Ripretinib as ≥4th-line treatment in patients with advanced gastrointestinal stromal tumour (GIST): Long-term update from the phase 3 INVICTUS study

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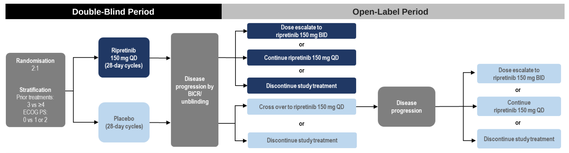
INTRODUCTION

- Ripretinib, a switch-control kinase inhibitor of KIT and PDGFRA, is approved for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) as ≥fourth-line treatment in the US, Canada, Australia, Hong Kong, and China.[1–4]
- In the INVICTUS study (NCT03353753)—a phase 3, double-blind, randomised trial in patients with ≥4th-line advanced GIST—ripretinib 150 mg once daily (QD) compared with placebo significantly improved median progression-free survival (mPFS, 6.3 vs 1.0 months), reduced the risk of disease progression or death by 85%, provided a clinically meaningful improvement in median overall survival (mOS, 15.1 vs 6.6 months), and showed an overall response rate (ORR) of 9.4% in the planned primary analysis[5]
- Ripretinib was well tolerated in the INVICTUS study. The most common treatment-related adverse events (AEs) observed included alopecia, myalgia, and nausea[5]
- Here, we present a long-term update of mature data of the INVICTUS study, with a data cutoff date 19 months after the primary analysis

METHODS

- Patients with advanced GIST previously treated with at least imatinib, sunitinib, and regorafenib were randomised (2:1) to ripretinib 150 mg QD or placebo (**Figure 1**)
- Following disease progression, as determined by blinded independent central review (BICR):
  - Patients randomised to placebo were permitted to cross over to ripretinib 150 mg QD
  - Patients randomised to ripretinib 150 mg QD had the option to dose escalate to receive ripretinib 150 mg twice daily
- Patients were evaluated for safety and efficacy according to Common Terminology Criteria for Adverse Events v4.03 and GIST-specific modified Response Evaluation Criteria in Solid Tumors v1.1, respectively
- The primary efficacy endpoint was PFS, summarised using the Kaplan-Meier method and associated two-sided 95% confidence interval (CI)
- Secondary endpoints included ORR (confirmed complete response and partial response assessed by BICR), OS (Kaplan-Meier method and associated two-sided 95% CI), time to best response, and duration of response (DOR)
- All updated data are reported as of January 15, 2021

Figure 1. Overall study design



[a]Data from this study (including the primary endpoint) were initially evaluated at the May 31, 2019, data cutoff.
BICR, blinded independent central review; BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Score; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily.

Table 1. Baseline characteristics

Characteristics	Ripretinib (n = 85)	Placebo (n = 44)	Total (n = 129)
Age, median (range), years	59 (29–82)	65 (33–83)	60 (29–83)
18–64	57 (67)	22 (50)	79 (61)
65–74	20 (24)	12 (27)	32 (25)
≥75	8 (9)	10 (23)	18 (14)
Sex			
Male	47 (55)	26 (59)	73 (57)
Female	38 (45)	18 (41)	56 (43)
ECOG Performance Status			
0	37 (44)	17 (39)	54 (42)
1 or 2	48 (56)	27 (61)	75 (58)
Number of prior therapies			
3	54 (64)	27 (61)	81 (63)
≥4[a] (range, 4–7)	31 (36)	17 (39)	48 (37)
Primary mutation (central testing of tumour tissue)			
KIT exon 9	14 (17)	6 (14)	20 (16)
KIT exon 11	47 (55)	28 (64)	75 (58)
Other KIT	2 (2)	2 (5)	4 (3)
PDGFRA	3 (4)	0	3 (2)
KIT wild-type/PDGFRA wild-type	7 (8)	3 (7)	10 (8)
Not available/not done[b]	12 (14)	5 (11)	17 (13)

Data are presented as n (%) unless otherwise noted.
[a]In addition to imatinib, sunitinib, and regorafenib, prior therapies received by ≥5% patients included pazopanib, nilotinib, sorafenib, and avapritinib.
[b]Not available: tumour tissue analysed for baseline mutations, but analysis failed; Not done: biopsy completed per protocol, but sample not received for analysis.
ECOG, Eastern Cooperative Oncology Group.

