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WORLD CONGRESS ON Gastrointestinal Cancer | 2020 VIRTUAL

Efficacy and safety of ripretinib as ≥4th-line therapy for patients with gastrointestinal stromal tumor (GIST) following crossover from placebo: Analyses from INVICTUS

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Disclosures

- Dr. César Serrano: advisory/consultancy role with Deciphera Pharmaceuticals, LLC, and Blueprint Medicines™ Corporation; serves as a speaker for Bayer Healthcare and Blueprint Medicines™ Corporation; receives research funding from Deciphera Pharmaceuticals, LLC, Bayer Healthcare, and Pfizer, Inc.; travel accommodations from PharmaMar, Pfizer, Inc., Bayer Healthcare, Novartis, and Eli Lilly and Company.
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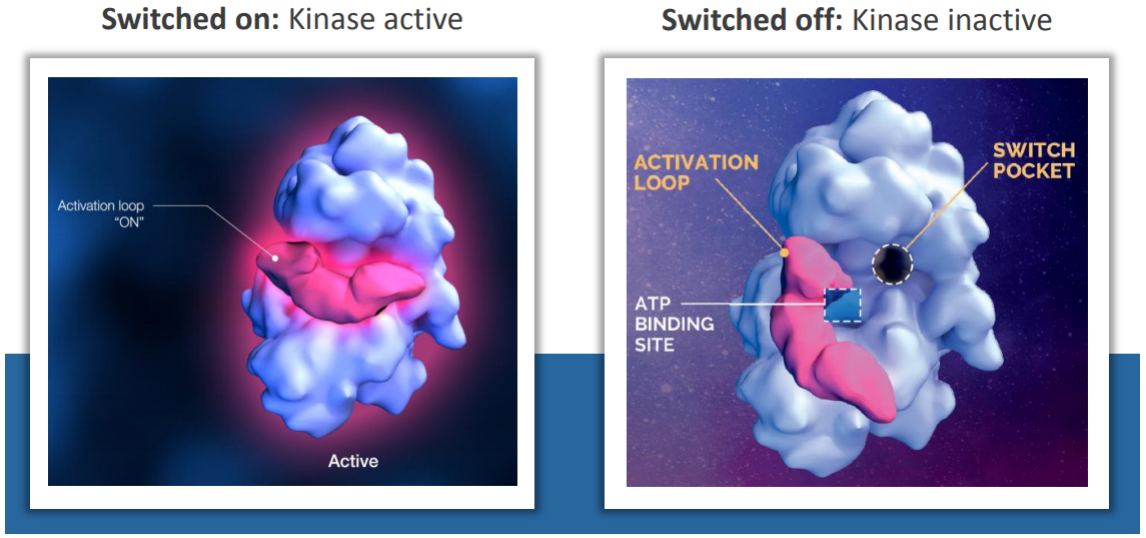
Background

KIT mutations drive approximately 80% of GIST

- GIST is the most common sarcoma of the gastrointestinal tract accounting for 1% to 2% of GI malignancies[1,2]
- Primary mutations in KIT or PDGFRA occur in >85% of patients with GIST[3]
- Mutations lead to activation of the kinase[4]
- Ripretinib is a novel tyrosine kinase **switch control** inhibitor engineered to broadly inhibit KIT and PDGFRA mutated kinases by using a unique **dual mechanism of action** that regulates the kinase switch pocket and activation loop[4]



