Crenolanib as Once Daily Dosing (200 or 340 mg)

- 9 patients initially treated with 200 mg QD and 4 patients dose escalated from 200 to 340 mg QD
- All patients achieved adequate levels of crenolanib in both cohorts

Crenolanib Administered as Split Doses

To decrease C\textsubscript{\text{tmax}} and potentially decrease toxicities, crenolanib was administered as split doses
- 7 patients were initially treated with 140 mg BID, 4 patients were escalated to BSA-dosing of 11.3 mg/m\textsuperscript{2} TID and 4 patients were initially based on the BSA-dosing

CR+PR: Complete response + partial response
SD: Stable disease

Crenolanib Inhibits the Drug-Resistant PDGFRA D842V Mutation Associated with Imatinib Resistance

- Crenolanib inhibited IC\textsubscript{50} = 0.86 mM and remained sensitive to PGDRA-D842V at IC\textsubscript{50} = 9.6 mM in CHO cells expressing PGFRA WT or D842V. Heinrich et al., 2012 Clin Can Res.

Design and Objectives

This was a dose-escalating study with 4 scoring cohorts to assess clinical benefit of crenolanib in patients with PDGFR\(\text{A}^{\text{D842V}}\) activating mutations. Secondary objectives included safety and pharmacokinetic analysis.

Methods: Crenolanib was administered at four dose-escalating regimens including 200 mg QD, 340 mg QD, 140 mg BID, and 73.3 mg/m\textsuperscript{2} TID. The dose that patients received on prior TKIs was equal or less than 73.3 mg/m\textsuperscript{2} TID. Results: 20 pts (12 males, 8 females, median age 61) were enrolled. 16/20 had prior disease after prior treatments (15); sunitinib (9), dasatinib (5), sorafenib (4), nilotinib (2), and regorafenib (2); 10/20 had undergone prior primary gastric resection; PK analysis was performed to assess adequate crenolanib absorbance. Conclusion: Crenolanib was well-tolerated when given to pts on a chronic basis. A randomized placebo-controlled trial of imatinib. Heinrich et al., 2015 Cancer Res Treat. Patients were unresponsive to imatinib with a median PFS of 9 months. Of the 20 patients, 13 were on a chronic basis, 73.3 mg/m\textsuperscript{2} therapy and were also treated at the 73.3 mg/m\textsuperscript{2} TID schedule.

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Crenolanib as a unique type I inhibitor of PDGFR\(\alpha\), with Crenolanib inhibited PDGFRA at IC\textsubscript{50}~11 nM and remained sensitive to PDGFRA D842V at IC\textsubscript{50} ~9 nM.

Crenolanib is the first and only TKI to show activity in PDGFRA D842V mutant GIST.

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