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

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INTRODUCTION

Ripretinib is a pan-KIT/PDGFRα inhibitor designed to broadly inhibit multiple KIT/PDGFRA mutations. In March 2020, the US FDA approved ripretinib for the treatment of adults with imatinib-resistant or -intolerant advanced gastrointestinal stromal tumors (GIST) or for patients who have disease progression on or after a KIT/PDGFRA-directed tyrosine kinase inhibitor (TKI) (Figure 1).

METHODS

• In a phase 3, randomized, double-blind, Placebo-controlled trial in patients with advanced GIST who were previously treated with imatinib monotherapy, ripretinib was compared with Placebo in 506 patients (NCT03158116). Patients were randomized 2:1 to receive ripretinib 150 mg BID or Placebo (Figure 1).

• Primary tumors were collected after patients received their last kinase inhibitor therapy prior to entry into the phase 3 INVICTUS study. The most recent serial tumor biopsy was selected for analysis.

• Patients were stratified by prior TKI treatment (imatinib, sunitinib, or both), prior treatment with 3 or more kinase inhibitors, and prior treatment with sunitinib.

• The trial is registered at ClinicalTrials.gov (NCT03158116).

RESULTS

Primary mutation subgroup analysis by tumor biopsy

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

- Patients were grouped into 7 subgroups: any KIT exon 9, any KIT exon 11, any KIT exon 15, and any KIT exon 17.
- Patients were included in multiple groups if they had mutations in two or more sites.
- For example, a patient that had a primary mutation in exon 11 and a secondary mutation in exon 15 would fall into both the any KIT exon 11 group and the any KIT exon 15 group.

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

- Patients receiving symptomatic PFS benefit are patients in all analyzed subgroups.

CONCLUSIONS

In this exploratory analysis, ripretinib demonstrated clinically meaningful activity in patients with tumors with advanced GIST with multiple, heterogeneous genetic subtypes of KIT/PDGFRA mutations.

- By combining tumor and liquid biopsy, 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/PDGFRα mutations in patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib.

- These results support the broad mechanism of action of ripretinib with its specific receptor binding properties.

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

Figure 6. Secondary mutations for patients with primary KIT exon 11 or 15 mutations by combined tumor and liquid biopsy

- Patients with any KIT exon 11 mutation had a substantial improvement in PFS compared with Placebo.
- Patients with any KIT exon 15 mutation had a substantial improvement in PFS compared with Placebo.

Figure 3. INVICTUS PFS results

References

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Acknowledgments

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References