Intra-patient dose escalation of ripretinib after disease progression in patients with advanced gastrointestinal stromal tumor: Analyses from the phase 3 INVICTUS study

John Zalcberg[1], Michael C. Heinrich[2], Suzanne George[3], Sebastian Bauer[4], Patrick Schöffski[5], César Serrano[6], Hans Gelderblom[7], Robin L. Jones[8], Steven Attia[9], Gina D'Amato[10], Ping Chi[11], Peter Reichardt[12], Neeta Somaiah[13], Julie Meade[14], Vienna Reichert[14], Kelvin Shi[14], Matthew L. Sherman[14], Rodrigo Ruiz-Soto[14], Margaret von Mehren[15], Jean-Yves Blay[16]

[1]Monash University, Melbourne, VIC, Australia; [2]OHSU Knight Cancer Institute, Portland, OR, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]West German Cancer Center, Essen, Germany; [5]University Hospitals Leuven, Leuven, Belgium; [6]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [7]Leiden University Medical Center, Leiden, Netherlands; [8]Royal Marsden and Institute of Cancer Research, London, UK; [9]Mayo Clinic, Jacksonville, FL, USA; [10]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; [11]Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, NY, USA; [12]Sarcoma Center, Helios Klinikum Berlin-Buch, Berlin, Germany; [13]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [14]Deciphera Pharmaceuticals, LLC, Waltham, MA, USA; [15]Fox Chase Cancer Center, Philadelphia, PA, USA; [16]Centre Leon Berard, Lyon, France

Abstract #11535

INTRODUCTION

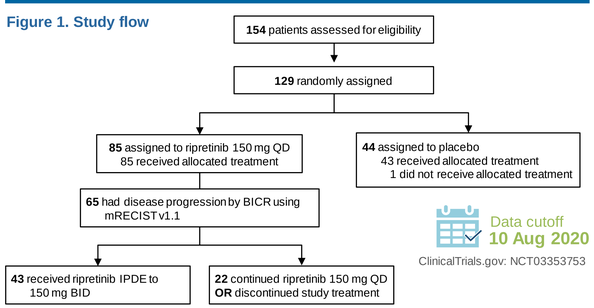
- Ripretinib, a switch control kinase inhibitor of KIT/PDGFRA, is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib[1]
- In the INVICTUS study (NCT03353753), patients with ≥fourth-line GIST receiving ripretinib 150 mg once daily (QD) had a median progression-free survival (PFS) of 6.3 months versus 1.0 month for placebo (hazard ratio [HR] = 0.15, p <0.0001) as of 31 May 2019[2]
- In the dose-escalation phase of phase 1 study (NCT02571036), the maximum tolerated dose was not reached with doses up to 200 mg twice daily (BID) and the starting dose of ripretinib 150 mg BID was well tolerated without significant dose-limiting toxicity[3]
- Patients in the INVICTUS study were offered the option of ripretinib intra-patient dose escalation (IPDE) to 150 mg BID after disease progression on ripretinib 150 mg QD[2]
- In this exploratory analysis, as of 10 Aug 2020, we report the safety and efficacy of ripretinib IPDE to 150 mg BID among patients randomized to ripretinib 150 mg QD in the INVICTUS study

METHODS

- In INVICTUS, patients with advanced GIST having received ≥3 prior anticancer therapies were randomized to ripretinib 150 mg QD (n = 85) or placebo (n = 44)
- Ripretinib IPDE to 150 mg BID was allowed after disease progression on ripretinib 150 mg QD as assessed by blinded independent central review using modified Response Evaluation Criteria in Solid Tumors (mRECIST) 1.1
- Tumor imaging was performed every 28-day cycle for the first 4 cycles in the ripretinib 150 mg QD period and then every other cycle, including the 150 mg BID period
- Among the ripretinib IPDE patients, PFS1 was the interval between the date of randomization until progressive disease (PD); PFS2 was the interval between the date of the first dose of ripretinib 150 mg BID to PD or death

RESULTS

Figure 1. Study flow



BICR, blinded independent central review; BID, twice daily; IPDE, intra-patient dose escalation; mRECIST, modified Response Evaluation Criteria in Solid Tumors; QD, once daily.

