#136 Dose Escalating Study of Crenolanib Besylate in Advanced GIST Patients with PDGFRA D842V Activating Mutations

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Abstract

Background: PDGFRA D842V mutated GIST is resistant to all available TKIs with a median PFS of ≤ 2.8m and a median OS 14.7m. Crenolanib is a unique type I inhibitor of PDGFRα, with *in vitro* activity against PDGFRA D842V (cellular IC_{50} 9 nM). We here report a phase I/II study evaluating safety, PKs, and antitumor efficacy of crenolanib in advanced GIST with PDGFRA D842V mutations.

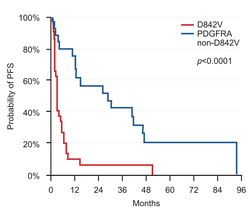
Methods: Crenolanib was administered at four dosing regimens including 200 mg QD, 340 mg QD, 140 mg BID and 73.3 mg/m^2/TID. Pts who had progressed on prior TKIs were eligible so long as they had measurable disease. As most pts had undergone prior gastrectomies, PK analysis was performed to assess adequate crenolanib absorption.

Results: 20 pts (12 males, 8 females, median age 61) were enrolled. 16/20 had progressed after prior imatinib (15), sunitinib (9), dasatinib (5), sorafenib (4), nilotinib (2), and regorafenib (2). 16/20 pts had undergone prior partial (14) or total (2) gastrectomy. Only 4 out of 20 pts were FDG-avid by a baseline PET scan (PDGFR GIST is typically PET negative).
Crenolanib was administered at 200 mg QD to the first 9 pts. 4/9 pts were subsequently escalated to 340 mg QD. PK demonstrated $t_{1/2}$ of 8.6 hrs, suggesting a BID or TID schedule would be more optimal to maintain adequate trough crenolanib levels. The next 7 pts were given crenolanib on a 140 mg BID schedule. 4/7 pts were escalated to an individualized BSA dosing of 73.3 mg/m^2/TID. 4 additional pts were also treated at the 73.3 mg/m^2/TID schedule.
2/16 pts achieved a PR while 3/16 pts achieved SD; clinical benefit rate was 31% (5/16 pts). 7 pts stayed on crenolanib for over 7 m and 1 pt each for 1yr and 2yrs. Grade 3/4 AEs included reversible LFT elevations (3 pts) and anemia (3 pts). 1 pt each with pre-existing ascites and pleural effusion developed worsening fluid accumulation in the context of disease progression. Despite prior gastrectomy, crenolanib reached clinically relevant concentration.

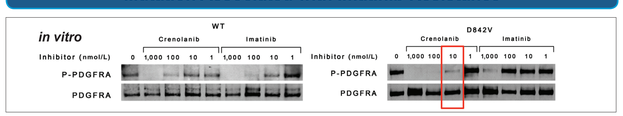
Conclusion: Crenolanib is the first and only TKI to show activity in PDGFRA D842V mutant GIST. Crenolanib was well-tolerated when given to pts on a chronic basis. A randomized placebo-controlled study of crenolanib in advanced D842V GIST is currently being initiated. NCT01243346

Unmet Need for Treatment in PDGFRA D842V Mutated GIST

- PDGFRA activating mutations account for approximately 5-10% of GISTs. Most PDGFRA mutations (especially D842V) are refractory to approved therapies:
  - Patients were unresponsive to imatinib with a median PFS of 2.8 months. Cassier et al., *2012 Clin Cancer Res.*
  - No objective response to imatinib and sunitinib (median PFS of 3.8 months and 1.9 months, respectively). Yoo et al., *2015 Cancer Res Treat.*
  - 3 patients showed PFS< 2 months in a phase III trial of imatinib. Heinrich et al., *2008 J Clin Oncol.*



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



Crenolanib inhibited PDGFRA at IC_{50}~11 nM and remained sensitive to PDGFRA D842V at IC_{50} ~9 nM in CHO cells overexpressing PDGFRA WT or D842V. Heinrich et al., *2012 Clin Can Res.*

Design and Objectives

This was a dose escalating study with 4 dosing cohorts to assess clinical benefit of crenolanib in patients with advanced GIST with PDGFRA D842V activating mutations. Secondary objectives included safety and pharmacokinetic analysis.

D842-related mutations and deletions in advanced GIST (N=20) → **Crenolanib 200 mg QD 340 mg QD 140 mg BID 73.3 mg/m² TID** → **Treat until lack of clinical benefit, unacceptable toxicity, or withdrawal of consent**

Demographics

Characteristic	Treated Patients (N = 20)
Age (years), median (range)	62 (47-76)
< 50 years	1 (5%)
50–60 years	8 (40%)
> 60 years	11 (55%)
Male, N (%)	12 (60%)
Years from diagnosis, median (range)	2 (0.6, 11.0)
Prior TKI, N (%)	16 (80%)
Gastrectomy, N (%)	16 (80%)

Patient Age/Sex	# Prior TKI	History of TKI Treatment
56/M	6	Imatinib→Sunitinib→Sorafenib→Nilotinib→Imatinib→Nilotinib
60/M	5	Nilotinib→Imatinib→Sunitinib→Regorafenib→Sorafenib
50/M	5	Imatinib→Sunitinib→Sorafenib→Crenolanib→Dasatinib
75/M	5	Imatinib→Sunitinib→Imatinib→Sorafenib→Regorafenib
75/F	4	Imatinib→Dasatinib→Sunitinib→Sorafenib
66/F	3	Imatinib→Sunitinib→Imatinib
45/M	3	Imatinib→Dasatinib→Imatinib
58/M	3	Imatinib→Sunitinib→Dasatinib
60/F	2	Imatinib→Sunitinib
51/M	2	Imatinib→Sunitinib
64/F	1	Imatinib
72/F	1	Imatinib
57/M	1	Imatinib
61/M	1	Dasatinib
72/F	1	Imatinib
73/M	1	Imatinib

