A Randomized, Double-Blind, Placebo-Controlled, Phase III Study of Crenolanib in Advanced or Metastatic GIST Patients Bearing a D842V Mutation in PDGFRα: The CrenoGIST Study.

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**Background**

An international survey reporting outcome of GIST patients with PDGFRα mutations

- After first-line imatinib, mPFS was 2.8 months vs 28.5 months for patients with and without D842V, respectively
- After second-line, mPFS was 2.1 months for patients with D842V, and 7.8 months for patients with other PDGFRα mutations

**Study Design and Endpoints**

A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Trial of Crenolanib in Subjects with Advanced or Metastatic Gastrointestinal Stromal Tumors with a D842V Mutation in the PDGFRα Gene

**Study Endpoints:**
- **Primary**
  - Progression-free survival (PFS)
- **Secondary**
  - Overall survival (OS)
  - Objective response rate (ORR; based on RECIST 1.1)
  - Subject incidence of treatment-emergent adverse events
  - Changes in laboratory values
- **Pharmacokinetic**
  - Pharmacokinetic profile of crenolanib

**Genomic Testing**

Genomic Panel via Knight Diagnostic Laboratories

- Screening for mutations in 23 genes commonly involved in GIST, using the GeneTrails® GIST Panel

**Key Inclusion Criteria:**
- Histologically confirmed advanced or metastatic GIST with a D842V mutation in the PDGFRα gene
- Progressive disease
- Subjects ≥ 18 years of age
- ECOG performance status of ≤ 2
- Prior TKI therapy is permitted

**Key Exclusion Criteria:**
- Severe liver disease (e.g., cirrhosis, non-alcoholic steatohepatitis, sclerosing cholangitis).
- Known, active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).
- Systemic anti-cancer treatment (e.g., chemotherapy, TKIs, immunotherapy, or investigational agents) or prior investigational therapy within 3 weeks or 5 half-lives of the study drug prior to randomization.

**Key Features:**
- 2:1 randomization: the majority of patients receive active drug
- Prior TKIs permitted
- Genomic testing included
- Primary endpoint of progression-free survival

**Study Status**

- This phase III study is actively enrolling.
- Please contact info.012@davacro.com or visit http://clinicaltrials.gov for more information or to participate.
- Clinicaltrials.gov identifier, NCT02847429; EudraCT number, 2015-000287-34
- For more information about crenolanib, please visit the following website: http://www.arogpharma.com/

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**Crenolanib inhibited the imatinib-resistant PDGFRαD842V mutation**

Crenolanib inhibits the phosphorylation of PDGFRαD842V at nanomolar concentrations in CHO cell line

- Significantly more inhibition in transiently transfected CHO cells expressing PDGFRαD842V as compared to imatinib

**Biochemical IC50 values for inhibition of kinase activity in cells expressing single mutation kinase**

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Exon</th>
<th>Model</th>
<th>Imatinib</th>
<th>Crenolanib</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGFRαD842V</td>
<td>18</td>
<td>CHO</td>
<td>1.353 ± 311</td>
<td>9 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PDGFRαD842V</td>
<td>18</td>
<td>BaF3</td>
<td>272 ± 163</td>
<td>2 ± 2</td>
<td>0.002</td>
</tr>
</tbody>
</table>

The values for crenolanib and imatinib represent the biochemical IC50 expressed in μmol/L units ± the SEM. Values represent the data from at least 3 replicate experiments per mutation. p < 0.05 by Wilcoxon rank sum test.

Crenolanib showed 32% clinical benefit in patients with PDGFRαD842V GIST

- 5/16 evaluable patients achieved clinical benefit:
  - 2 (13%) patients achieved PR
  - 3 (19%) patients maintained SD

**Patient Population**

- Patient achieved a PR with rapid 92% tumor reduction seen after 4 cycles of crenolanib

**Patient Population**

- Strong metabolic response in GIST D842V patient following 20 days of crenolanib therapy

**Study Overview**

This randomized phase III study is enrolling adult subjects with histologically or cytologically confirmed advanced or metastatic GIST with a PDGFRαD842V mutation. Prior treatment with TKI is allowed. Approximately 120 subjects will be randomized in a 2:1 ratio to receive either crenolanib 100 mg or matching placebo orally 3 times daily in combination with best supportive care. Randomization will be stratified by prior TKI exposure and ECOG performance status. The primary objective is PFS and the key secondary objective is OS. A formal interim analysis is planned after approximately 50 subjects have met the primary outcome. This study is already opened in the US, France, Norway, Spain, and Poland, and will soon be open in Germany, Italy, UK and Asia.

**Patient Population**

- Evaluable Patients (N=16)
  - Partial Response (PR)
  - Stable Disease (SD)
  - Overall clinical benefit (PR+SD)

**Key Exclusion Criteria:**
- This phase III study is actively enrolling.
- Please contact info.012@davacro.com or visit http://clinicaltrials.gov for more information or to participate.
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