 (95% CI 4.6–8.4) months and 1.0 (95% CI 0.9–1.7) months in the placebo group.

Ripretinib OS was increased compared with placebo with a median OS of 15.1 vs 6.6 months, respectively (HR 0.36, 95% CI 0.21–0.62; figure 2B) inclusive of the double-blind and open-label periods. Events were reported in 26 (30.6%) of 85 patients receiving ripretinib and 26 (59.1%) of 44 patients receiving placebo. At 6 months, the estimated OS rate was 84.3% (95% CI 74.5–90.6) for ripretinib and 55.9% (95% CI 39.9–69.2) for placebo. At 12 months, the estimated OS rate remained higher for ripretinib (65.4% [95% CI 51.6–76.1]) compared with placebo (25.9% [95% CI 7.2–49.9]). Owing to hierarchical testing procedures of the endpoints, OS could not be formally tested for statistical significance. An OS benefit was also seen in patients who crossed over to ripretinib from placebo (Appendix, pp 4).

Investigator assessment of PFS showed a benefit of ripretinib compared with placebo (mPFS 4.7 vs 1 months; HR 0.19, 95% CI 0.12–0.32). The overall discordance rate was 20.2% (26 of 129 patients): 7% (9 of 129 patients) discordance where the investigator assessed PD and BICR assessed non-PD, and 13.2% (17 of 129 patients) discordance where the investigator assessed non-PD and BICR assess PD.

Role and physical functioning, as assessed by EORTC-QLQ-30, from baseline to Cycle 2 Day 1, remained stable in the ripretinib group with adjusted mean scores of 3.5 (95% CI -3.4–10.5) and 1.6 (95% CI -2.5–

5·7), respectively, compared with a decrease with placebo of 17·1 (95% CI -27·0—7·1) and 8·9 (95% CI -14·8—3·0), respectively (table 2). The minimally important clinical difference according to two studies in gastrointestinal malignancies were defined as a >10% mean score change²² or a 5-point change.²³ Overall health, as assessed by EQ-VAS, from baseline to Cycle 2 Day 1, also remained stable with ripretinib with adjusted mean scores of 3·7 (95% CI -1·1—8·6) compared with a decrease with placebo of 8·9 (95% CI -15·9—1·9). Using either of these criteria, our results demonstrated a clinically relevant difference between ripretinib and placebo. Owing to hierarchical testing procedures of the endpoints, the QOL endpoint could not be formally tested for statistical significance.

Treatment-related TEAEs are summarized in table 3. The most common (≥20% of patients on ripretinib) treatment-related TEAEs in patients receiving ripretinib were alopecia, myalgia, nausea, fatigue, palmar-plantar erythrodysesthesia (PPES; hand-foot syndrome), and diarrhea. PPES occurred exclusively in ripretinib-treated patients and all events were grade 1 (11 [12·9%] of 85 patients) or 2 (7 [8·2%] of 85 patients). The most common (>2%) grade 3 or 4 treatment-related TEAEs in the ripretinib group included lipase increased, hypertension, fatigue, and hypophosphatemia. In the placebo group, grade 3 or 4 treatment-related TEAEs were anemia, fatigue, diarrhea, decreased appetite, dehydration, hyperkalemia, acute kidney injury, and pulmonary edema (table 3). One grade 5 event was reported in both treatment groups. Treatment-related SAEs were reported in 8 (9·4%) of 85 patients receiving ripretinib and 3 (7·0%) of 43 patients receiving placebo. Among the 8 patients in the ripretinib group, there was 1 report of each of the following: anemia, cardiac failure, death, dyspnea, fecaloma, gastroesophageal reflux disease, hyperkalemia, hypophosphatemia, nausea, and upper gastrointestinal hemorrhage. Among the 3 patients in the placebo group, there was 1 report of each of the following: hyperkalemia, dehydration, pulmonary edema, and septic shock.