RESULTS

Patient disposition

- Overall, 129 patients were randomised, and 128 received treatment (ripretinib or placebo)
- Of the 44 patients randomised to placebo during the double-blind period, 30 patients crossed over to ripretinib during the open-label period after progression

Efficacy and duration of response in the double-blind period

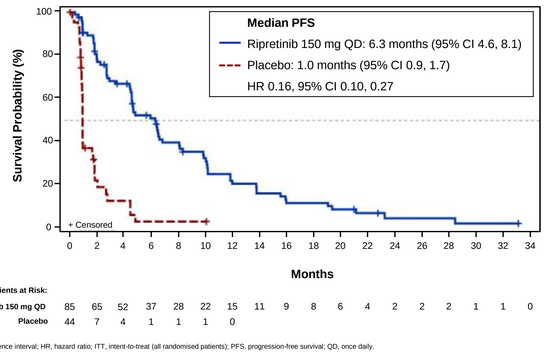
- Patients randomised to ripretinib had an mPFS of 6.3 (95% CI 4.6–8.1) vs 1.0 (95% CI 0.9–1.7) months for placebo with a hazard ratio of 0.16 (**Figure 2**)
- ORR was 11.8% in the ripretinib group compared with 0% in the placebo group (**Table 2**)
  - Percent change in sum of diameters of target lesions in all patients is shown in **Figure 3**
  - Percent change in sum of diameters of target lesions over time for the 10 patients with confirmed responses is shown in **Figure 4**
  - Median DOR was 14.5 months (**Table 2**)
  - In all subgroups assessed, ripretinib showed a PFS benefit vs placebo (**Figure 5**)

Table 2. Objective response rate and estimated PFS in the ITT population

	Ripretinib (n = 85)	Placebo (n = 44)
Events, n (%)	71 (84)	37 (84)
Censored, n (%)	14 (17)	7 (16)
PFS 6 months, % (95% CI)	51.0 (39.4, 61.4)	3.2 (0.2, 13.8)
PFS 12 months, % (95% CI)	22.2 (13.4, 32.4)	NE (NE, NE)
PFS 18 months, % (95% CI)	11.8 (5.6, 20.6)	NE (NE, NE)
ORR, n (%) 95% CI	10 (11.8) 5.8, 20.6	0 0.0, 8.0
DOR, months, median, (95% CI)	14.5 (3.7, NE)	NE (NE, NE)

CI, confidence interval; DOR, duration of response; ITT, intent-to-treat (all randomised patients); NE, not estimable; ORR, objective response rate; PFS, progression-free survival.

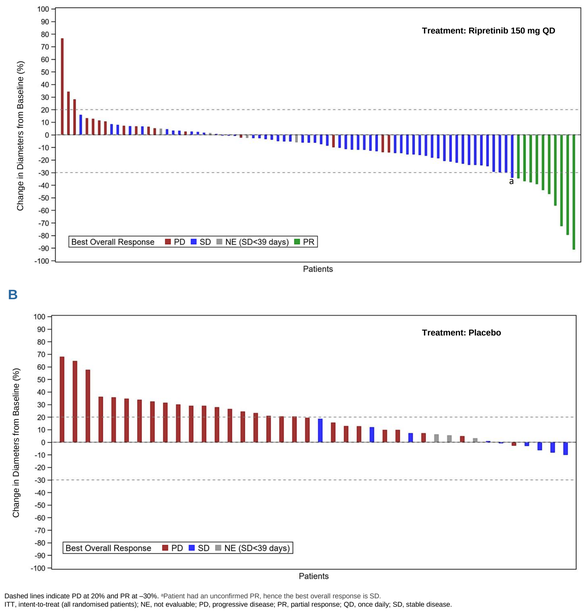
Figure 2. Progression-free survival in the ITT population



Patients at Risk:																			
Ripretinib 150 mg QD	85	65	52	37	28	22	15	11	9	8	6	4	2	2	2	1	1	0	
Placebo	44	7	4	1	1	1	0												