ATP, adenosine triphosphate

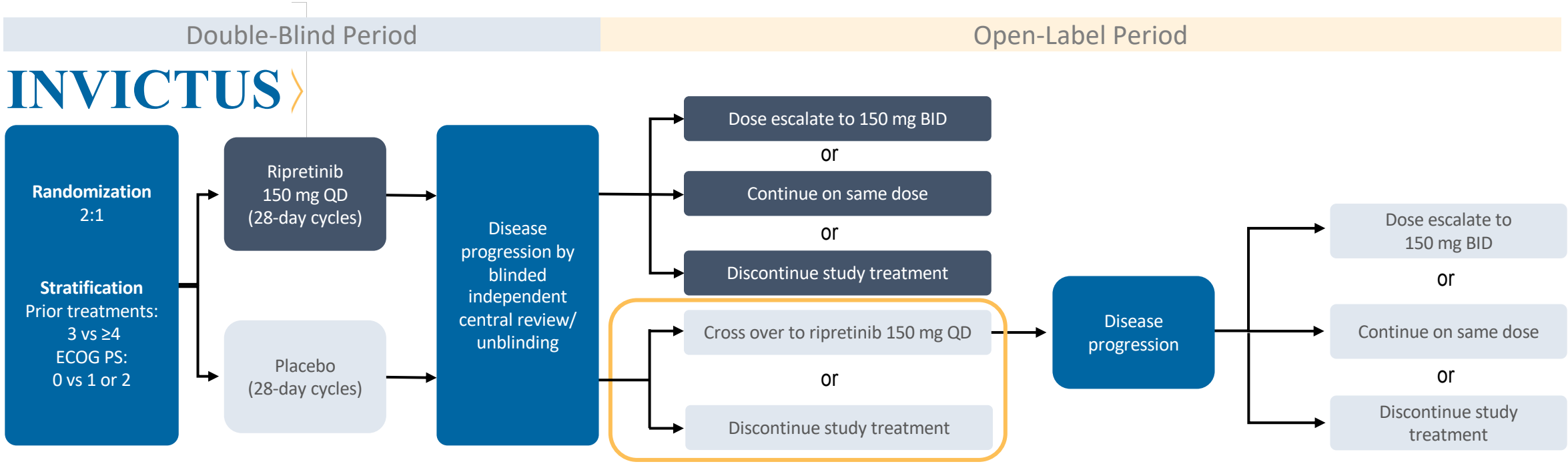
- In the phase 3 INVICTUS trial, ripretinib significantly improved progression-free survival (6.3 vs. 1.0 months) and showed a clinically meaningful overall survival (15.1 vs 6.6 months) vs placebo in patients with 4th-line advanced GIST
- **In May 2020, the US FDA approved ripretinib for the treatment of adult patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib**

GIST, gastrointestinal stromal tumor; PDGFRA, platelet-derived growth factor receptor alpha; US FDA, United States Food and Drug Administration.

1. Parab TM, et al. *J Gastrointest Oncol*. 2019;10:144-154. **2**. Mah GL, et al. *Cancer Epidemiol Biomarkers Prev.* 2015;24:298-302. **3.** Hsueh YS, et al. *PLOS One*.2013;e65762. **4**. Smith BD, et al. *Cancer Cell*. 2019;35:738-751.

INVICTUS: Randomized phase 3 study design

*Patients on placebo were given the option to **cross over** to ripretinib after disease progression*



Primary endpoint

PFS

(per modified RECIST based on **Blinded Independent Central Review** [BICR])

Select Secondary endpoints

- **Objective response rate (ORR)** assessed by BICR (Key endpoint)
- **Overall survival (OS)**