35% Patients Stayed on Study for ≥7 Months

- **Median duration on crenolanib: 109 days**

Patient Study ID	# of Days 200 mg QD	# of Days 340 mg QD	# of Days 140 mg QD	# of Days 73.3 mg/m² TID	Total duration
OHSU-004			776		776
OHSU-002	168	274		29	471
FCCC-001	357				357
OHSU-006			180	140	320
FCCC-004	195	80			275
FCCC-006	262				262
OHSU-007			168	56	224

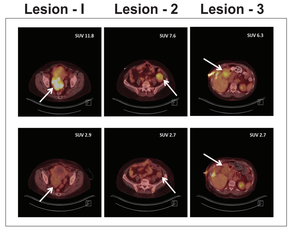
Crenolanib as Once Daily Dosing (200 or 340 mg)

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

75/F: Remained on study for 357 days

- Patient achieved a partial remission at 200 mg QD showing **metabolic response within 20 days**
- A rapid decrease (48%) in lesion size of pelvis was observed by **C2D28 (15 cm to 7.8 cm).**



72/F: Remained on study for 471 days

- Patient maintained a **stable response,** achieving adequate drug levels with 200 mg QD.
- After 4 cycles, the patient began to progress, at which time she was administered 340 mg QD with rapid decrease in lesion size, including a **20% reduction in the largest gastric lesion.**
- Due to increased nausea/vomiting, the patient required a dose reduction at which time she began to progress

Baseline	–	200 mg QD
C3D1	SD	200 mg QD
C5D2	PD	200 mg QD
C5D29	PD with new lesions	200 mg QD
C8D26	SD	340 mg QD
C10D1	SD	340 mg QD
C11D1	SD	340 mg QD
C13D1	PD	280 mg QD
C15D28	PD	280 mg QD
Follow-up	PD	280 mg QD

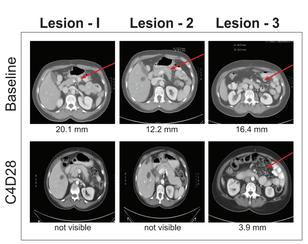
Crenolanib Administered as Split Doses

To decrease C_{max} 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 73.3 mg/m² TID and 4 patients were initially started on the BSA dose

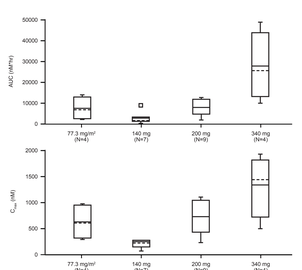
62/F: Remained on study for 776 days

- Patient achieved a **partial remission at 140 mg BID**
- A rapid **92% tumor reduction** was seen after 4 cycles of crenolanib treatment

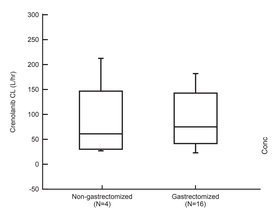


PK analysis of all 4 cohorts

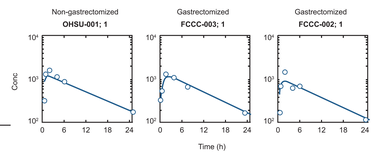
- PK shows **decrease in C_{max} but maintenance of adequate trough and AUC level** with split dose administration



No Impact of Gastrectomy on Crenolanib Absorption



- PK analysis in patients w/wo gastrectomy administered with crenolanib 200 mg QD shows no impact on crenolanib absorption



31% Clinical Benefit in Patients with D842V Mutated GIST

Evaluable Patients (N=16*)		
Response	**# of Patients**	**Percentage (%)**
PR	2	13%
Stable Disease	3	19%
Overall clinical benefit (CR+PR+SD)	5	31%

- 5/16 evaluable patients achieved clinical benefit with 2 patients achieving PR and 3 patients achieving SD

*Non-evaluable patients included: 3 patients off study prior to 1 full cycle and 1 did not have recurrent GIST (aggressive fibromatosis).

Crenolanib has Favorable Safety Profiles

Grade 3 or 4 TEAEs reported in ≥ 10% of patients during treatment, irrespective of attribution

Event	Grade 3	Grade 4
Anaemia	4 (20%)	1 (5%)
Abdominal pain	3 (15%)	0
Fatigue	2 (10%)	0
Aspartate aminotransferase increased	2 (10%)	0
Gamma-glutamyltransferase increased	2 (10%)	0
Hyperglycaemia	2 (10%)	0
Hypokalaemia	2 (10%)	0

- Most commonly reported AEs were GI toxicities, including nausea, vomiting and diarrhea, which were Grade 1 or 2 in severity.
- Most patients were anemic at baseline and had further declines in hemoglobin during treatment.
- 1 patient each with pre-existing ascites and pleural effusion developed worsening fluid accumulation in the context of disease progression.

Conclusions

- Crenolanib showed efficacy in patients with D842V mutated GIST.
- No significant difference in crenolanib absorption was observed between patients with or without gastrectomy.
- Crenolanib was well tolerated. QTc prolongation or hand-foot syndrome was not observed.
- TID dosing schedule is more appropriate for future trials.
- Crenolanib has a half-life of 6.5-8.9 hrs

Additional Studies

- A placebo controlled randomized phase III trial with crenolanib in patients with PDGFRA D842V mutated GIST is being initiated. (EudraCT Number: 2015-000287-34) www.arogpharma.com/clinicaltrials

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