Clinical benefit with ripretinib as ≥fourth-line treatment in patients with advanced gastrointestinal stromal tumor: Update from the phase 3 INVICTUS study

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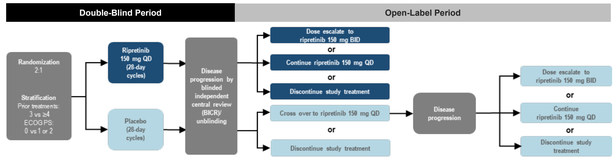
INTRODUCTION

- Ripretinib received FDA approval on May 15, 2020, based on the INVICTUS study (NCT03353753), for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received 3 or more prior tyrosine kinase inhibitors (TKI), including imatinib[1]
- Ripretinib is a switch-control TKI with a unique dual mechanism of action (MOA) designed to broadly inhibit mutant KIT and PDGFRA kinase signaling
  - By binding to the switch pocket and preventing access by the activation loop, ripretinib locks the kinase in an inactive state, preventing downstream signaling[2]
  - Click for a video of ripretinib's MOA
- In the INVICTUS study, a phase 3 randomized, double-blind, placebo-controlled trial in ≥fourth-line advanced GIST, ripretinib compared with placebo significantly improved median progression-free survival (PFS, 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 (OS; 15.1 vs 6.6 months), and showed an overall response rate (ORR) of 9.4% (planned primary analysis data, May 31, 2019)[3,4]
- During the INVICTUS trial, ripretinib was well tolerated; common adverse events (AEs) included alopecia, myalgia, and nausea[3]
- Here, we report the updated results from the INVICTUS study after an additional 9 months of follow-up

METHODS

- Patients with advanced GIST previously treated with at least imatinib, sunitinib, and regorafenib were randomized (2:1) to ripretinib 150 mg once daily (QD) or placebo (**Figure 1**)
- Upon disease progression determined by blinded independent central review (BICR)
  - Patients randomized to placebo had the option to cross over to ripretinib 150 mg QD
  - Patients randomized to ripretinib 150 mg QD had the option to dose escalate to receive ripretinib 150 mg twice daily (BID)
- 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, summarized 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
- All updated data are reported as of March 9, 2020

Figure 1. Overall study design



Primary Endpoint	Select Secondary Endpoints
PFS (per mRECIST based on BICR)	Objective response rate (ORR) assessed by BICR (key endpoint) Overall survival (OS)

Post-primary follow-up analysis[a]
Data cutoff
March 9, 2020

ClinicalTrials.gov: NCT 03353753

[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.

RESULTS

Patient disposition and baseline characteristics

- Overall, 129 patients were randomized, and 128 received treatment (ripretinib or placebo)
- Patient baseline characteristics and mutational status are shown in **Table 1**
  - Patients received a minimum of 3 prior therapies
  - Of 129 patients, 99 (77%) had a KIT primary mutation and 3 (2%) had a PDGFRA mutation

Table 1. Baseline characteristics and demographics

	Ripretinib (n = 85)	Placebo (n = 44)	Total (n = 129)
Age (years), median (min, max)	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)
Gender			
Male	47 (55)	26 (59)	73 (57)
Race			
White	64 (75)	33 (75)	97 (75)
Region			
US	40 (47)	20 (46)	60 (47)
ECOG PS			
0	37 (44)	17 (39)	54 (42)
1/2	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 tumor 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/PDGFRA wild type	7 (8)	3 (7)	10 (8)
Not available/not done[b]	12 (14)	5 (11)	17 (13)

Data shown as n (%) unless otherwise indicated.
[a]In addition to imatinib, sunitinib, and regorafenib, prior therapies received by ≥5% of patients included pazopanib, nilotinib, sorafenib, and avapritinib. [b]Not available, tumor tissue analyzed for baseline mutations, but analysis failed; Not done, biopsy completed per protocol, but sample not received for analysis
ECOG PS, Eastern Cooperative Oncology Group performance status; max, maximum; min, minimum.

Efficacy and duration of response

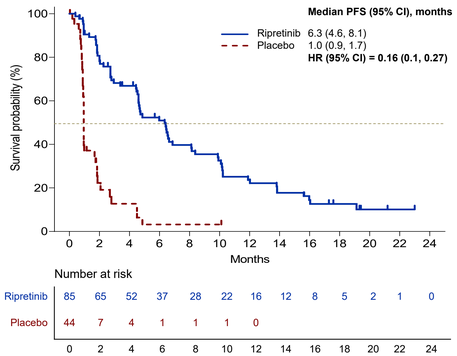
- Patients randomized to ripretinib had a median PFS of 6.3 (95% CI 4.6–8.1) vs 1.0 (95% CI 0.9–1.7) months for patients on placebo, with a hazard ratio of 0.16 (**Figure 2**)
- In the ripretinib group, 10 patients achieved a partial response compared with no patients in the placebo group (**Table 2**)
  - 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 duration of response was 14.5 months (**Table 2**)
  - In all subgroups assessed, ripretinib showed PFS benefit vs placebo (**Figure 5**)

Table 2. Progression-free survival and objective response rate in the ITT population