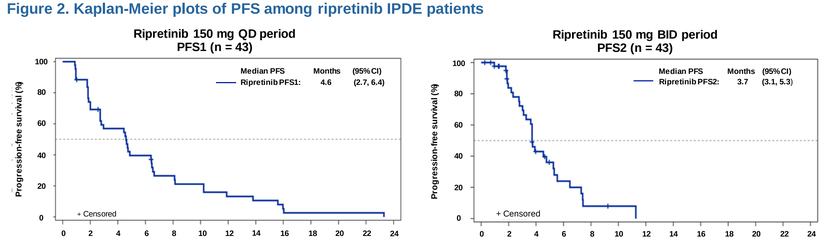
- Of the 85 patients randomized to ripretinib 150 mg QD, 43 received ripretinib IPDE to 150 mg BID after disease progression by blinded independent central review using mRECIST v1.1

Table 1. Baseline characteristics at study entry

Characteristics	Patients with PD receiving ripretinib IPDE to 150 mg BID (n = 43)	Patients with PD not receiving ripretinib IPDE (n = 22)
Age at study entry, median (range), years	59 (36–79)	57 (40–82)
18-64	27 (63)	18 (82)
65-74	12 (28)	1 (5)
≥75	4 (9)	3 (14)
Sex		
Male	25 (58)	13 (59)
Female	18 (42)	9 (41)
ECOG Performance Status		
0	21 (49)	8 (36)
1	17 (40)	11 (50)
2	5 (12)	3 (14)
Primary mutation (central testing of tumor tissue)		
KIT exon 11	25 (58)	12 (55)
KIT exon 9	7 (16)	3 (14)
Other *KIT*	1 (2)	0
PDGFRA	1 (2)	2 (9)
KIT wild type/*PDGFRA* wild type	3 (7)	2 (9)
Not available[a] or not done[b]	6 (14)	3 (14)

Data are presented as n (%) unless otherwise noted.
[a]Tumor tissue analyzed for baseline mutations, but analysis failed.
[b]Biopsy completed per protocol, but sample not received for analysis.
BID, twice daily; ECOG, Eastern Cooperative Oncology Group; IPDE, intra-patient dose escalation; PD, progressive disease; PDGFRA, platelet-derived growth factor receptor alpha.

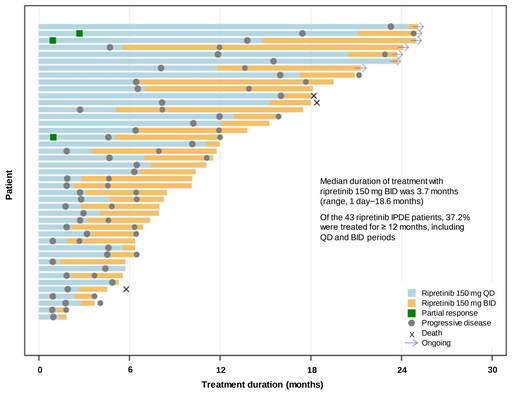
Figure 2. Kaplan-Meier plots of PFS among ripretinib IPDE patients



Of the 43 ripretinib IPDE patients, 3 with progressive disease during ripretinib 150 mg QD were censored due to new anti-cancer therapy or surgery/radiation.
BID, twice daily; CI, confidence interval; IPDE; intra-patient dose escalation; PFS, progression-free survival, QD, once daily

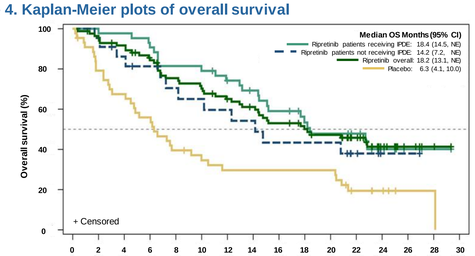
- Among the 43 patients in the ripretinib arm receiving IPDE, median PFS1 (mPFS1) was 4.6 months (95% confidence interval [CI], 2.7–6.4) and mPFS2 was 3.7 months (95% CI, 3.1–5.3); the ratio of mPFS2/mPFS1 was 80%

Figure 3. Total duration of treatment in ripretinib patients receiving IPDE to 150 mg BID



BID, twice daily; IPDE, intra-patient dose escalation; QD, once daily.

Figure 4. Kaplan-Meier plots of overall survival



CI, confidence interval; IPDE, intra-patient dose escalation; NE, not estimable; OS, overall survival.