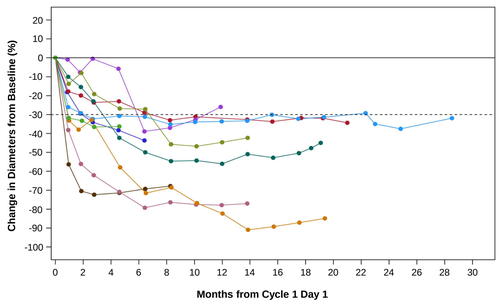
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat (all randomised patients); PFS, progression-free survival; QD, once daily.

Figure 3. Percent change from baseline in sum of diameters of target lesions in the ITT population for patients receiving ripretinib (A) or placebo (B)



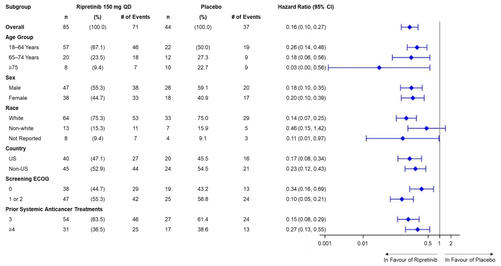
Dashed lines indicate PD at 20% and PR at –30%. [a]Patient had an unconfirmed PR, hence the best overall response is SD.
ITT, intent-to-treat (all randomised patients); NE, not evaluable; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease.

Figure 4. Change from baseline in sum of diameters of target lesions in patients with a confirmed response based on BICR



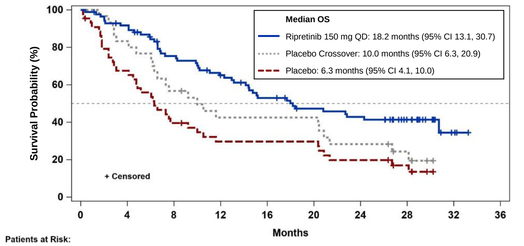
Dashed line indicates PR at –30%.
BICR, blinded independent central review; PR, partial response.

Figure 5. Ripretinib showed PFS benefit in all assessed patient subgroups



CI, confidence interval; ECOG, European Cooperative Oncology Group; PFS, progression-free survival; QD, once daily.

Figure 6. Kaplan-Meier plots of overall survival



Patients at Risk:											
Ripretinib	85	76	59	49	39	32	29	18	3	0	
Placebo Crossover	30	25	17	12	12	12	8	5	0		
Placebo	44	29	17	12	12	12	8	5	0		

CI, confidence interval; OS, overall survival.

Table 3. Estimated overall survival in the ITT population

	Ripretinib (n = 85)	Placebo (n = 44)
Events, n (%)	46 (54)	36 (82)
Censored, n (%)	39 (46)	8 (18)
OS 6 months, % (95% CI)	84.3 (74.5, 90.6)	55.9 (39.9, 69.2)
OS 12 months, % (95% CI)	65.1 (53.6, 74.5)	29.7 (16.8, 43.7)
OS 18 months, % (95% CI)	50.1 (38.5, 60.7)	29.7 (16.8, 43.7)
OS 24 months, % (95% CI)	42.8 (31.5, 53.7)	19.8 (9.4,33.0)

CI, confidence interval; ITT, intent-to-treat (all randomised patients); OS, overall survival.

- With 19 months of additional follow-up after the primary analysis:
  - mOS was 18.2 months with ripretinib vs 6.3 months with placebo (hazard ratio 0.41, 95% CI 0.26–0.65; **Figure 6**)
  - mOS was 10 months in the placebo patients who crossed over to ripretinib (**Figure 6**)
  - Estimated OS for patients randomised to ripretinib was 65.1% at 12 months and 42.8% at 24 months (**Table 3**)

Safety in the double-blind period

- Safety findings were consistent with the primary analysis results[5]; most treatment-emergent AEs (TEAEs) were Grade 1/2
- Common (≥15% of patients) TEAEs and additional Grade 3/4 TEAEs in >4% of patients are shown in **Table 4**
- With 19 months of additional follow-up after the primary analysis, the increase in TEAEs (**Table 4**) and the number of new TEAEs leading to dose modification or death (**Table 5**) in patients were minimal