Data cutoff
May 31, 2019

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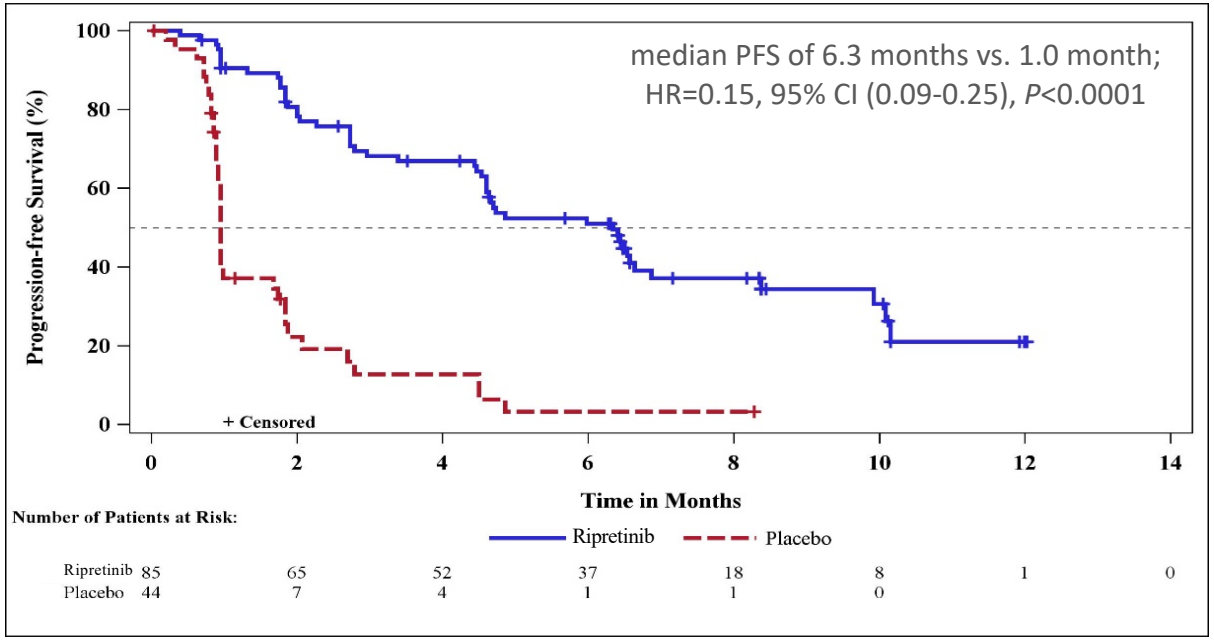
BID, twice daily; ECOG, Eastern Cooperative Oncology Group; QD, once daily.

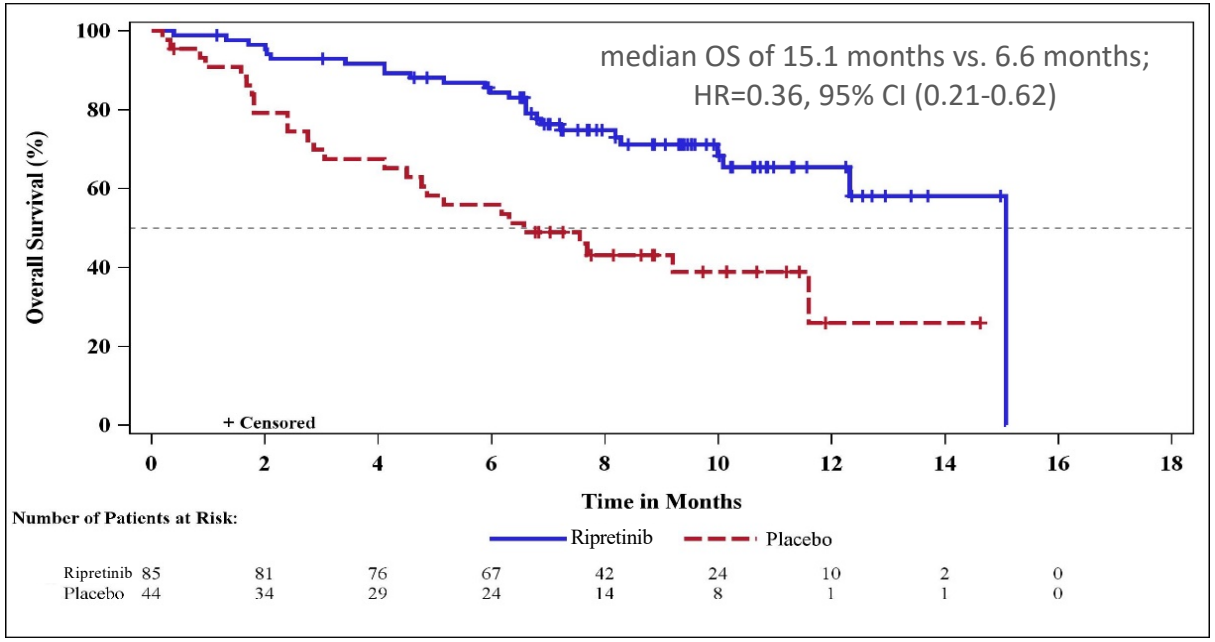
INVICTUS: Efficacy results

Ripretinib provided meaningful clinical benefit in patients with 4th-line advanced GIST