	Ripretinib (n = 85)	Placebo (n = 44)
Events, n (%)	66 (77.6)	37 (84.1)
Censored, n (%)	19 (22.4)	7 (15.9)
PFS 6 months, % (95% CI)	51.0 (39.4, 61.4)	3.2 (0.2, 13.8)
PFS 12 months, % (95% CI)	23.6 (14.6, 34.0)	NE (NE, NE)
PFS 18 months, % (95% CI)	12.6 (6.0, 21.9)	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)

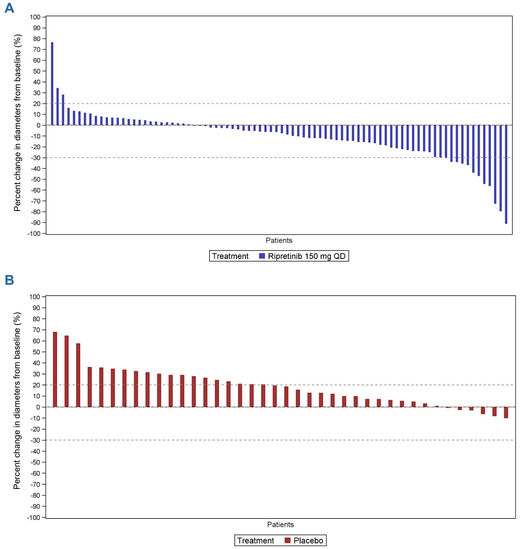
CI, confidence interval; DOR, duration of response; ITT, intent-to-treat (all randomized patients); NE, not estimable; ORR, objective response rate; PFS, progression-free survival.

Figure 2. Progression-free survival in the ITT population[a]



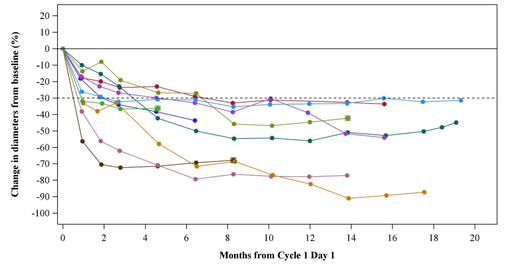
[a]The only patient remaining on placebo at the May 31, 2019, data cutoff crossed over to the ripretinib 150 mg QD treatment without BICR PD after study unblinding in August 2019. PFS for this patient was censored on the last day before crossover.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat (all randomized patients); PD, progressive disease; PFS, progression-free survival; QD, once daily.

Figure 3. Percent change from baseline in sum of diameters of target lesions in the ITT population



Dash lines indicate PD at 20% and PR at –30%. ITT, intent-to-treat (all randomized patients); PD, progressive disease; PR, partial response; QD, once daily.

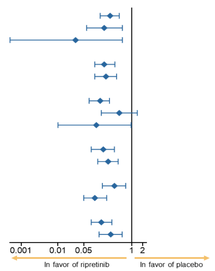
Figure 4. Change from baseline in sum of diameters of target lesions of confirmed responders based on BICR



Dash line indicates PR at –30%. BICR, blinded independent central review.

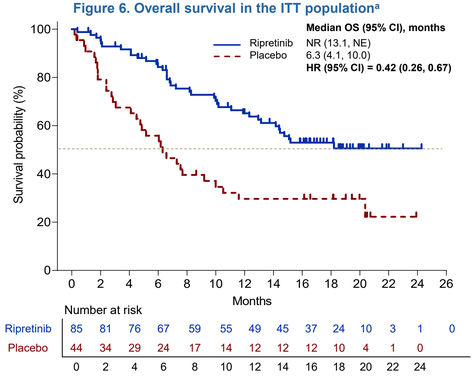
Figure 5. Ripretinib showed PFS benefit in all assessed patient subgroups

	Ripretinib 150 mg QD (n)	Placebo (n)	Hazard ratio (95% CI)
Age group			
18–64 years	57	22	0.26 (0.14, 046)
65–74 years	20	12	0.18 (0.06, 0.56)
≥75 years	8	10	0.03 (0.00, 0.56)
Gender			
Male	47	26	0.18 (0.10, 0.35)
Female	38	18	0.20 (0.10, 0.39)
Race			
White	64	33	0.14 (0.07, 0.25)
Non-White	13	7	0.46 (0.15, 1.42)
Not reported	8	4	0.11 (0.01, 0.97)
Country			
US	40	20	0.17 (0.08, 0.34)
Non-US	45	24	0.23 (0.12, 0.43)
Screening ECOG			
0	38	19	0.34 (0.16, 0.69)
1 or 2	47	25	0.10 (0.05, 0.21)
Prior anti-cancer treatments			
3	54	27	0.15 (0.08, 0.29)
≥4	31	17	0.27 (0.13, 0.55)



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

Figure 6. Overall survival in the ITT population[a]



[a]OS data include all time periods, including dose escalation to 150 mg BID. Placebo curve includes patients who crossed over to ripretinib treatment
BID, twice daily; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat (all randomized patients); NE, not estimable; NR, not reached; OS, overall survival.

