PRELIMINARY REPORT OF CRENOLANIB IN THE TREATMENT OF ADVANCED PLATELET DERIVED GROWTH FACTOR A (PDGFRα) D842V MUTANT GASTROINTESTINAL STROMAL TUMOR (GIST)


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BACKGROUND

Many patients with advanced GIST treated with approved tyrosine kinase inhibitors have prolonged disease control with a median survival of 5 years. Rare subsets of GIST do not derive the same benefit from treatment. One such subset is GIST that carries a mutation in PDGFRα exon 18, D842V. In vitro, approved therapies do not cause a decrease in cell proliferation or loss of PDGFRα phosphorylation1. In clinical trials, available data suggests no response to standard therapies2.

Crenolanib is a benzimidazole compound3 being developed for the treatment of GIST patients with PDGFRαD842V. Crenolanib is a potent and specific inhibitor of type III tyrosine kinases.

In CHO cell lines transiently transfected with PDGFRαD842V, crenolanib inhibits the phosphorylation of the mutant PDGFRA with an IC₅₀ of 9nM and IC₉₀ of 44nM.

STUDY DESIGN

This is an open label phase II study conducted at 2 centers (FCCC and OHSU) (NCT01243346).

Key Inclusion criteria:
- At least 18 years of age
- ECOG PS ≤ 1
- History of GIST with a documented PDGFRα D842V mutation
- Liver function tests ≤ 2X the ULN in the setting of liver metastases, and ≤ 1.5X the ULN with no liver metastases

Endpoints:
- Primary endpoint: Response rate to crenolanib, measured by RECIST
- Secondary endpoint: 6-month PFS and evaluation of PK in this patient population with prior gastric resections.

Treatment Plan:
- Crenolanib 200 mg po QD (4 weeks - one cycle)
- Dose reductions to 160mg QD and 100mg QD for toxicities
- PET at baseline and at 4 weeks recommended
- CT/MRI repeat imaging every 2 cycles

PHARMACOKINETICS

- Serum pharmacokinetics samples were obtained pre dose and at 30 (± 10), 60 (± 15), 120 (± 15) minutes and at 4 (±1), 8 (±2), and 24 (±4) hours after crenolanib administration
- Analysis was performed by an isocratic high performance liquid chromatography assay with tandem mass spectrometry
- Crenolanib was rapidly absorbed, with a t₁/₂ of ~2 hours
- Serum trough concentrations of crenolanib (at 24hrs) were ~12% the peak concentration.

TOLERABILITY

- Significant AEs included elevation of liver function tests and anemia.
- Anemia requiring transfusion was observed in 3 pts, and was associated with intratumoral bleeding, following no evidence of bleeding or hemolysis. These AEs have not been observed with crenolanib therapy in patients with other solid tumors including non-GIST sarcomas.
- Ascites (2 pts) and pleural effusions (1 pt) have also been observed, including hemorrhagic ascites in 1 pt.

CONCLUSIONS

- Crenolanib is the only available TKI with in vitro activity against PDGFRαD842V.
- Absorption of crenolanib does not appear to be affected by gastrectomy.
- Toxicities have mirrored phase I experience, with nausea and vomiting managed with daily ondansetron administration.
- Two patients have experienced anemia attributed to bloody ascites, possibly related to crenolanib.
- Preliminary metabolic response was observed in one of seven patients treated.
- Accrual into this trial is ongoing.
- Future trials are planned to optimize the dose and schedule of crenolanib in this patient population.

REFERENCES