Treatment-related TEAEs leading to a dose reduction were reported in 5 (5·9%) of 85 patients and 1 (2·3%) of 43 patients on ripretinib and placebo, respectively (Appendix, pp 1). Treatment-related TEAEs

leading to study treatment discontinuation in the ripretinib group were reported in 4 (4.7%) of 85 patients (n=1, cardiac failure; n=1, death; n=1, general physical health deterioration; n=1, PPES) and 1 (2.3%) of 43 patients (fatigue) receiving placebo (Appendix, pp 1). Overall deaths were reported in 12 (14.1%) of 85 patients (n=11, disease progression; n=1, death, unknown reason) in the ripretinib group and 13 (30.2%) of 43 patients (n=11, disease progression; n=2, adverse event [n=1, acute kidney injury; n=1, septic shock) in the placebo group. Treatment-related deaths were similar between the 2 groups with 1 death in the placebo group (septic shock and pulmonary edema) and 1 death in the ripretinib group (death, the patient died during sleep, the reason unknown).

Discussion

Results of the INVICTUS study showed that ripretinib as ≥fourth-line therapy in advanced GIST significantly improved mPFS and reduced the risk of PD as assessed by BICR or death over placebo by 85% (HR 0.15, 95% CI 0.09–0.25; $p < 0.0001$). Patients were stratified by ECOG PS and prior lines of therapy, known prognostic variables. Although the ORR was not statistically significant, the median OS was increased with ripretinib, which is clinically relevant in this patient population. Furthermore, ripretinib had a favorable safety profile and showed clinically meaningful maintenance of role and physical function and health status when compared with placebo.

The mPFS for ripretinib was 6.3 months and the ORR was 9.4%. Historically, the respective mPFS and ORR were 5.6 months and 6.8% for second-line sunitinib, 4.8 months and 4.5% for third-line regorafenib, 1.8 months and 0%, for ≥third-line imatinib (rechallenge after failure of prior imatinib), and 3.4 months and 0% for ≥third-line pazopanib.^{4,15,16,24,25} Responses in patients treated with ripretinib were durable, with the median duration of response not yet reached; only 1 of 8 responders had PD as of data cutoff. Additionally, more patients receiving ripretinib had SD for 12 weeks and less PD than patients on placebo. The large percentage of patients receiving ripretinib with SD is notable as the absence of

progression is considered an important marker of therapeutic benefit in GIST.^{26,27} Unlike many other advanced solid tumors, the absence of progression (whether a PR or SD) is predictive of PFS and OS benefit in advanced GIST patients.²⁷ ORR for ripretinib did not meet our predefined assumption of 22% . This estimated assumption was for the purpose of a power calculation in the study design. Our results, despite not meeting the predefined ORR assumption, support that treatment of advanced GIST is more about control of the disease rather than response according to mRECIST v1.1 criteria.

In oncology clinical trials, OS is considered to be the gold standard for showing clinical benefit, as it provides a direct benefit to patients and is not subject to investigator interpretation. Ripretinib increased the median OS over placebo in the double-blind and open-label periods. Notably, 29 (66%) of 44 patients in the placebo group crossed over to ripretinib at time of progression, and thus the improvement in OS is potentially underestimated (Appendix, pp 4). Patients (n=15 of 44) did not cross over to ripretinib primarily because of death and PD (figure 1). In contrast to our results, minimal to no median OS benefit has been observed with sunitinib (17.0 vs 14.9 months, respectively; p=0.161) or regorafenib (17.4 vs 17.4 months, respectively; p=0.572) as second- or third-line therapies compared with placebo in the respective pivotal trials in which crossover also occurred.^{4,5} The rapid clinical decline in patients receiving placebo, which may have prevented approximately one-third of patients from crossing over to ripretinib, highlights the need for new treatments and may ultimately limit the use of placebo controls in future studies evaluating ≥fourth-line therapies in GIST.

In our study, a specific mutational status was not required for enrollment. The frequency of primary mutations and *KIT/PDGFR*A wild-type, excluding the 17 patients for whom mutational status was not available or not done, was consistent with those reported in the literature with the exception of a slight increase in primary exon 9 mutations and a lower frequency of *PDGFR*A mutations (table 1).^{18,28} Although the prevalence of secondary mutations is not reported here, secondary resistance mutations in GIST usually occur in the kinase switch pocket (encoded by *KIT* exons 13 and 14 or *PDGFR*A exons 14

and 15) or in the activation loop switch (encoded by *KIT* exons 17 and 18 and *PDGFRA* exon 18) and lead to dysregulated switch function and loss of physiologic conformational control.^{10,20,29,30} In contrast to sunitinib and regorafenib, which are selectively active for secondary *KIT* exon 13 and 14 mutations or a subset of secondary *KIT* exon 17 mutations respectively, ripretinib demonstrated broad activity preclinically.^{8,12,15,31} In this study, which included an unselected population of advanced GIST patients, including 10 (8%) of 129 patients with *KIT/PDGFRA* wild-type mutational status, ripretinib significantly improved mPFS and showed broad activity in ≥fourth-line treatment of GIST, in which a variety of secondary mutations would be anticipated in the disease of individual patients.