- Median overall survival (mOS) was 18.4 months in patients randomized to ripretinib 150 mg QD with PD and receiving IPDE to 150 mg BID (n = 43) and 14.2 months in those randomized to ripretinib 150 mg QD with PD and not receiving IPDE (n = 22) (HR 0.74, 95% CI 0.37–1.49)
- Among the intention-to-treat population of INVICTUS, mOS was 18.2 months (95% CI, 13.1–not estimable) in the ripretinib group (n = 85) versus 6.3 months (95% CI, 4.1–10 months) in patients randomized to the placebo group (n = 44) (HR 0.42, 95% CI 0.27–0.67)

Table 2. TEAEs in >10% of patients receiving ripretinib IPDE

Preferred term, n (%)	Ripretinib 150 mg QD period (n = 43)		Ripretinib 150 mg BID period (n = 43)[a]	
	All grades	Grade 3–4	All grades	Grade 3–4
Abdominal pain	18 (42)	2 (5)	13 (30)	3 (7)
Decreased appetite	13 (30)	1 (2)	11 (26)	2 (5)
Anemia	5 (12)	1 (2)	10 (23)	6 (14)
Nausea	13 (30)	1 (2)	10 (23)	1 (2)
Blood bilirubin increased	8 (19)	0	8 (19)	0
Constipation	16 (37)	0	8 (19)	0
Diarrhea	11 (26)	0	7 (16)	0
Fatigue	19 (44)	1 (2)	7 (16)	2 (5)
Myalgia	15 (35)	1 (2)	7 (16)	0
Palmar-plantar erythrodysesthesia	8 (19)	0	7 (16)	1 (2)
Alopecia	26 (60)	—	6 (14)	—
Asthenia	7 (16)	0	6 (14)	1 (2)
Dyspnea	4 (9)	0	6 (14)	1 (2)
Vomiting	7 (16)	1 (2)	6 (14)	1 (2)
Muscle spasms	6 (14)	0	5 (12)	0
Edema peripheral	7 (16)	0	5 (12)	0
Weight loss	9 (21)	0	5 (12)	0

[a] Data represent new or worsening TEAEs in the ripretinib 150 mg BID period. The ongoing TEAEs from the ripretinib 150 mg QD period were not included if they remained at the same or lower grade.
BID, twice daily; IPDE, intra-patient dose escalation; QD, once daily; TEAE, treatment-emergent adverse event.

Table 3. Dose modifications

Parameters, n (%)	Ripretinib 150 mg QD period (n = 43)	Ripretinib 150 mg BID period (n = 43)[a]
Any dose interruption	6 (14)	11 (26)
Any dose reduction	2 (5)	8 (19)
Any TEAE leading to treatment discontinuation	N/A	7 (16)[b]

[a]Data only includes dose interruption/dose reduction/treatment discontinuation in the ripretinib 150 mg BID period.
[b]7 patients had 10 TEAEs leading to treatment discontinuation.
BID, twice daily; N/A, not available; QD, once daily; TEAE, treatment-emergent adverse event.

- Ripretinib 150 mg BID was well tolerated with new or worsening Grade 3–4 treatment-emergent adverse events (TEAEs) of anemia in 6 (14%) and abdominal pain in 3 (7%) patients
- Ripretinib 150 mg BID was discontinued due to TEAEs in 7 (16%) patients

CONCLUSIONS

- Based on this exploratory analysis of the phase 3 INVICTUS study, ripretinib IPDE to 150 mg BID after disease progression on ripretinib 150 mg QD provided clinical benefit for patients with advanced GIST receiving ≥fourth-line therapy
- The safety profile for ripretinib 150 mg BID was acceptable with a similar tolerability profile to the 150 mg QD dosing

Presented at the 2021 ASCO Annual Meeting, June 4–8, 2021

Acknowledgments

The study was sponsored by Deciphera Pharmaceuticals, LLC, Waltham, MA, USA. Medical writing was provided by Uma Chandrasekaran, PhD (Deciphera Pharmaceuticals, LLC); editorial support was provided by AlphaBioCom, LLC (King of Prussia, PA, USA), and was funded by Deciphera Pharmaceuticals, LLC.

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Corresponding Author

John Zalcberg (john.zalcberg@monash.edu)

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