Ripretinib significantly improved **progression-free survival** vs. placebo**,** reducing the risk of progression or death by **85%**



Ripretinib showed a clinically meaningful benefit in **overall survival** vs. placebo, reducing the risk of death by **64%**



Key secondary endpoint of objective response rate was 9.4% compared with 0% for placebo (P = 0.0504)

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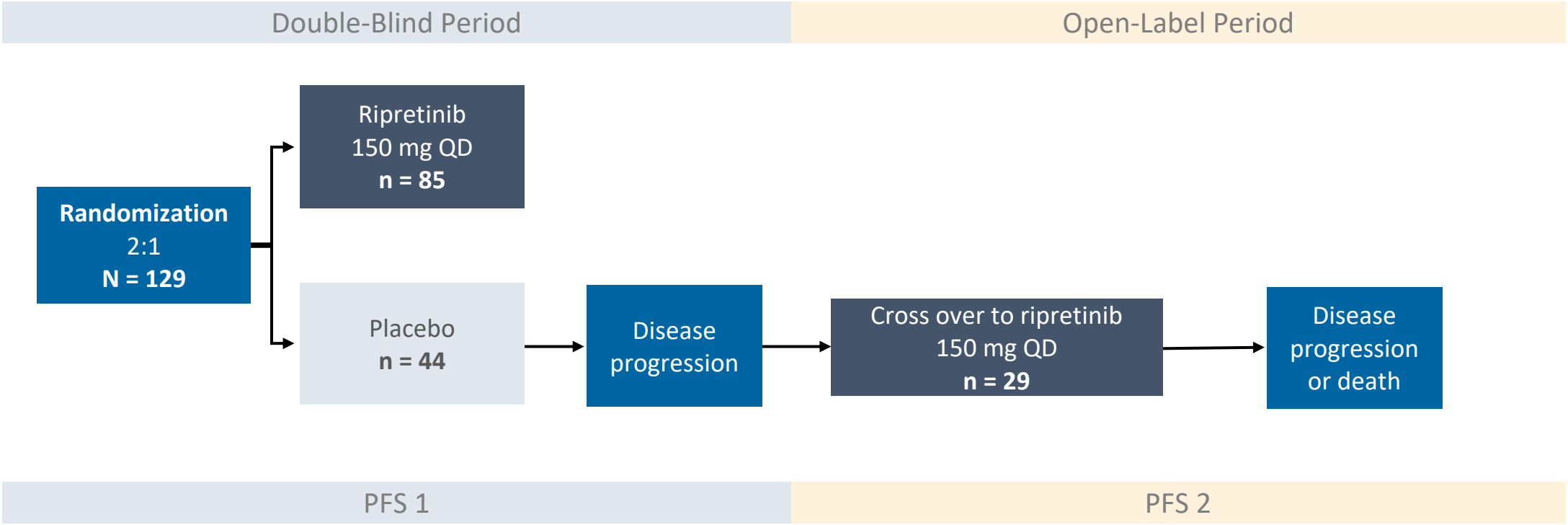
CI, confidence interval; GIST, gastrointestinal stromal tumor; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Patient disposition

Of 44 patients randomized to placebo during the double-blind period, 29 patients crossed over to ripretinib during the open-label period after progression



- A total of 15 patients who originally received placebo during the double-blind period were unable to cross over
  - 4 patients died, 3 patients had clinical progression without PD by BICR, 2 patients did not cross over due to adverse events, 1 patient transitioned to hospice, 1 patient was unable to take oral medications, 1 patient did not cross over due to physician decision, 1 patient withdrew consent, 1 patient was ongoing on placebo, and 1 patient never received the study drug

PFS2, for crossover patients time from ripretinib initiation to progression or death.
BICR, blinded independent central review; PD, disease progression; PFS, progression-free survival; QD, once daily.