The safety profile of ripretinib was favorable. One of the most common treatment-related TEAEs reported with ripretinib was alopecia and was primarily grade 1 (grade 1, 32 [37.6%] of 85 patients; grade 2, 10 [11.8%] of 85 patients); 1 patient interrupted treatment due to alopecia. Compared with the overall treatment-related alopecia incidence in 42 (49.4%) of 85 patients, alopecia with ripretinib was reported more in female patients (24 [63.2%] of 38 patients), perhaps due to reporting bias, although this was not assessed. Although alopecia in advanced GIST patients has also been reported with imatinib and regorafenib, the incidence in our study was higher compared with those agents.^{15,32} The pathogenesis of alopecia with ripretinib is unclear but may be due to differences in the target kinases inhibited, the effect on associated downstream pathways, and the role targeted molecules may play in hair follicle biology.³³⁻³⁶ *In vitro*, ripretinib inhibited kinases (eg, *KIT*; *PDGFRA*; *VEGFR2*; *BRAF*) that have been associated with alopecia.^{20,34,36} Similarly, treatment-related PPES was reported in 18 (21.2%) of 85 patients receiving ripretinib but was limited to grade 1 (11 [12.9%] of 85 patients) and 2 (7 [8.2%] of 85 patients). For reference, PPES in advanced GIST patients has also been reported with sunitinib (19 [9%] of 202 patients, grade 1 or 2; 9 [4%] of 202 patients, grade 3) and regorafenib (74 [56.1%] of 132 patients, any grade; 26 [19.7%] of 132 patients, grade 3).^{14,15} PPES was managed with routine care of the

affected skin area, with 2 patients requiring study treatment interruption and 1 patient discontinuing study treatment because of treatment-related PPES.

Limitations of our study included the small sample size which made stratifying patients by more baseline parameters difficult. Our study also allowed crossover from placebo to ripretinib at PD which prevented a pure placebo group in the OS assessment. However, the design of our study afforded certain strengths including the placebo group which permitted an unbiased assessment of the effects of ripretinib in terms of PFS and safety. The 2:1 randomization design used was also more ethical by reducing patient exposure to placebo.

In conclusion, results from the INVICTUS study showed the efficacy and safety of ripretinib in advanced GIST patients as \geq fourth-line treatment. Ripretinib represents a potential new standard of care in patients with advanced GIST and is being evaluated in an ongoing phase 3 study (intrigue) in second-line compared with sunitinib (NCT03673501).

Figure Legends

Figure 1: Trial profile

Data reported as of the cutoff date for the primary completion date (May 31, 2019) are shown. At disease progression by BICR during the double-blind period, patients randomized to receive ripretinib were allowed to dose escalate to 150 mg twice daily (BID), continue on ripretinib 150 mg daily QD, or discontinue ripretinib; patients receiving placebo were allowed to cross over to ripretinib 150 mg QD or discontinue the study. Patients who crossed over to ripretinib from placebo and had further disease progression by investigator assessment were permitted to dose escalate to ripretinib 150 mg BID, continue on ripretinib 150 mg QD, or discontinue ripretinib. ITT, intent-to-treat.

Figure 2A-B: Efficacy of ripretinib compared with placebo as fourth-line treatment in advanced GIST patients

Panel A shows the Kaplan-Meier estimates of PFS by BICR among patients receiving ripretinib or placebo in the double-blind part of the study. Panel B shows Kaplan-Meier estimates of OS in patients receiving ripretinib or placebo in the double-blind and open-label periods. Owing to hierarchical testing procedures of the endpoints, the OS endpoint could not be formally tested because the ORR was not statistically significant.

Figure 3: Response with ripretinib

The time to response and duration of response of the 8 patients who responded. As of data cutoff, the median duration of response has not been reached and only 1 of 8 responders had disease progression.

