Ripretinib demonstrated activity across all KIT/PDGFRA mutations in patients with fourth-line advanced gastrointestinal stromal tumor: Analysis from the phase 3 INVICTUS study

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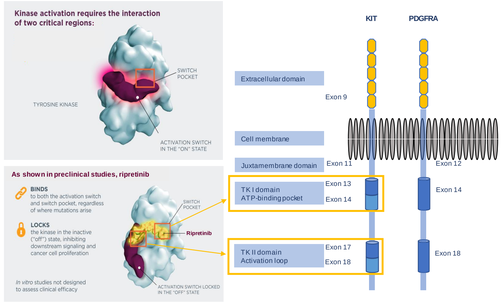
INTRODUCTION

- Ripretinib is a switch-control tyrosine kinase inhibitor designed to broadly inhibit mutant KIT/PDGFRA kinases (**Figure 1**)
- In May 2020, the US FDA approved ripretinib for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who received prior treatment with 3 or more kinase inhibitors, including imatinib[1]
- In the INVICTUS study, ripretinib significantly improved progression-free survival (PFS) compared with placebo (median PFS 6.3 vs 1.0 months, hazard ratio [HR] 0.15, *P* <0.0001), reducing the risk of disease progression or death by 85% and showing a clinically meaningful improvement in overall survival (OS, median OS 15.1 vs 6.6 months, HR 0.36)[1]
- KIT/PDGFRA mutations are early oncogenic events in patients with GIST and remain oncogenic drivers in the metastatic setting[2–4] (**Figure 1**)
- Clonal evolution of additional mutations represent the major mechanism of resistance to KIT tyrosine kinase inhibitors, and previously approved drugs inhibit only a limited number of mutations on the spectrum of resistance[5]
- Here, we report the results of an exploratory analysis from INVICTUS assessing the efficacy of ripretinib across KIT/PDGFRA mutation subgroups

Figure 1. KIT/PDGFRA structure and ripretinib mechanism of action



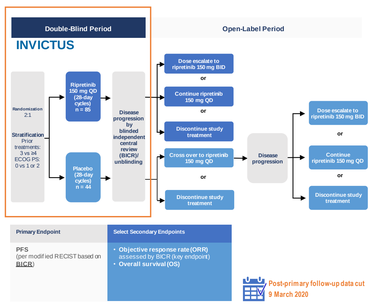
TK, tyrosine kinase.

Adapted from Ding, et al. 2020; and Corless, et al. 2011.

METHODS

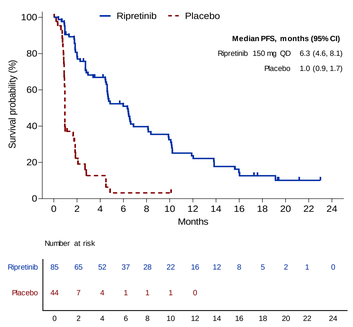
- INVICTUS (NCT03353753) is a phase 3, randomized, double-blind, placebo-controlled trial in which patients with advanced GIST who were previously treated with at least imatinib, sunitinib, and regorafenib were randomized (2:1) to ripretinib 150 mg once daily or placebo (**Figure 2**)
- Tumor biopsies were collected after patients received their last anticancer therapy prior to entry into the phase 3 INVICTUS study
- Tumor biopsies were sequenced using a next-generation sequencing panel (324 genes) from FoundationOne
- Plasma circulating tumor DNA (ctDNA) was collected predose on Cycle 1 Day 1, and was profiled using a next-generation sequencing liquid biopsy assay (73 genes) from Guardant360
- Primary mutation subgroups and KIT/PDGFRA wild-type (WT) status were determined via tumor biopsy
- Secondary mutation subgroups were determined by combining results from tumor and liquid biopsies
- Correlations between KIT/PDGFRA mutational status and clinical outcomes from the INVICTUS study were assessed
- This retrospective analysis was not part of the study protocol
- The data cutoff for this analysis was March 9, 2020

Figure 2. INVICTUS study design



Presentation only shows data from the double-blind period (highlighted with orange box).
BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance score; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; QD, once daily.