Baseline characteristics

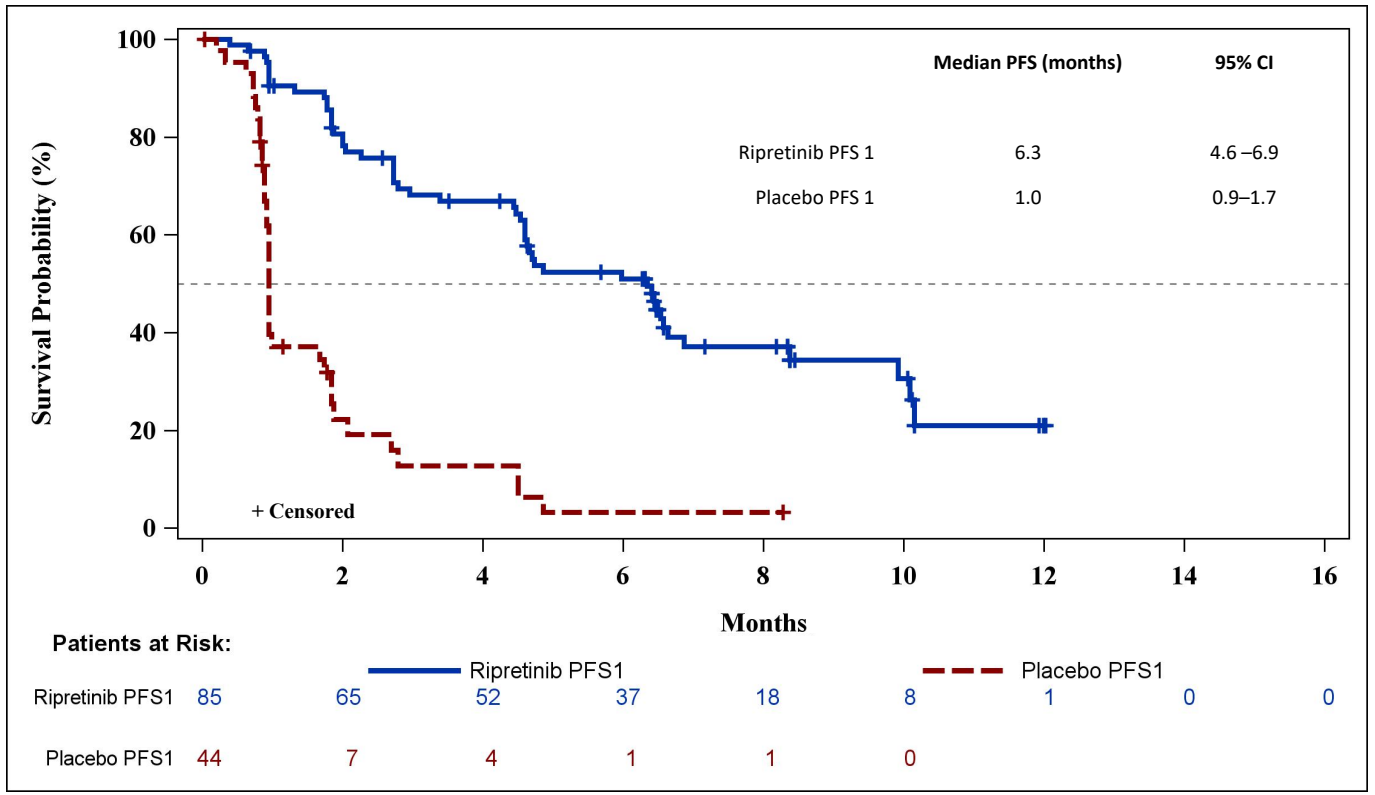
Baseline characteristics of patients that crossed over were comparable to those of patients from both arms of the double-blind study

	Open-label period	Double-blind period	
	Crossover to ripretinib (n=29)	Ripretinib (n=85)	Placebo (n=44)
Age, years			
Median (min, max)	68 (33, 81)	59 (29, 82)	65 (33, 83)
18-64, n (%)	12 (41)	57 (67)	22 (50)
65-74, n (%)	10 (34)	20 (24)	12 (27)
≥75, n (%)	7 (24)	8 (9)	10 (23)
Sex, n (%)			
Male	16 (55)	47 (55)	26 (59)
ECOG score at screening, n (%)			
0	11 (38)	37 (44)	17 (39)
1/2	18 (62)	48 (56)	27 (61)
Total number of prior systemic anticancer therapies, n (%)			
3	19 (66)	54 (64)	27 (61)
≥4 (range 4–7)	10 (34)	31 (36)	17 (39)

ECOG, Eastern Cooperative Oncology Group.