*Patient responding at time of data cutoff.

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Contributors

J-YB, CS, MCH, JZ, SB, HG, PS, RLJ, SA, GD, PC, PR, SG, and MvM were involved in data collection and contributed to the provision of study materials and patients. KS performed the statistical analysis. JYB and MvM participated in the writing of the study protocol. All authors contributed to data interpretation, critical review, editing and revision of manuscript drafts, and approval of the final version.

Declaration of interests

J-YB reports grants and personal fees from Deciphera Pharmaceuticals, LLC, during the conduct of the study; grants and personal fees from Novartis, Pfizer, Bayer, and grants from Blueprint Medicines, outside the submitted work. CS reports grants (laboratory research) and personal fees (advisory board) from Deciphera Pharmaceuticals, LLC, during the conduct of the study; grants (laboratory research grant), personal fees (lectures), and non-financial support (travel grant) from Bayer AG, grants (laboratory research grant) and non-financial support (travel grant) from Pfizer Inc, personal fees (lecture; advisory role) from Blueprint medicines, non-financial support (travel grants) from Pharmamar, Novartis, and Lilly, outside the submitted work. MCH reports grants and personal fees from Deciphera Pharmaceuticals, LLC, during the conduct of the study; personal fees (consulting) and other (equity interest) from MolecularMD, personal fees from Novartis (consulting, expert testimony), and grants and

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Link to protocol: will be provided if article is accepted for publication.

Data sharing statement:

Question	Author's Response
<p>Will the data collected for your study be made available to others?</p>	<p>Deciphera will share the redacted INVICTUS study protocol in the publication supplement. Qualified scientific and medical researchers may make requests for individual participant data that underlie the results (text, tables, figures, and appendices) reported in this article, after de-identification, at info@deciphera.com.</p> <p>Methodologically sound proposals for such data will be evaluated and approved by Deciphera in its sole discretion. All approved researchers must sign a data access agreement prior to accessing the data. Data will be available as soon as possible but no later than within 1 year of the acceptance of the article for publication, and for 3 years croing article publication.</p>

	Deciphera will not share identified participant data or a data dictionary.
Which data in particular will be shared?	See above
What other documents will be available?	See above
When will the data be available (start and end dates)?	See above
With whom?	See above
For what types of analyses?	See above
By what mechanism will data be made available?	See above