Table 3. Estimated overall survival in the ITT population

	Ripretinib (n = 85)	Placebo (n = 44)
Events, n (%)	38 (44.7)	31 (70.5)
Censored, n (%)	47 (55.3)	13 (29.5)
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)	53.0 (41.3, 63.3)	29.7 (16.8, 43.7)
OS 24 months, % (95% CI)	50.6 (38.5, 61.4)	NE (NE, NE)

CI, confidence interval; ITT, intent-to-treat (all randomized patients); NE, not estimable; OS, overall survival.

- With 9 months of additional follow-up after the primary analysis, the median OS for patients randomized to ripretinib has extended from 15.1 months to "not reached" (**Figure 6**)
- Estimated OS at 12 months was 65.1% and 50.6% at 24 months for patients randomized to ripretinib (**Table 3**)

Safety

- Safety findings were consistent with the previous primary analysis results[4]
- Commonly reported (≥15% of patients) treatment-emergent AEs (TEAEs) and additional Grade 3/4 TEAEs in ≥4% of patients are shown in **Table 4**
- After 9 months of additional follow-up, the increase in TEAEs (**Table 4**) and the number of new TEAEs leading to dose modification or death (**Table 5**) in patients were minimal
- The majority of TEAEs were Grade 1/2

Table 4. TEAEs in >15% of patients 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)	0	2 (4.7)	0
Fatigue	40 (47)	3 (3.5)	10 (23)	1 (2.3)
Nausea	35 (41)	3 (3.5)	5 (12)	0
Abdominal pain	34 (40)	6 (7.1)	13 (30)	2 (4.7)
Constipation	31 (37)	1 (1.2)	9 (21)	0
Myalgia	30 (35)	2 (2.4)	5 (12)	0
Decreased appetite	26 (31)	1 (1.2)	9 (21)	2 (4.7)
Diarrhea	26 (31)	1 (1.2)	6 (14)	1 (2.3)
PPES	19 (22)	0	0	0
Vomiting	19 (22)	3 (3.5)	3 (7.0)	0
Headache	17 (20)	0	2 (4.7)	0
Weight decreased	17 (20)	0	5 (12)	0
Arthralgia	16 (19)	0	2 (4.7)	0
Muscle spasms	16 (19)	0	2 (4.7)	0
Edema peripheral	16 (19)	1 (1.2)	3 (7.0)	0
Blood bilirubin increased	15 (18)	1 (1.2)	2 (4.7)	0
Anemia	14 (17)	9 (11)	8 (19)	6 (14)
Dry skin	14 (17)	0	5 (12)	0
Hypertension	13 (15)	6 (7.1)	2 (4.7)	0
Additional grade 3/4 TEAEs in ≥ 4% of patients				
Hypophosphatemia	9 (10.6)	4 (4.7)	0	0
Lipase increased	9 (10.6)	4 (4.7)	1 (2.3)	0
Blood alkaline phosphatase increased	6 (7.1)	4 (4.7)	1 (2.3)	1 (2.3)

[a]Corresponding grade 3/4 TEAEs to TEAEs in >15% of patients receiving ripretinib. [b]Forty-four patients were randomized to placebo, but 1 did not receive treatment.
TEAE, treatment-emergent adverse event; PPES, Palmar-plantar erythrodysesthesia syndrome.

Table 5. Summary of events leading to dose modification

	Ripretinib (n = 85)	Placebo (n = 43)[a]
TEAEs leading to dose interruption	22 (26)	9 (21)
TEAEs leading to dose reduction	7 (8.2)	1 (2.3)
TEAEs leading to treatment discontinuation	7 (8.2)	5 (12)
TEAEs leading to death[b]	6 (7.1)	10 (23)

Data shown as n (%).
[a]Forty-four patients were randomized to placebo, but 1 did not receive treatment. [b]One death in each arm considered possibly related to blinded study drug.
TEAE, treatment-emergent adverse event.

CONCLUSIONS

- With an additional 9 months of follow-up from the primary results of the phase 3 randomized INVICTUS trial, ripretinib continues to provide clinically meaningful benefit with a well-tolerated safety profile in patients with advanced GIST who have received ≥3 prior TKIs
  - Median PFS was 6.3 months with ripretinib vs 1.0 month with placebo
  - Median OS was not reached with ripretinib vs 6.3 months with placebo
  - ORR was 11.8% with ripretinib vs 0 with placebo
  - Safety findings were consistent with the previous primary analysis results
- Ripretinib is approved for the treatment of patients with fourth-line GIST in the United States (FDA), Canada (Health Canada), and Australia (TGA)
- Enrollment is ongoing in INTRIGUE, a phase 3, randomized, multicenter, open-label study of ripretinib vs sunitinib in patients with advanced GIST after treatment with imatinib (NCT03673501)

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References

1) Qinlock™ (ripretinib) [package insert]. Deciphera; May 2020; **2)** Smith et al. *Cancer Cell.* 2019; 35: 738–51; **3)** Blay et al. *Lancet Oncol.* 2020; 21:923–34; **4)** von Mehren et al. *Ann Oncol.* 2019; 30 (suppl 5): v851–v934.