Table 4. TEAEs in ≥15% of patients (regardless of drug-relatedness) and additional Grade 3/4 TEAEs in >4% of patients

	Ripretinib		Placebo	
Preferred term, n (%)	Any grade (n = 85)	Grade 3/4 (n = 85)[a]	Any grade (n = 43)[b]	Grade 3/4 (n = 43)[a,b]
TEAEs in ≥15% of patients				
Alopecia	44 (52)	N/A	2 (5)	N/A
Fatigue	40 (47)	3 (4)	10 (23)	1 (2)
Nausea	35 (41)	3 (4)	5 (12)	0
Abdominal pain	34 (40)	6 (7)	13 (30)	2 (5)
Constipation	32 (38)	1 (1)	9 (21)	0
Myalgia	31 (37)	1 (1)	5 (12)	1 (2)
Diarrhoea	28 (33)	1 (1)	6 (14)	1 (2)
Decreased appetite	25 (29)	1 (1)	9 (21)	2 (5)
Palmar-plantar erythrodysesthaesia	19 (22)	0	0	0
Vomiting	19 (22)	3 (4)	3 (7)	0
Headache	18 (21)	0	2 (5)	0
Oedema peripheral	18 (21)	1 (1)	3 (7)	0
Arthralgia	17 (20)	0	2 (5)	0
Weight decreased	17 (20)	0	5 (12)	0
Anemia	16 (19)	9 (11)	8 (19)	6 (14)
Dry skin	16 (19)	0	5 (12)	0
Muscle spasms	16 (19)	0	2 (5)	0
Blood bilirubin increased	15 (18)	1 (1)	2 (5)	0
Dyspnoea	13 (15)	0	0	0
Hypertension	13 (15)	6 (7)	2 (5)	0
Insomnia	13 (15)	0	6 (14)	0
Additional Grade 3/4 TEAEs in >4% of patients				
Hypophosphataemia	9 (11)	4 (5)	0	0
Lipase increased	9 (11)	4 (5)	1 (2)	0

[a]Corresponding Grade 3/4 TEAEs to TEAEs in ≥15% of patients receiving ripretinib.
[b]Forty-four patients were randomised to placebo, but 1 did not receive treatment.
N/A, not applicable; TEAE, treatment-emergent adverse event.

Table 5. Summary of events leading to dose modification

Parameters, n (%)	Ripretinib (n = 85)	Placebo (n = 43)[a]
Any TEAEs leading to dose interruption	24 (28)	10 (23)
Any TEAEs leading to dose reduction	8 (9)	1 (2)
Any TEAEs leading to treatment discontinuation	7 (8)	5 (12)
Any TEAEs leading to death[b]	6 (7)	10 (23)

[a]Forty-four patients were randomised to placebo, but 1 did not receive treatment.
[b]Three deaths considered possibly related to blinded study drug; 2 in ripretinib arm (respiratory failure and death) and 1 in placebo arm (due to 2 events of septic shock and pulmonary oedema).
TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Evaluation of primary and secondary endpoints in the phase 3 INVICTUS study, with a cutoff date 19 months after the primary analysis, demonstrate stable mPFS with no change since the primary analysis/data release and improved mOS among patients receiving ripretinib
  - mPFS was 6.3 months with ripretinib vs 1.0 month with placebo
  - mOS was 18.2 months with ripretinib vs 6.3 months with placebo
  - mOS was 10 months in placebo patients who crossed over to ripretinib
- These more mature data continue to support the clinically meaningful benefit in PFS and OS for ripretinib with an acceptable safety profile in patients with advanced GIST previously treated with 3 or more prior tyrosine kinase inhibitors

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Dr. von Mehren acts in an advisory/consultancy role for Deciphera, Blueprint Medicines, and Exelixis; receives research funding from Novartis; and receives travel/accommodations/expenses from Deciphera and NCCN; Dr. von Mehren's institution receives research funding from Deciphera, Blueprint Medicines, Arog, Novartis, Gradalis, GenMab, and ASCO.

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