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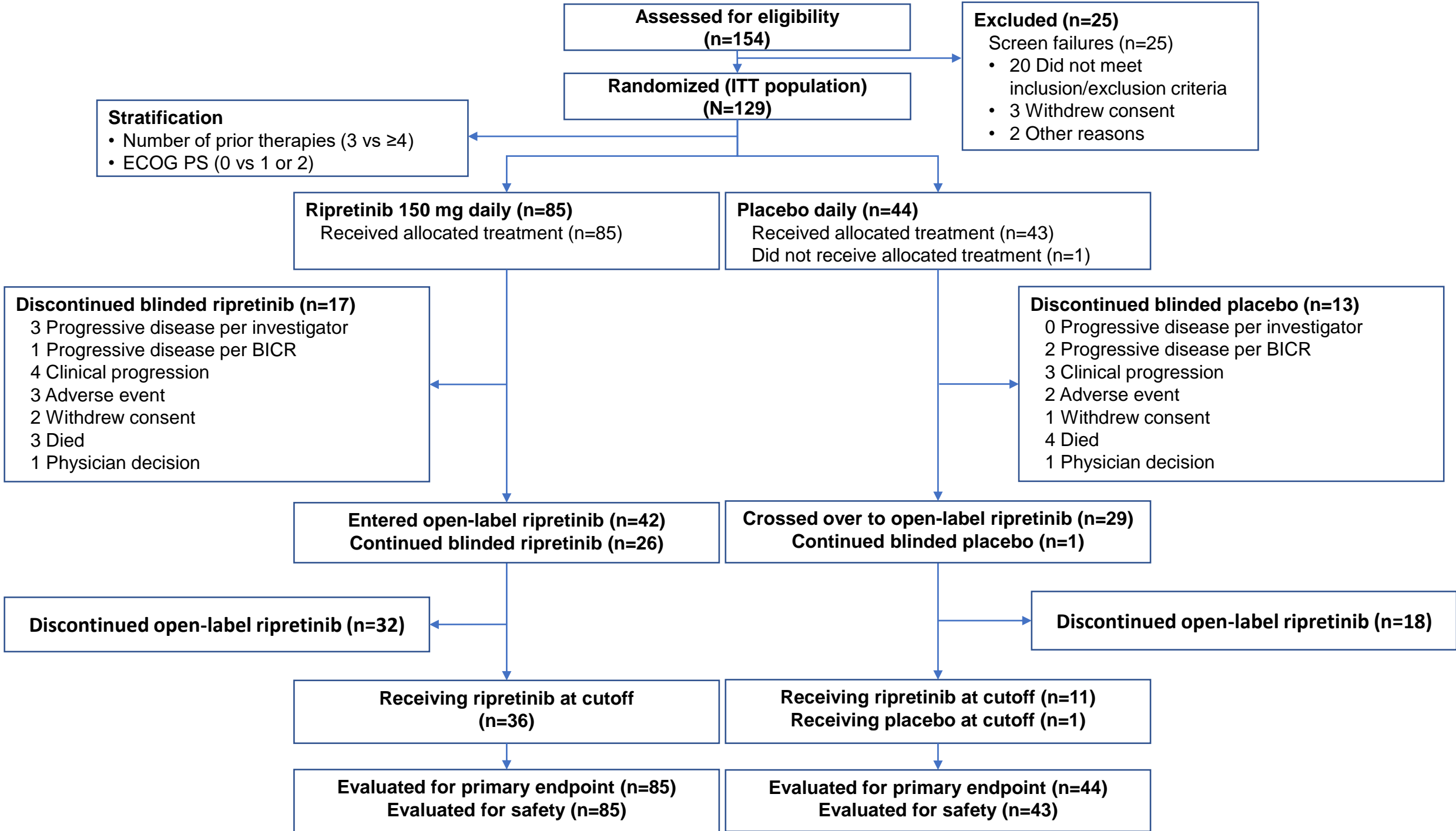
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