Progression-free survival

Ripretinib significantly improved PFS compared with placebo (6.3 vs 1.0 months)



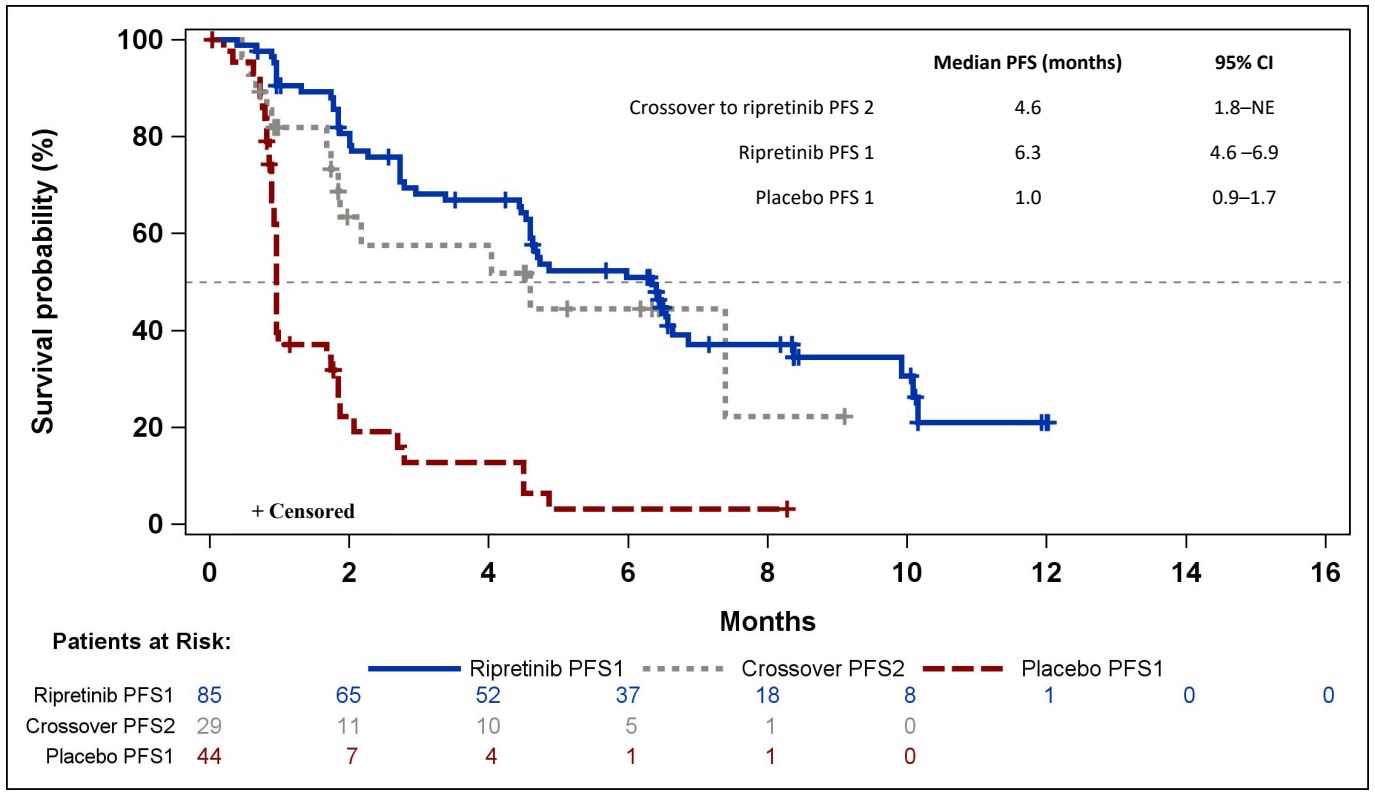
		Double-blind period	
		Ripretinib PFS 1 (n=85)	Placebo PFS 1 (n=44)
Events, n (%)		51 (60)	37 (84)
Censored, n (%)		34 (40)	7 (16)
Median PFS (months), % (95% CI)		6.3 (4.6, 6.9)	1.0 (0.9, 1.7)

CI, confidence interval

PFS, progression-free survival.

