Safety profile of ripretinib, including impact of alopecia and palmar-plantar erythrodysesthesia syndrome (PPES) on patient reported outcomes (PROs), in ≥4th-line advanced gastrointestinal stromal tumors (GIST): Analyses from INVICTUS

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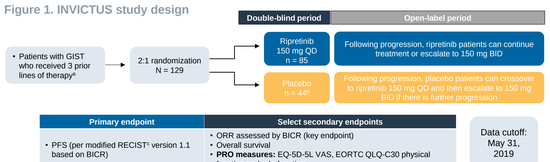
INTRODUCTION

- 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 progressed on imatinib, sunitinib, and regorafenib
  - Ripretinib demonstrated a significant improvement in median progression free survival (PFS) vs placebo (6.3 vs 1 months, respectively; hazard ratio [HR] = 0.15 [95% CI, 0.09–0.25]; P <0.0001) and a 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]
- Patients receiving ripretinib had improved scores on patient reported outcome (PRO) measures compared with a decline in patients receiving placebo (**see ASCO 2020 poster #423 for more details**)
- Here, we report further details regarding the safety of ripretinib and the impact of alopecia and palmar-plantar erythrodysesthesia syndrome (PPES) on patient reported outcomes (PROs)

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**)
- 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, **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-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.

Statistical analyses

- Generalized estimating equation (GEE) models:
  - Repeated measures models across visits where the outcome was 1 of the 5 PROs
  - Models were built only for ripretinib patients
  - For patients with alopecia, 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
  - 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

RESULTS

- In the ripretinib arm, alopecia occurred in 44 patients (52%) and PPES occurred in 18 patients (21%, **Table 2**)
  - The highest common terminology criteria for adverse events (CTCAE) severity classification for alopecia is grade 2; therefore, no patients in either arm had grade 3/4 alopecia (**Table 2**)
  - The incidence of alopecia was 57% in females and 43% in males
  - In the ripretinib arm, 21% of patients reported PPES; no patients had grade 3 PPES (grade 3 is the highest CTCAE severity classification for PPES, **Table 2**)
- Anemia was the most common grade 3/4 TEAE (9.4%) in the ripretinib arm; grade 3/4 anemia was higher (14%) in placebo and likely due to underlying GIST
- There were no serious adverse events of alopecia or PPES reported

Table 2. TEAEs in >20% of patients receiving ripretinib[6]

Preferred Term, n (%)	Ripretinib (n = 85)		Placebo (n = 43)	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Alopecia[a]	**44 (52)**	**0**	**2 (4.7)**	**0**
Fatigue	36 (42)	3 (3.5)	10 (23)	1 (2.3)
Nausea	33 (39)	3 (3.5)	5 (12)	0
Abdominal pain	31 (37)	6 (7.1)	13 (30)	2 (4.7)
Constipation	29 (34)	1 (1.2)	8 (19)	0
Myalgia	27 (32)	1 (1.2)	5 (12)	0
Diarrhea	24 (28)	1 (1.2)	6 (14)	1 (2.3)
Decreased appetite	23 (27)	1 (1.2)	9 (21)	1 (2.3)
PPES[b]	**18 (21)**	**0**	**0**	**0**
Vomiting	18 (21)	3 (3.5)	3 (7.0)	0

[a]The highest severity classification for alopecia is grade 2. [b]The highest severity classification for PPES is grade 3.
PPES, palmar-plantar erythrodysesthesia syndrome; TEAE, treatment-emergent adverse event.

- Within the ripretinib arm, 8.2%, 24%, and 7.1% of patients experienced a TEAE leading to treatment discontinuation, dose interruption, or dose reduction compared with 12%, 21%, and 2.3% in the placebo arm (**Table 3**)

Table 3. TEAEs leading to dose modification

Categories, n (%)	Ripretinib (n = 85)	Placebo (n = 43)
Any TEAE leading to treatment discontinuation	7 (8.2)	5 (12)
Discontinuation due to alopecia	0	0
Discontinuation due to PPES	1 (1.2)	N/A[a]
Any TEAE leading to dose interruption	20 (24)	9 (21)
Dose interruption due to alopecia	1 (1.2)	0
Dose interruption due to PPES	2 (2.4)	N/A
Any TEAE leading to dose reduction	6 (7.1)	1 (2.3)
Dose reduction due to alopecia	1 (1.2)	0
Dose reduction due to PPES	1 (1.2)	N/A

[a]There were no patients with PPES in the placebo group.
N/A, not applicable; PPES, palmar-plantar erythrodysesthesia syndrome; TEAE, treatment-emergent adverse event.

- Of the 44 patients receiving ripretinib that developed alopecia, the majority (34/44; 77%) reported a severity of grade 1 (**Table 4**)
- Similarly, of the 18 patients receiving ripretinib that developed PPES, the majority (11/18; 61%) reported a severity of grade 1 (**Table 4**)

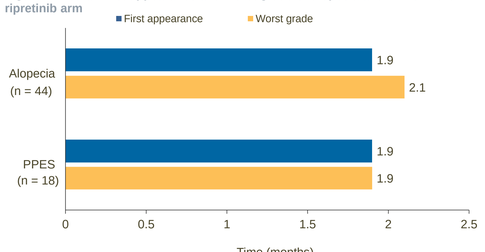
Table 4. Graded TEAEs for alopecia and PPES

Categories, n (%)	Ripretinib (n = 85)	Placebo (n = 43)
Alopecia	**44**	**2**
Grade 1	34 (77)	2 (100)
Grade 2	10 (23)	0
PPES	**18**	**0**
Grade 1	11 (61)	0
Grade 2	7 (39)	0

Graded percentages represent proportion of patients with the TEAE.
PPES, palmar-plantar erythrodysesthesia syndrome; TEAE, treatment-emergent adverse event.