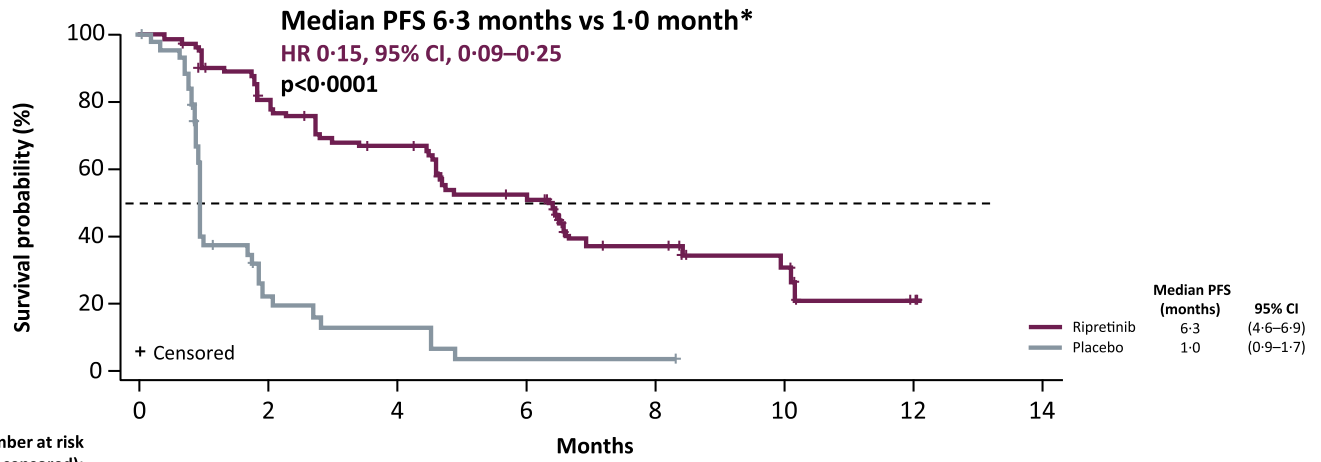
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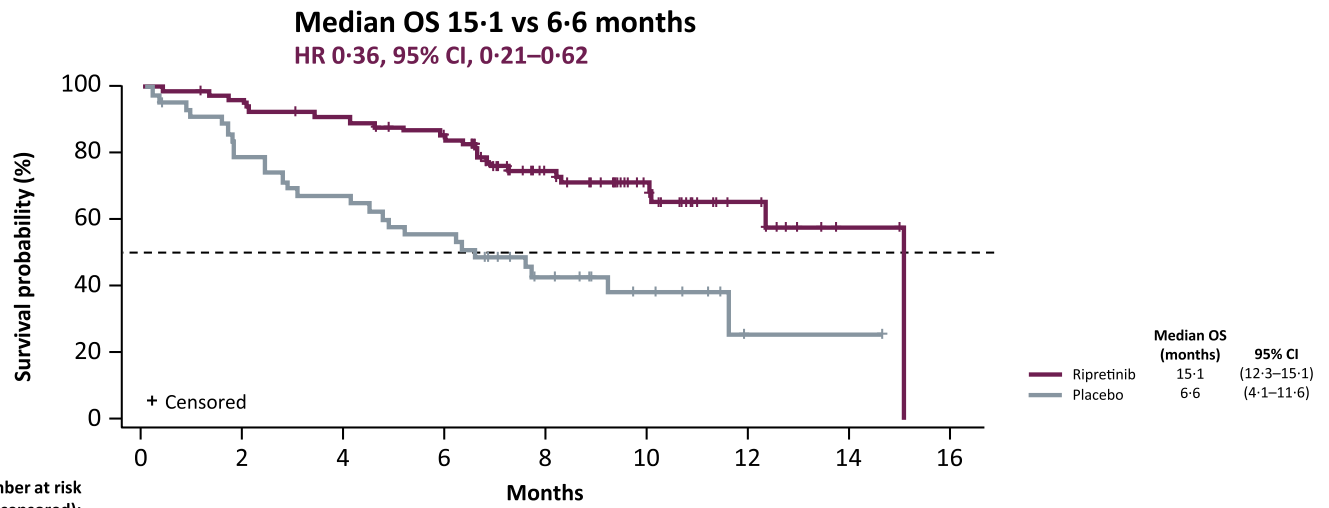