Exploratory analysis of progression-free survival

Placebo patients that crossed over derived benefit from ripretinib (PFS2 = 4.6 months)



PFS2, for crossover patients time from ripretinib initiation to progression or death.
PFS, progression-free survival.

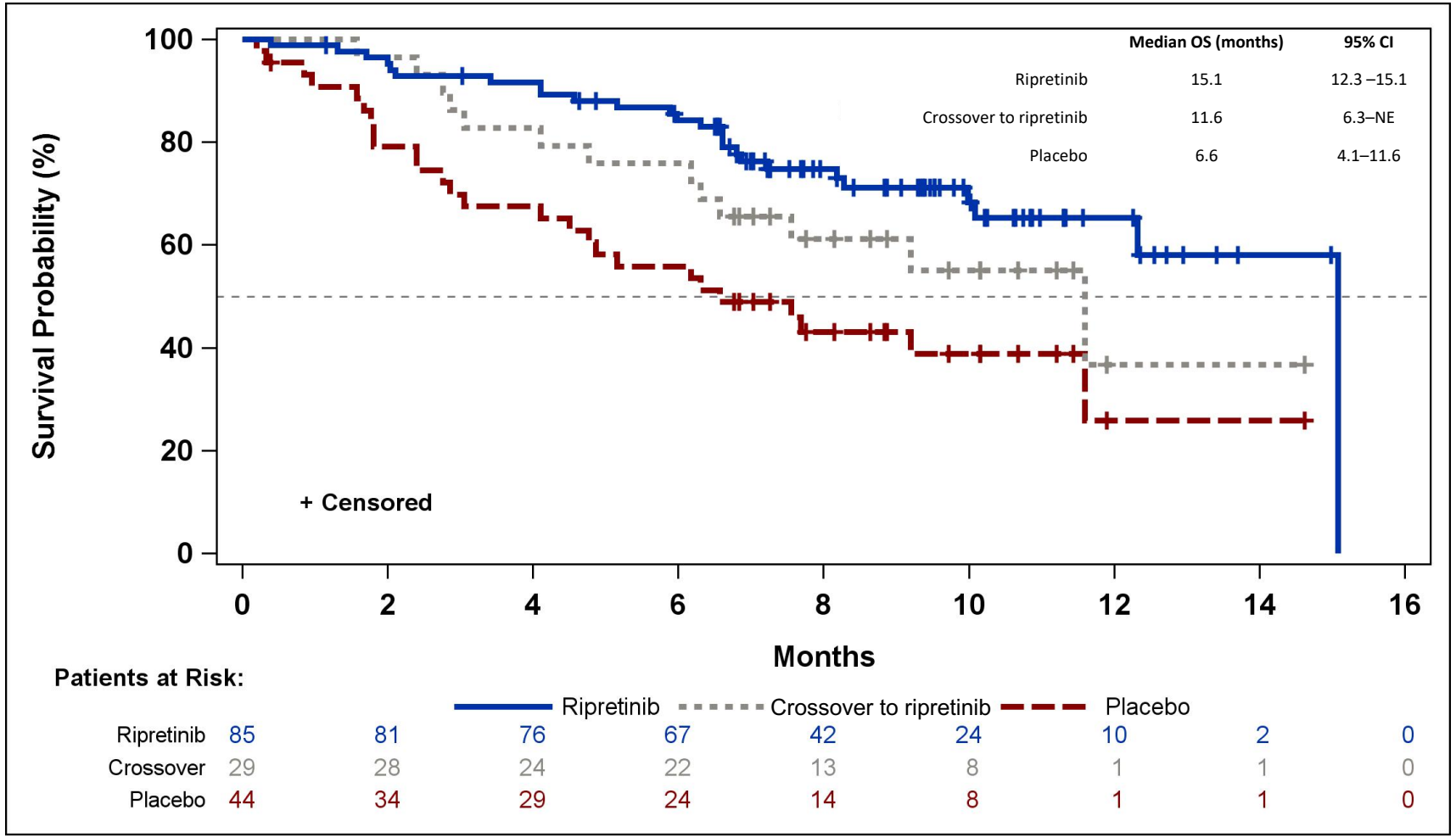
	Open-label period	Double-blind period	
	Crossover to ripretinib PFS 2 (n=29)	Ripretinib PFS 1 (n=85)	Placebo PFS 1 (n=44)
Events, n (%)	13 (45)	51 (60)	37 (84)
Censored, n (%)	16 (55)	34 (40)	7 (16)
Median PFS (months), % (95% CI)	4.6 (1.8, NE)	6.3 (4.6, 6.9)	1.0 (0.9, 1.7)