Figure 3. INVICTUS PFS results



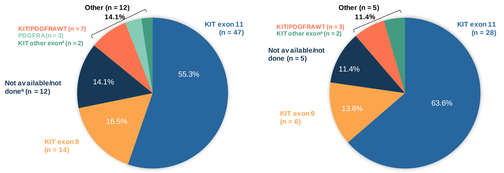
CI, confidence interval; PFS, progression-free survival; QD, once daily.

RESULTS

Primary mutation subgroup analysis by tumor biopsy

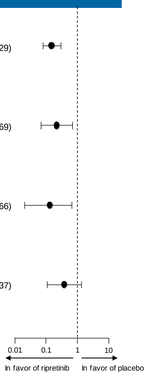
Figure 4. Distribution of primary mutations and hazard ratios of PFS grouped by primary mutation

A)



B)

Baseline primary mutation	Ripretinib 150 mg QD n (%)	Placebo n (%)	Hazard ratio of PFS (95% CI)
KIT exon 11	47 (55.3)	28 (63.6)	0.15 (0.08, 0.29)
KIT exon 9	14 (16.5)	6 (13.6)	0.22 (0.07, 0.69)
Not available/not done[b]	12 (14.1)	5 (11.4)	0.13 (0.02, 0.66)
Other[c]	12 (14.1)	5 (11.4)	0.38 (0.11, 1.37)



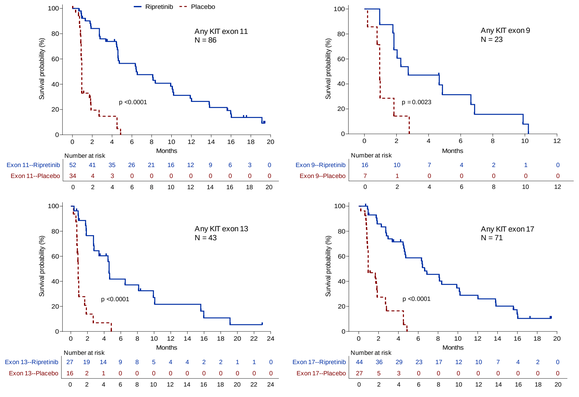
Patients grouped by tumor biopsy analysis only. KIT/PDGFRA WT patients had either no detectable mutations, or mutations in SDH or NF1. Plot represents hazard ratio of PFS by primary mutation with 95% CI error bars.
[a]KIT other exon includes any mutation in a KIT exon that is not 9 or 11. [b]Includes patients who failed sequencing due to low tumor content and patients with no specimen. [c]Includes other KIT exon mutations, PDGFRA mutations, and KIT/PDGFRA WT patients. Please refer to Figure 4A
CI, confidence interval; PFS, progression-free survival; QD, once daily; WT, wild-type.

- Patients in the INVICTUS study were not randomized by stratification of primary mutation status
- Independent of mutational status, in INVICTUS, ripretinib demonstrated a significant improvement in PFS compared with placebo (**Figure 3**)
- More than half of the patients in each treatment arm had primary KIT exon 11 mutations (**Figure 4A**)
- Ripretinib showed PFS benefit in all primary mutation subgroups compared with placebo (**Figure 4B**)
- KIT/PDGFRA WT status was similar among the randomization arms (2:1 randomization; 7 ripretinib, 3 placebo)
- The median PFS for KIT/PDGFRA WT patients receiving ripretinib was 5.7 months, while the median PFS for KIT/PDGFRA WT patients receiving placebo was 2.1 months

KIT mutation analysis by combined tumor and liquid biopsy

- Patients were grouped into 4 subsets: any KIT exon 9, any KIT exon 11, any KIT exon 13, and any KIT exon 17
- Patients were included in multiple groups if they had mutations in two or more exons
  - For example, a patient that has a primary mutation in exon 11 and a secondary mutation in exon 17 would fall into both the any KIT exon 11 group and the any KIT exon 17 group

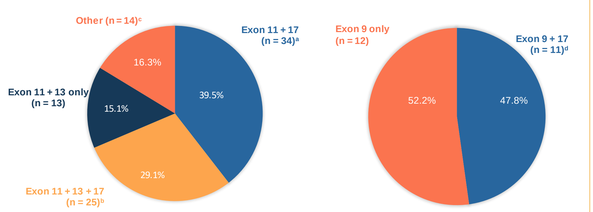
Figure 5. PFS by KIT mutation subgroup by combined tumor and liquid biopsy



Patients may be included in multiple subgroups if they had multiple mutations. Due to low numbers, patients with any KIT exon 14 (n = 6), any KIT exon 18 (n = 6), or PDGFRA (n = 3) mutations were excluded from this analysis.
PFS, progression-free survival.