Number at risk (number censored):

	0	2	4	6	8	10	12	14
Ripretinib 150 mg QD	85 (0)	64 (4)	52 (6)	37 (9)	18 (20)	8 (28)	1 (33)	0 (34)
Placebo	44 (0)	7 (6)	4 (6)	1 (6)	1 (6)	0 (7)	(7)	(7)

*Double-blind period.

A.



Number at risk (number censored):

	0	2	4	6	8	10	12	14	16
Ripretinib	85 (0)	81 (1)	76 (2)	67 (5)	42 (23)	24 (38)	10 (51)	2 (58)	0 (59)
Placebo	44 (0)	34 (1)	29 (1)	24 (1)	14 (6)	8 (11)	1 (17)	1 (17)	0 (18)

B.

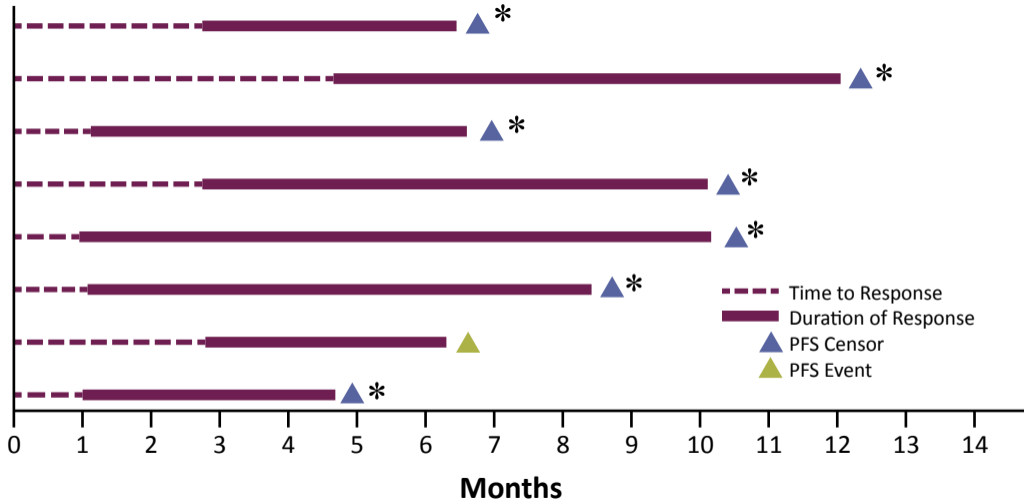


Table 1: Baseline patient characteristics

Characteristic	Ripretinib (n=85)	Placebo (n=44)
	<i>number of patients (percent)</i>	
Age, median (min, max), y	59 (29, 82)	65 (33, 83)
18–64	57 (67%)	22 (50%)
65–74	20 (24%)	12 (27%)
≥75	8 (9%)	10 (23%)
Sex		
Male	47 (55%)	26 (59%)
Race		
White	64 (75%)	33 (75%)
Region		
United States	40 (47%)	20 (46%)
Number of prior therapies		
3	54 (64%)	27 (61%)
≥4 (range, 4–7)	31 (36%)	17 (39%)
ECOG PS		
0	37 (44%)	17 (39%)
1 or 2	48 (56%)	27 (61%)
Primary tumor site		
Gastric	40 (47.1%)	18 (40.9%)
Jejunum/ileum	20 (23.5%)	8 (18.2%)

Mesenteric/omental	6 (7.1%)	6 (13.6%)
Other	7 (8.2%)	4 (9.1%)
Duodenum	2 (2.4%)	8 (18.2%)
Colon/rectum	9 (10.6%)	0
Unknown	1 (1.2%)	0
Sum of longest diameters of target lesions (mm), median (range)*	123.1 (28–495)	141.7 (17–412)
Primary mutation (central testing of tumor tissue)		
<i>KIT</i> exon 9	14 (17%)	6 (14%)
<i>KIT</i> exon 11	47 (55%)	28 (64%)
Other <i>KIT</i>	2 (2%)	2 (5%)
<i>PDGFRA</i>	3 (4%)	0
<i>KIT</i> / <i>PDGFRA</i> wild-type	7 (8%)	3 (7%)
Not available/not done [†]	12 (14%)	5 (11%)

*Independent assessment.

[†]Not available=tumor tissue analyzed for baseline mutations but analysis failed; not done=biopsy completed per protocol but sample not received for analysis.

Table 2: ORR* and quality of life

	Ripretinib		Placebo		p value
	(n=85)		(n=44)		
	n (%)	95% CI	n (%)	95% CI	
Confirmed objective response rate	8 (9.4%)	4.2–17.7	0	0.0–8.0	0.050
Complete response	0	0.0–4.2	0	0.0–8.0	
Partial response	8 (9.4%)	4.2–17.7	0	0.0–8.0	
Stable disease (6 weeks)	56 (65.9%)	54.8–75.8	8 (18.2%)	8.2–32.7	
Stable disease (12 weeks)	40 (47.1%)	36.1–58.2	2 (4.5%)	0.6–15.5	
Progressive disease	16 (18.8%)	11.2–28.8	28 (63.6%)	47.8–77.6	
Not evaluable	4 (4.7%)	..	3 (6.8%)	..	
No response assessment	1 (1.2%)	..	4 (9.1%)	..	
EORTC-QLQ-30†	Ripretinib	95% CI	Placebo	95% CI	
<i>Role Functioning</i>					
Baseline, mean (SD)	(n=74)		(n=42)		
	69.4 (30.1)	62.4–76.3	73.8 (30.4)	64.3–83.3	
Cycle 2 Day 1, mean (SD)	(n=79)		(n=33)		
	75.1 (26.1)	69.3–81.0	65.2 (27.8)	55.3–75.0	
Change from baseline, adjusted mean	(n=70)		(n=32)		
	3.5	-3.4–10.5	-17.1	-27.0–7.1	
Treatment difference (95% CI)		20.6 (8.6–32.6)			

Physical Functioning

Baseline, mean (SD)	(n=74)		(n=42)	
	75.7 (21.6)	70.7–80.7	76.0 (26.5)	67.8–84.3
Cycle 2 Day 1, mean (SD)	(n=80)		(n=33)	
	79.4 (17.3)	75.5–83.3	75.2 (20.2)	68.0–82.3
Change from baseline, adjusted mean	(n=71)		(n=32)	
	1.6	-2.5–5.7	-8.9	-14.8–3.0
Treatment difference (95% CI)		10.5 (3.4–17.6)		

