Quality of life (QoL) and self-reported function with ripretinib in ≥4th-line therapy for patients with gastrointestinal stromal tumors (GIST): Analyses from INVICTUS

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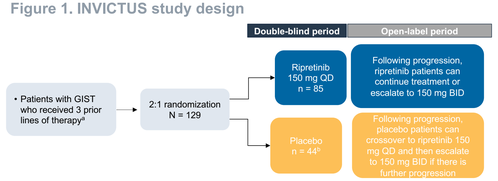
INTRODUCTION

- Gastrointestinal stromal tumor (GIST) is a rare sarcoma accounting for 1%–2% of GI malignancies[1]
- Primary mutations in receptor tyrosine kinase (KIT) or platelet derived growth factor receptor alpha (PDGFRA) occur in >85% of patients with GIST[2]
- In May 2020, the US FDA approved ripretinib for the treatment of adult patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib
- Ripretinib is a novel switch-control tyrosine kinase inhibitor (TKI) that is designed to broadly inhibit KIT and PDGFRA kinase signaling through a dual mechanism of action[3]
- INVICTUS (NCT03353753) is a randomized, double-blind, placebo-controlled phase 3 study of ripretinib in advanced GIST patients who received at least imatinib, sunitinib, and regorafenib
- Ripretinib demonstrated a significant improvement in median progression free survival vs placebo (6.3 vs 1 months, respectively; hazard ratio [HR] = 0.15 [95% 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 patients receiving placebo from the INVICTUS trial

METHODS

- In INVICTUS, 129 patients were randomized 2:1 to receive ripretinib 150 mg once daily (n = 85) or placebo (n = 44; one patient did not receive drug, **Figure 1**)
- PROs were assessed using 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, **Table 1**)

Figure 1. INVICTUS study design



Primary endpoint	Select secondary endpoints	
• PFS (per modified RECIST[c] version 1.1 based on BICR)	• ORR assessed by BICR (key endpoint) • Overall survival • **PRO measures:** EQ-5D-5L VAS, EORTC QLQ-C30 physical function and role function	Data cutoff: May 31, 2019

[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-5D-5L, EuroQol-5D; GIST, gastrointestinal stromal tumor; ORR, objective response rate; PFS, progression-free survival; QD, once daily; RECIST, response evaluation criteria in solid tumors; VAS, visual analog scale.

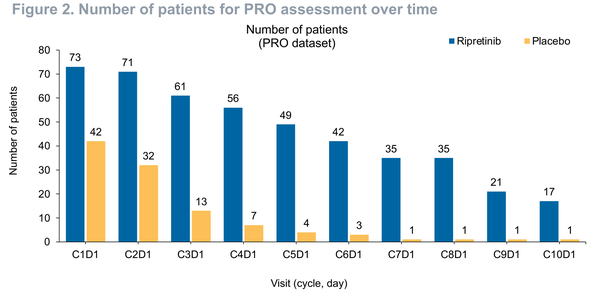
Table 1. Patient reported outcome assessments

Patient reported outcomes	Description
EQ-5D-5L	
Visual analogue scale (VAS)	• Records self-rated health on a vertical visual analogue scale • 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.
EQ-5D-5L, EuroQol-5D; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire.

- 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 this point (**Figure 2**)

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.

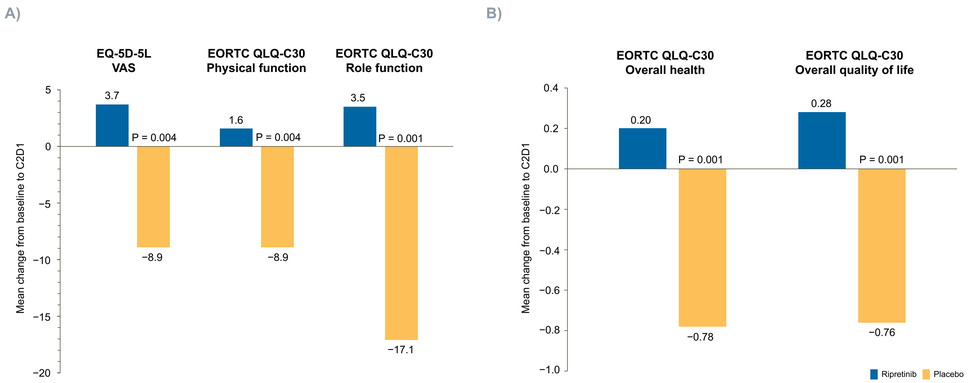
Statistical analyses

- For the EQ-5D-5L visual analogue scale (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 (ECOG) score at baseline, and the number of prior anti-cancer treatments

RESULTS

- Ripretinib was associated with an increase in the patients' self-reported health status on the EQ-5D-5L 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 compared with the decline observed in patients receiving placebo (P = 0.004; P = 0.001; **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)[5]
- 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-5D-5L VAS and EORTC QLQ-C30 PRO measures

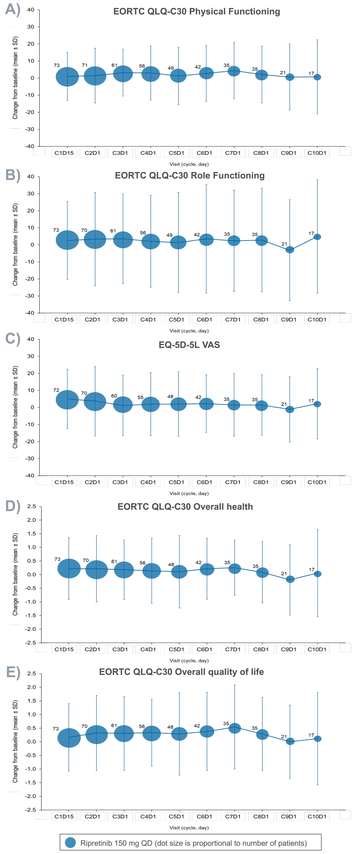


P-values are nominal and no statistical significance is being claimed. The Physical and Role Function questions were rolled up to a score out of 100; questions C29 and C30 are based on 7-point scales.
C2D1, cycle 2 day 1; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol-5D; VAS, visual analogue scale.

CONCLUSIONS

- In the INVICTUS phase 3 study, ripretinib demonstrated a significant improvement in PFS and a clinically meaningful overall survival benefit compared with placebo; five key quality of life measures tested 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

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



EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol-5D; SD, standard deviation; VAS, visual analogue scale.

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