

Time until definitive deterioration in patient-reported outcomes with ripretinib vs sunitinib in patients with advanced gastrointestinal stromal tumor previously treated with imatinib who harbor *KIT* exon 11 + 17/18 mutations: Exploratory analysis from INTRIGUE

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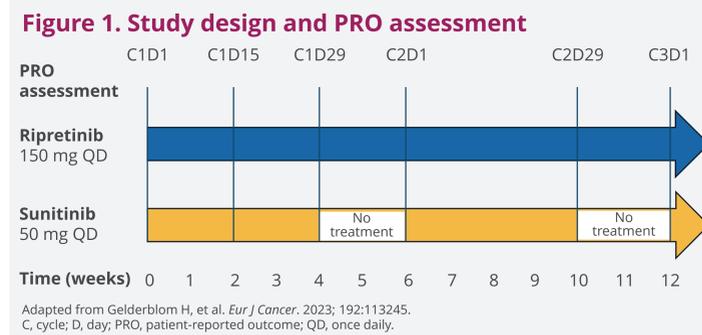
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Background

- INTRIGUE was a randomized, open-label, global, multicenter phase 3 study comparing the efficacy and safety of ripretinib vs sunitinib in patients with advanced gastrointestinal stromal tumor (GIST) who had disease progression on or were intolerant to first-line treatment with imatinib¹
- The primary endpoint of superior progression-free survival with ripretinib vs sunitinib was not met; however, ripretinib demonstrated comparable efficacy and a more favorable safety profile compared with sunitinib¹
- In a secondary analysis from INTRIGUE, patients with advanced GIST receiving ripretinib experienced more favorable tolerability and reported significantly less decline in health-related quality of life (HRQoL) vs sunitinib, as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)²
- An exploratory baseline circulating tumor DNA (ctDNA) analysis from INTRIGUE showed that patients harboring primary *KIT* exon 11 mutations and secondary mutations exclusively in *KIT* exons 17/18 (*KIT* exon 11 + 17/18), derived greater clinical benefit from ripretinib compared with sunitinib³
- Here, we explore the time until definitive deterioration (TUDD) for patient-reported outcomes (PROs) in the subgroup of patients with *KIT* exon 11 + 17/18 mutations

Methods

- In INTRIGUE (NCT03673501), adults with advanced GIST and disease progression on or intolerance to imatinib were randomized 1:1 to ripretinib 150 mg once daily (QD) or sunitinib 50 mg QD (4 weeks on/2 weeks off)¹
- Baseline ctDNA was analyzed in peripheral whole blood with a 74-gene next-generation sequencing-based assay (Guardant360)³
- Patients with GIST harboring *KIT* exons 11 + 17/18 mutations were analyzed
 - EORTC QLQ-C30 data were collected using an electronic system at baseline, cycle (C) 1 day (D) 15 and D29 (± 1 day), as well as D1 and D29 (± 3 days) of every cycle thereafter, and at the end of treatment (Figure 1)²
 - Patients with missing baseline values, without any postbaseline values, or with missing dates were not included



- The evaluated EORTC QLQ-C30 scales are described in Table 1

Table 1. EORTC QLQ-C30 scales⁴

Scale	Description
Global health status	Two questions asking patients to rate their overall health and overall quality of life
Physical functioning	Five questions evaluating strength, endurance, and daily physical functioning
Role functioning	Two questions evaluating limitations in everyday activities
Cognitive functioning	Two questions evaluating difficulties with concentration and memory
Emotional functioning	Four questions evaluating mood
Social functioning	Two questions evaluating the impact of the patient's condition or treatment on family and social activities
Appetite loss	One question: Have you lacked appetite?
Constipation	One question: Have you been constipated?
Diarrhea	One question: Have you had diarrhea?
Nausea and vomiting	Two questions: Have you felt nauseated? Have you vomited?
Fatigue	Three questions evaluating the patient's need to rest and their perceptions of feeling weak or tired
Insomnia	One question: Have you had trouble sleeping?
Pain	Two questions evaluating incidence of pain and its impact on daily activities
Dyspnea	One question: Were you short of breath?

Global health status questions were rated on a scale of "1-very poor" to "7-excellent." All other questions were rated on a scale ranging from "1-not at all" to "4-very much." All questions except those in the physical functioning domain were asked relative to the past week.