EQ-5D-5L

EQ-VAS

Baseline, mean (SD)	(n=74)		(n=42)	
	63.9 (22.1)	58.8–69.0	65.6 (22.9)	58.5–72.8
Cycle 2 Day 1, mean (SD)	(n=78)		(n=33)	
	69.5 (20.5)	64.9–74.2	64.1 (23.3)	55.9–72.4
Change from baseline, mean (SD)	(n=70)		(n=32)	
	3.7 (20.4)	-1.1–8.6	-8.9 (19.3)	-15.9–1.9

*Assessed by blinded independent central review.

†Either a >10% mean score change or score change of 5-points was considered the minimally important clinical difference.^{22,23}

SD, standard deviation.

Table 3: Treatment-related TEAEs*

Preferred Term	Ripretinib (n=85)				Placebo (n=43 [†])			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
<i>number of patients (percent)</i>								
Alopecia	42 (49.4%) [‡]	1 (2.3%)
Myalgia	23 (27.1%)	1 (1.2%)	4 (9.3%)	0
Nausea	21 (24.7%)	1 (1.2%)	1 (2.3%)	0
Fatigue	20 (23.5%)	2 (2.4%)	6 (14.0%)	1 (2.3%)
PPES	18 (21.2%)	0	0	0
Diarrhea	17 (20.0%)	1 (1.2%)	0	0	2 (4.7%)	1 (2.3%)	0	0
Constipation	13 (15.3%)	0	0	0	3 (7.0%)	0	0	0
Decreased appetite	12 (14.1%)	1 (1.2%)	0	0	2 (4.7%)	1 (2.3%)	0	0
Weight decreased	13 (15.3%)	0	3 (7.0%)	0
Blood bilirubin increased	12 (14.1%)	0	0	..	0	0	0	..
Arthralgia	10 (11.8%)	0	0	0
Muscle spasms	10 (11.8%)	0	2 (4.7%)	0
Hypertension	4 (4.7%)	3 (3.5%)	0	0	1 (2.3%)	0	0	0
Lipase increased	4 (4.7%)	4 (4.7%)	0	..	0	0	0	..
Pain in extremity	5 (5.9%)	1 (1.2%)	1 (2.3%)	0
Hypophosphatemia	3 (3.5%)	2 (2.4%)	0	0	0	0	0	0
Anemia	2 (2.4%)	0	1 (1.2%)	0	1 (2.3%)	2 (4.7%)	1 (2.3%)	0

Blood triglycerides increased	1 (1.2%)	1 (1.2%)	0	0	0	0	0	0
Dermatosis	1 (1.2%)	1 (1.2%)	0	0	0	0	0	0
Dehydration	1 (1.2%)	0	0	0	0	1 (2.3%)	0	0
GERD	1 (1.2%)	1 (1.2%)	0	0
Hyperkalemia	0	1 (1.2%)	0	0	0	1 (2.3%)	0	0
Hypokalemia	0	1 (1.2%)	0	0	0	0	0	0
Anal abscess	0	1 (1.2%)	0	0	0	0	0	0
Ascites	0	1 (1.2%)	0	0	0	0	0	0
Cardiac failure	0	1 (1.2%)	0	0	0	0	0	0
Death	1 (1.2%)	0
Fecaloma	0	1 (1.2%)	0	0	0	0	0	0
Skin infection	0	1 (1.2%)	0	0	0	0	0	0
Syncope	..	1 (1.2%)	0
Upper GI hemorrhage	0	1 (1.2%)	0	0	0	0	0	0
Acute kidney injury	0	0	0	0	0	1 (2.3%)	0	0
Pulmonary edema	0	0	0	0	0	0	1 (2.3%)	0
Septic shock	0	0	0	1 (2.3%)

*Data are n (%). Treatment-related TEAEs are listed that occurred in $\geq 10\%$ of patients in either treatment group or were reported as grade 3, 4, or 5 in either treatment group.

[†]44 patients were randomized to placebo, but 1 did not receive treatment.

[‡]24 of 38 (63.2%) female patients treated with ripretinib reported alopecia.

GERD, gastroesophageal reflux disease; GI, gastrointestinal; PPES, palmar-plantar erythrodysesthesia syndrome.