Patient quality of life and self-reported function with ripretinib as ≥4th-line therapy for gastrointestinal stromal tumor: INVICTUS phase 3 study

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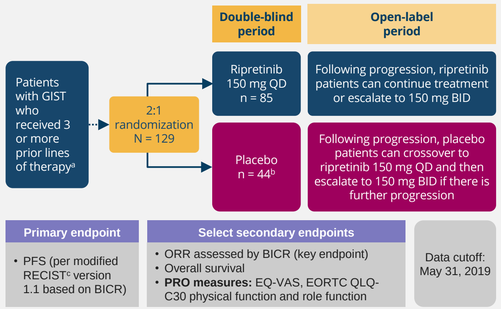
INTRODUCTION

- Gastrointestinal stromal tumor (GIST) is a rare sarcoma accounting for 1%–2% of GI malignancies[1]
- Primary mutations in *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) occur in >85% of patients with GIST[2]
- Ripretinib is approved in several regions (including the EU) for the treatment of adult patients with advanced GIST who received prior treatment with 3 or more kinase inhibitors, including imatinib[3,4]
- Ripretinib is a novel switch-control tyrosine kinase inhibitor that is designed to broadly inhibit KIT and PDGFRA kinase signaling through a dual mechanism of action[4]
- INVICTUS (NCT03353753) was a randomized, double-blind, placebo-controlled phase 3 study of ripretinib in patients with advanced GIST who received at least imatinib, sunitinib, and regorafenib[4]
- Ripretinib demonstrated a significant improvement in median progression-free survival (PFS) vs placebo (6.3 vs 1.0 months, respectively; hazard ratio [HR] = 0.15 [95% confidence interval (CI), 0.09–0.25]; *P* <0.0001) and clinically meaningful median overall survival vs placebo (15.1 vs 6.6 months; HR = 0.36 [95% CI, 0.21–0.62]; nominal *P* = 0.0004), with a well-tolerated safety profile[4]
- Here, we summarize patient-reported outcomes (PROs) from patients receiving ripretinib vs placebo from the INVICTUS trial[5]

METHODS

- In INVICTUS, 129 patients were randomized 2:1 to receive ripretinib 150 mg once daily (n = 85) or placebo (n = 44; 1 patient did not receive drug; **Figure 1**)
- PROs were assessed using the EuroQol Visual Analog Scale (EQ-VAS) and questions from the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30; **Table 1**)

Figure 1. INVICTUS study design



[a]Patients previously received at least imatinib, sunitinib, and regorafenib. [b]One patient did not receive drug. [c]GIST-specific mRECIST per regorafenib registrational GRID study.
BICR, blinded independent central review; BID, twice daily; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-VAS, EuroQol Visual Analog Scale; GIST, gastrointestinal stromal tumor; mRECIST, modified RECIST; ORR, objective response rate; PFS, progression-free survival; PRO, patient-reported outcome; QD, once daily; RECIST, response evaluation criteria in solid tumors.

Table 1. Patient-reported outcome assessments

Patient-reported outcomes	Description
EQ-VAS	• Records self-rated health on a vertical VAS • Ranges from 0 (worst imaginable state of health) to 100 (best imaginable state of health)
EORTC QLQ-C30	
Physical function	• Five questions evaluating strength, endurance, and daily physical functioning • Four-point rating scale ranging from "1 (not at all)" to "4 (very much)" • Responses were rolled up to a score ranging from 0 to 100, in which a larger value is better
Role function	• Two questions evaluating limitations during everyday activities • Four-point rating scale ranging from "1 (not at all)" to "4 (very much)" • Responses were rolled up to a score ranging from 0 to 100, in which a larger value is better
Overall health (question C29)[a]	• One question asking patients to rate their overall health during the past week on a scale of "1 (very poor)" to "7 (excellent)"
Overall quality of life (question C30)[a]	• One question asking patients to rate their overall quality of life during the past week on a scale of "1 (very poor)" to "7 (excellent)"

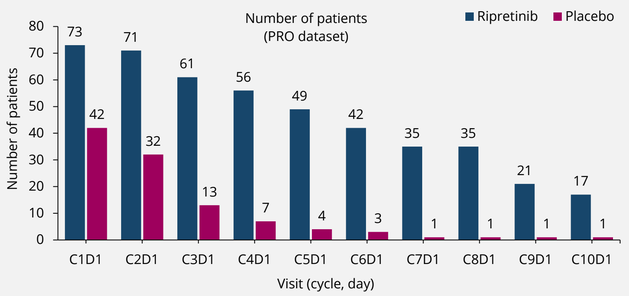
[a]Questions C29 and C30 were additional analyses; all other analyses were pre-specified.
EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-VAS, EuroQol Visual Analog Scale.