- In patients receiving ripretinib, the median time to first appearance of alopecia and the median time to worst grade of alopecia were similar (**Figure 2**)
- In patients receiving ripretinib, the median time to first appearance and the median time to worst grade of PPES were the same (**Figure 2**)

Figure 2. Median first appearance and worst grade of alopecia and PPES in the ripretinib arm



PPES, palmar-plantar erythrodysesthesia syndrome

- In a repeated measures analysis, there was a numerical trend toward an improvement of the 5 PROs among patients with alopecia (**Table 5**)
  - The presence of alopecia was associated with a trend toward better self-reported overall quality of life (compared with no alopecia, **Table 5**); P = 0.03, but did not exceed the threshold for meaningful change[5]
- There was no association between PPES and the 5 PRO measures (**Table 5**)

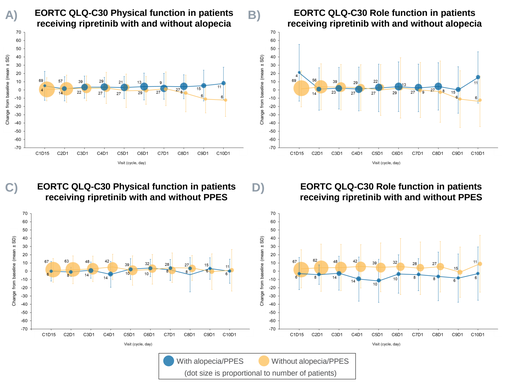
Table 5. GEE analysis summary of the association between alopecia and PPES with the 5 PRO measures in patients taking ripretinib

	Mean estimate[a]	Confidence interval	P-value
Alopecia			
EORTC QLQ-C30			
Overall health	0.17	(−0.10, 0.44)	0.22
Overall quality of life	0.35	(0.03, 0.67)	0.03
Physical function	3.17	(−0.29, 6.64)	0.07
Role function	4.50	(−2.87, 11.87)	0.23
EQ-5D-5L			
VAS	3.01	(−0.64, 6.67)	0.11
PPES			
EORTC QLQ-C30			
Overall health	0.06	(−0.29, 0.41)	0.75
Overall quality of life	0.12	(−0.26, 0.50)	0.54
Physical function	3.03	(−0.92, 6.99)	0.13
Role function	2.83	(−5.52, 11.17)	0.51
EQ-5D-5L			
VAS	1.65	(−2.11, 5.41)	0.39

[a]This indicates the impact on PRO score in patients with alopecia or PPES, vs patients without alopecia or PPES, while keeping other variables constant (ie, gender and ECOG status).
EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol-5D; GEE, general estimating equation; PPES, palmar-plantar erythrodysesthesia syndrome; VAS, visual analogue scale.

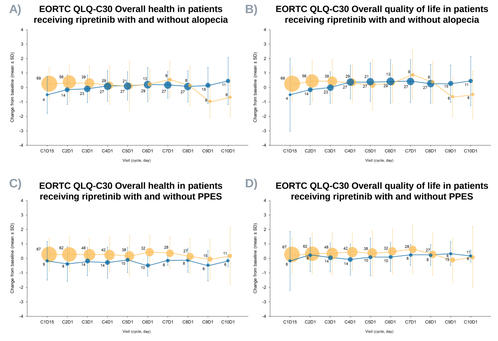
- Longitudinal graphs out to cycle 10 day 1 demonstrate responses for the 5 PROs (mean change from baseline) are generally maintained for patients receiving ripretinib that developed alopecia or PPES and those that did not (**Figures 3–5**)

Figure 3. Mean change from baseline in physical function (A,C) and role function (B,D) scores for patients receiving ripretinib with and without alopecia (A,B) or PPES (C,D)



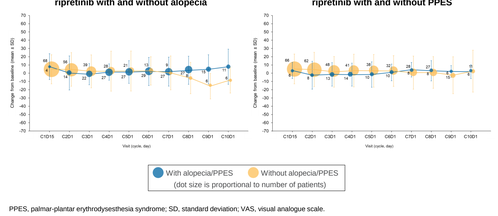
PPES, palmar-plantar erythrodysesthesia syndrome; SD, standard deviation.

Figure 4. Mean change from baseline in overall health (A,C) and overall quality of life (B,D) scores for patients receiving ripretinib with and without alopecia (A,B) or PPES (C,D)



PPES, palmar-plantar erythrodysesthesia syndrome; SD, standard deviation.

Figure 5. Mean change from baseline in state of health (VAS) scores for patients receiving ripretinib with and without alopecia (A) or PPES (B)



PPES, palmar-plantar erythrodysesthesia syndrome; SD, standard deviation; VAS, visual analogue scale.

CONCLUSIONS

- In the phase 3 INVICTUS trial, ripretinib demonstrated a significant improvement in PFS and a clinically meaningful overall survival benefit vs placebo and had a well-tolerated safety profile
- For both alopecia and PPES, the majority of the events were of lower severity grades and did not generally worsen over time
- When stratified by alopecia and PPES, patient-reported assessments of function, overall health, and overall quality of life were generally stable

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