CI, confidence interval; NE, Not Estimable

- Patients that cross over from placebo to ripretinib began to derive benefit as soon as 1 month after starting treatment
- There were two patients with confirmed partial responses after crossover to ripretinib

Overall survival benefit

Placebo patients that crossed over had an overall survival benefit of 11.6 months



Overall survival from time of initial randomization for all 3 groups.

OS, overall survival; CI, confidence interval.

von Mehren M et al. Presentation at: ESMO 2019. Madrid, Spain.

TEAEs in >15% of patients

No new safety signals were observed in the crossover population that were not already observed in patients from the double-blind period

Preferred Term	Open-label period		Double-blind period			
	Crossover to ripretinib n=29		Ripretinib n=85		Placebo n=43	
	Grade 1-4 n (%)	Grade 3-4 n (%)	Grade 1-4 n (%)	Grade 3-4 n (%)	Grade 1-4 n (%)	Grade 3-4 n (%)
Anemia	10 (35)	6 (21)	12 (14)	8 (9.4)	8 (19)	6 (14)
Fatigue	10 (35)	3 (10)	36 (42)	3 (3.5)	10 (23)	1 (2.3)
Myalgia	10 (35)	0	27 (32)	1 (1.2)	5 (12)	0
Constipation	9 (31)	1 (3.4)	29 (34)	1 (1.2)	8 (19)	0
Abdominal pain	8 (28)	2 (6.9)	31 (37)	6 (7.1)	13 (30)	2 (4.7)
Alopecia	8 (28)	0	44 (52)	0	2 (4.7)	0
Decreased appetite	6 (21)	0	23 (27)	1 (1.2)	9 (21)	1 (2.3)
Weight decreased	6 (21)	0	16 (19)	0	5 (12)	0
PPES	5 (17)	0	18 (21)	0	0	0

AEs reported after crossover reflect only onset of new or worsening events. 44 patients were randomized to placebo, but 1 patient did not receive treatment.
PPES, Palmar-plantar erythrodysaesthesia syndrome; TEAE, treatment-emergent adverse event.

Conclusions

- In the phase 3 randomized INVICTUS trial, patients with 4th-line GIST exhibited a clinically meaningful benefit from ripretinib after crossover from placebo and had a well-tolerated safety profile that was generally consistent with previously reported data from the double-blind period
  - The median PFS2 (from initiation of ripretinib treatment to progression) for patients that crossed over to ripretinib was 4.6 months
  - The median OS for patients that crossed over to ripretinib was 11.6 months
- These data suggest that for patients who were able to cross over, ripretinib established disease control despite delayed initiation of treatment; however, maximum benefit is achieved when ripretinib is used immediately after failure of prior therapy in patients with ≥4th-line advanced GIST

Enrollment is ongoing in INTRIGUE, a Phase 3, interventional, randomized, multicenter, open-label study of ripretinib vs sunitinib in patients with advanced GIST after treatment with imatinib (NCT03673501)

GIST, gastrointestinal stromal tumor; OS, overall survival; PFS, progression-free survival.