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

- TUDD was evaluated for each EORTC QLQ-C30 scale and was defined as the time until a clinically meaningful decline that did not increase back to above the minimal clinically important differences (MCIDs) when measured at a future assessment
- MCIDs were used to define the smallest change in a treatment outcome that patients perceive as meaningful
 - MCIDs for global health status, most functioning scales, and symptom scales were 0.5 \times standard deviation of baseline values
 - MCID for physical functioning/role functioning was a commonly-used 10-point change⁵
- Multivariable Cox proportional hazards regression assessed treatment effect adjusting for age, sex, race, and baseline score
- Patients without definitive deterioration were censored on the date of their last available PRO assessment; disease progression and death were not incorporated into the TUDD endpoint

Results

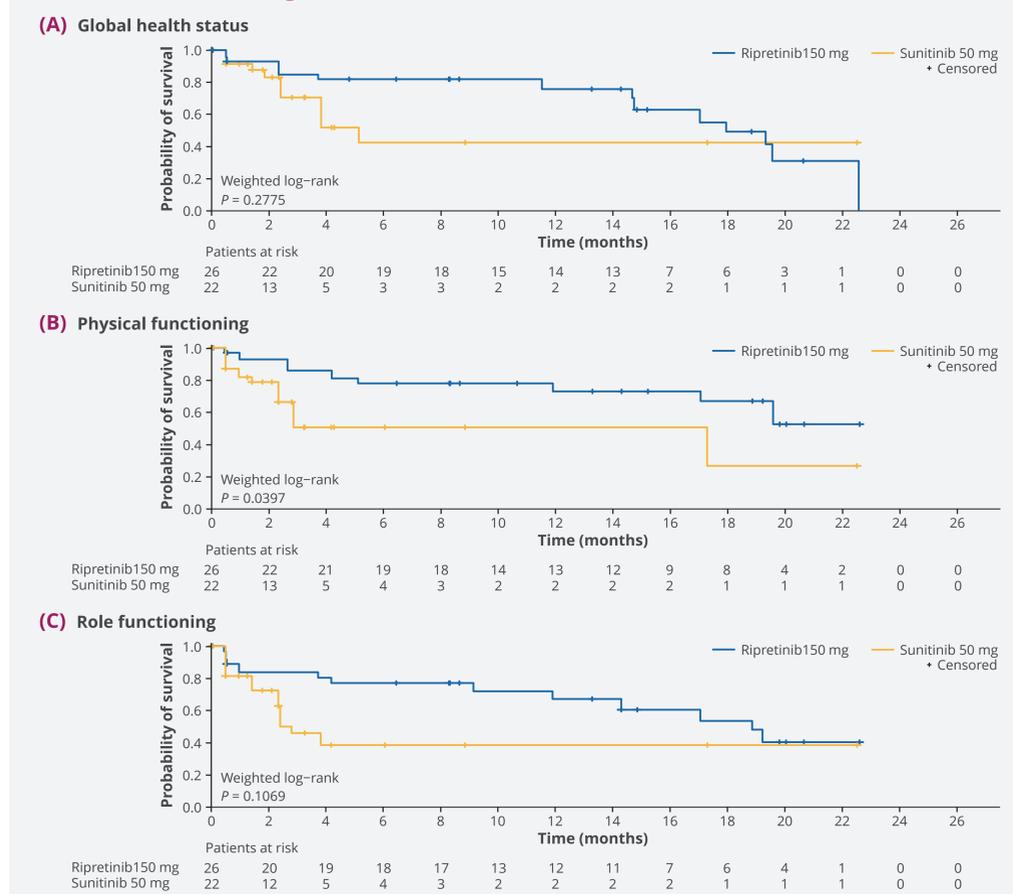
Patient disposition

- Of 453 randomized patients, baseline ctDNA was analyzed for 362 (80%); 52 had mutations exclusively in *KIT* exon 11 + 17/18 (riporetinib, n = 27; sunitinib, n = 25)³

TUDD for EORTC QLQ-C30 global health status, functional scales, and symptom scales

