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 therapies 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 PDGFRA exon 18, D842V. In vitro, approved therapies do not cause a decrease in cell proliferation or loss of PDGFRA phosphorylation. In clinical trials, available data suggests no response to standard therapies.

Crenolanib is a benzimidazole compound being developed for the treatment of GIST patients with PDGFRA D842V. Crenolanib is a potent and specific inhibitor of type III tyrosine kinases.

In CHO cell lines transiently transfected with PDGFRA D842V, 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 PDGFRA 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 endpoints: 6-month PFS and evaluation of PK in this patient population with prior gastric resections.

Treatment Plan:
- Crenolanib 200 mg po QD (4 weeks on – 1 week cycle)
- Dose reductions to 150mg QD and 100mg QD for toxicities
- PET at baseline and at 4 weeks recommended
- CT/MRI repeat imaging every 4 cycles

PATIENT CHARACTERISTICS
- To date, 7 patients (4 F, 3 M) have been accrued.
- All had metastatic disease in liver and/or mesenteric/retroperitoneum.
- Best response to prior therapy was stable disease.
- Safety data is available in 6 patients and efficacy in 6 patients.

TOLERABILITY
- Significant AEs included elevation of liver function tests and anemia.
- Anemia requiring transfusion was observed in 3 pts, and was ascribed to 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.

TOXICITIES
- 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 isochronic high performance liquid chromatography assay with tandem mass spectrometry
- Crenolanib was rapidly absorbed, with a tmax of ~2 hours
- Serum trough concentrations of crenolanib (at 24hrs) were ~12% the peak concentration.

PHARMACOKINETICS
- Serotonin reuptake inhibitors are recommended in patients with a history of prior treatment with a medication that causes serotonin syndrome.

CONCLUSIONS
- Crenolanib is the only available TKI with in vitro activity against PDGFRA D842V.
- Absorption of crenolanib does not appear to be affected by gastrectomy.
- Toxicities have mirrored phase 1 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.

REFERENCES