- Patients receiving ripretinib showed PFS benefit over placebo in all assessed subgroups (**Figure 5**)

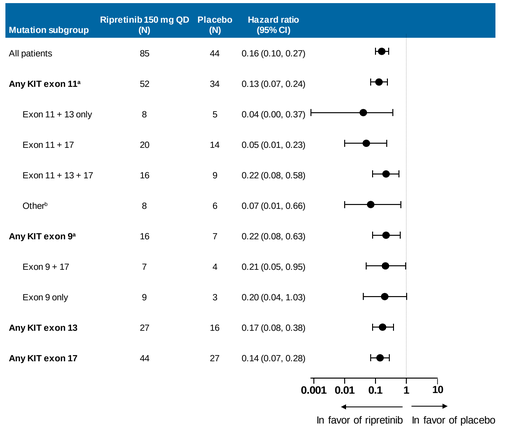
Figure 6. Secondary mutations for patients with primary KIT exon 11 or 9 mutations by combined tumor and liquid biopsy



A subset of patients did not have exon 11 or 9 primary mutations: exon 13 only (n = 2), exon 17 only (n = 1), and exon 13+14+17 (n = 1).
[a]Includes patients with exon 11+17 only mutations (n = 32), exon 11+17+18 mutations (n = 1), and exon 9+11+14+17 mutations (n = 1); [b]Includes patients with exon 11+13+17 only mutations (n = 21), exon 11+13+14+17 mutations (n = 1), exon 11+13+17+18 mutations (n = 2) and exon 11+13+14+17+18 mutations (n = 1); [c]Includes patients with exon 11 only mutations (n = 13) and exon 11+18 mutations (n = 1). [d]Includes patients with exon 9+17 only mutations (n = 6), exon 9+14+17 mutations (n = 1), exon 9+11+17+18 mutations (n = 1), exon 9+13+17 mutations (n = 2), and exon 9+11+14+17 mutations (n = 1).

- Patients from this study had tumors with complex and heterogenous mutational landscapes (**Figure 6**)
- By combining tumor and liquid biopsies, a wider array of secondary resistance mutations was detected as compared with conventional tumor-based mutational analysis
- Combined tumor and liquid biopsies allowed for detection of resistance mutations in 73% of patients; resistance mutations were detected in up to 4 exons within a single patient

Figure 7. Hazard ratio of PFS with different mutation groups by combined tumor and liquid biopsy



Patients may be included in multiple subgroups if they had multiple mutations. Due to low numbers, patients with any KIT exon 14 (n = 6), any KIT exon 18 (n = 6), or PDGFRA (n = 3) mutations were excluded from this analysis. Please refer to Figure 6 for each subgroup.
[a]One patient had both KIT exon 11 and KIT exon 9 mutations detected in liquid biopsy. [b]Includes exon 11 only mutations (n = 13) and exon 11+18 mutations (n = 1). [c]Positive for KIT exon 9 mutation and negative for KIT exon 17 mutation. CI, confidence interval; PFS, progression-free survival; QD, once daily.

- The HRs of PFS within different mutation subgroups all favored treatment with ripretinib, which is in line with the primary outcome of this clinical trial (**Figure 7**)

CONCLUSIONS

- In this exploratory analysis, ripretinib demonstrated clinically meaningful activity in patients with ≥fourth-line advanced GIST with multiple, heterogeneous genetic subsets of KIT/PDGFRA mutations
  - Ripretinib showed PFS benefit vs placebo in all primary mutation subgroups
  - By combining tumor and liquid biopsy (ctDNA), a wide array of secondary mutations were detected, and ripretinib showed PFS benefit in all mutation subgroups
- Overall, these results demonstrate that ripretinib can inhibit a broad spectrum of KIT/PDGFRA mutations in patients with advanced GIST who have received prior treatment with ≥3 kinase inhibitors, including imatinib
- These results support the proposed broad mechanism of action of ripretinib with its specific receptor binding properties

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Disclaimer

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