- All analyses compared the change from baseline on cycle 1 day 1 (C1D1) to cycle 2 day 1 (C2D1) between ripretinib and placebo
- Comparisons were only made out to C2D1 due to the low number of patients in the placebo arm after C2D1 (**Figure 2**)

Statistical analysis

- For the EQ-VAS, a t-test was performed between the ripretinib and placebo group for their change from baseline to C2D1 scores
- For the questions from the EORTC QLQ-C30 (physical function, role function, overall health, overall quality of life), analysis of covariance (ANCOVA) models were built for change from baseline to C2D1
  - Fixed effects were treatment, Eastern Cooperative Oncology Group score at baseline (0 vs 1/2), and the number of prior anticancer treatments (3 vs ≥4)

Figure 2. Number of patients for PRO assessment over time

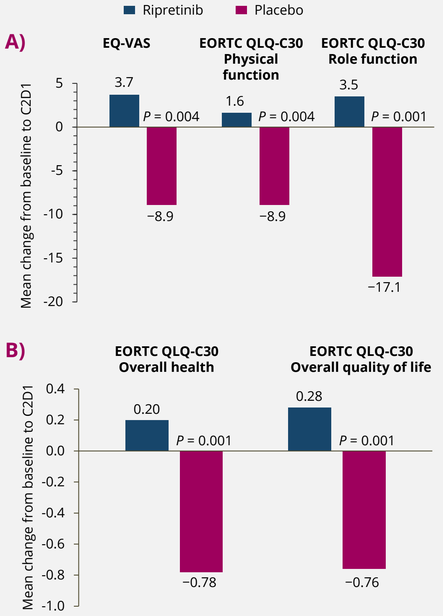


At C1D1, 73 patients were evaluable in the ripretinib arm and 42 patients were evaluable in the placebo arm.
C, cycle; D, day; PRO, patient-reported outcome.

RESULTS

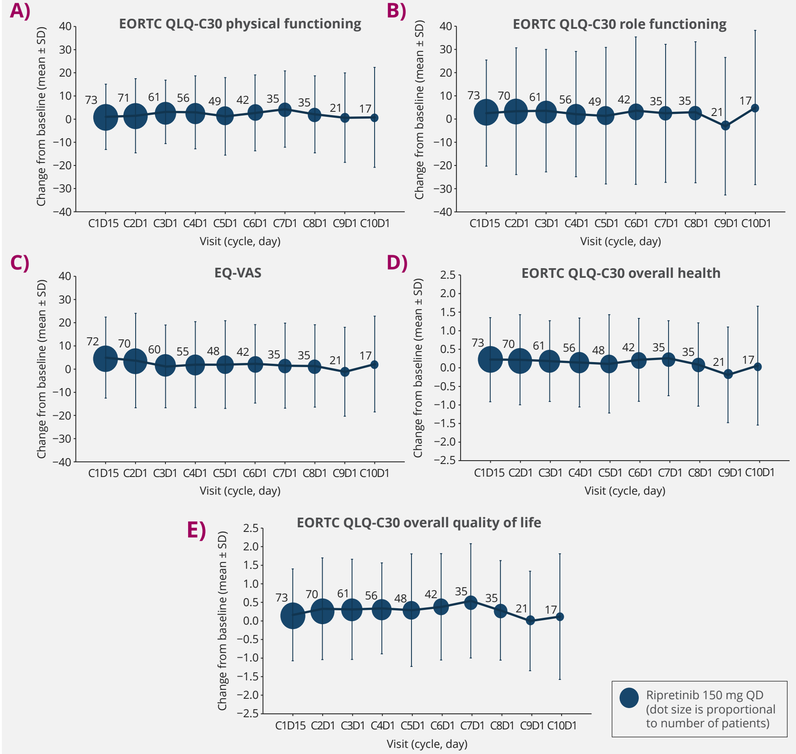
- Ripretinib was associated with an increase in the patients' self-reported health status on the EQ-VAS while placebo was associated with a decline (*P* = 0.004; **Figure 3A**)
- Patients receiving ripretinib reported better physical and role functioning on the EORTC QLQ-C30 (*P* = 0.004 and *P* = 0.001, respectively) compared with the decline observed in patients receiving placebo (**Figure 3A**)
- Patients receiving ripretinib had higher perceptions of their overall health and quality of life compared with patients receiving placebo (both *P* = 0.001, **Figure 3B**)
- Differences between treatment arms were clinically significant (using threshold for meaningful change)[6]
- Patients receiving ripretinib reported stable scores on all PRO measures out to cycle 10 (**Figure 4**)

Figure 3. Change from baseline to C2D1 in EQ-VAS and EORTC QLQ-C30 PRO measures



P-values are nominal and no statistical significance is being claimed. The physical and role function questions were rolled up to a score out of 100; questions C29 and C30 are based on 7-point scales.
C2D1, cycle 2 day 1; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-VAS, EuroQol Visual Analog Scale; PRO, patient-reported outcome.

Figure 4. Longitudinal change in PRO scores from baseline in the ripretinib arm



C, cycle; D, day; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-VAS, EuroQol Visual Analogue Scale; PRO, patient-reported outcome; QD, once daily; SD, standard deviation.

CONCLUSIONS

- In the INVICTUS phase 3 study, ripretinib demonstrated a significant improvement in PFS and a clinically meaningful overall survival benefit compared with placebo; secondary endpoints included 5 key quality of life measures that showed improvement in patients with 4th-line advanced GIST receiving ripretinib compared with declining measures in patients receiving placebo
- Patients in the ripretinib arm had consistently stable PROs and the measures suggest these patients were able to maintain quality of life while PROs declined sharply in the placebo arm
- The differences in PRO measurements between patients receiving ripretinib and those receiving placebo were clinically significant

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