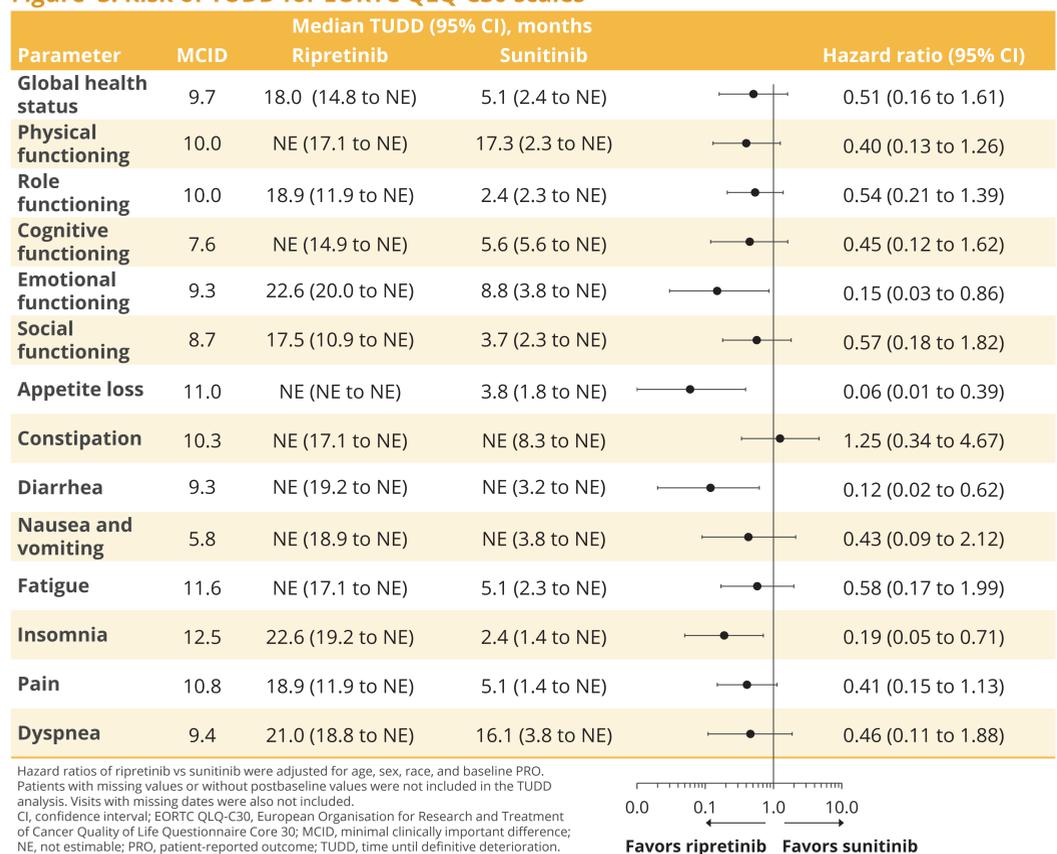
- Global health status and physical and role functioning are often more critical to clinical outcomes and patient-centered care than other, more specialized scales
 - Kaplan-Meier curves for those 3 scales are shown in Figure 2
- Median TUDD for global health status, physical functioning, and role functioning with ripretinib vs sunitinib was 18.0 vs 5.1 months, not reached vs 17.3 months, and 18.9 vs 2.4 months, respectively

Figure 2. TUDD for EORTC QLQ-C30 (A) global health status, (B) physical functioning, and (C) role functioning



- There was a numerically lower risk of TUDD with ripretinib vs sunitinib for almost all scales, including global health status, physical functioning, and role functioning (Figure 3), and a nominally statistically significant difference for physical functioning ($P = 0.0397$; Figure 2)
- Constipation was the only analyzed EORTC QLQ-C30 scale that numerically favored sunitinib vs ripretinib (Figure 3)

Figure 3. Risk of TUDD for EORTC QLQ-C30 scales



CONCLUSIONS

- Similar to the overall patient population in INTRIGUE, this exploratory analysis of patients harboring *KIT* exon 11 + 17/18 mutations showed clinically meaningful improvement in HRQoL with ripretinib compared with sunitinib, including global health status, functional scales, and most symptom scales
 - Constipation was the only assessed EORTC QLQ-C30 parameter that showed a more numerically favorable outcome with sunitinib vs ripretinib
- The ongoing INSIGHT phase 3 trial (NCT05734105) will further investigate outcomes with ripretinib vs sunitinib in the *KIT* exon 11 + 17/18 subgroup