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

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CRENOGIST

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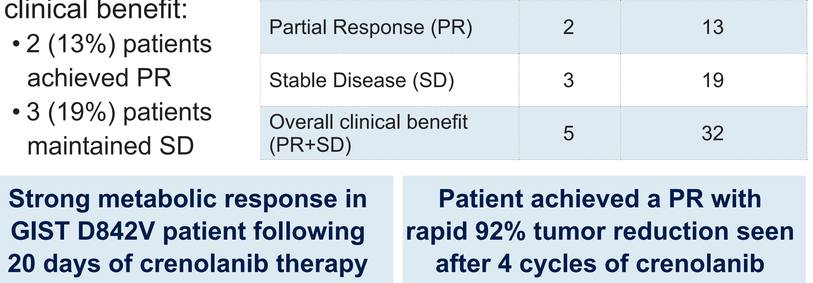
Background

Advanced or metastatic PDGFRA^{D842V} mutated GIST progresses rapidly and does not respond to imatinib

An international survey reporting outcome of GIST patients with *PDGFRA* 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 *PDGFRA* mutations

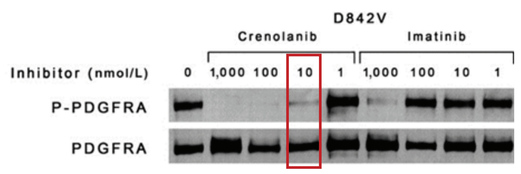
PFS of GISTs with or without PDGFRA^{D842V} mutations



Cassier at al., Clin Cancer Res. 2012

Crenolanib inhibits the imatinib-resistant PDGFRA^{D842V} mutation

Crenolanib inhibits the phosphorylation of PDGFRA^{D842V} at nanomolar concentrations in CHO cell line



Heinrich et al., Clin Can Res. 2012.

- Significantly more inhibition in transiently transfected CHO cells expressing PDGFRA^{D842V} as compared to imatinib

Biochemical IC_{50} values for inhibition of kinase activity in cells expressing single mutation kinase

Kinase	Exon	Model	Imatinib	Crenolanib	*p*
PDGFRA^{D842V}	18	CHO	1,353 ± 311	9 ± 3	<0.001
PDGFRA^{D842V}	18	BaF3	272 ± 163	2 ± 2	0.002

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

Heinrich et al., Clin Can Res. 2012.

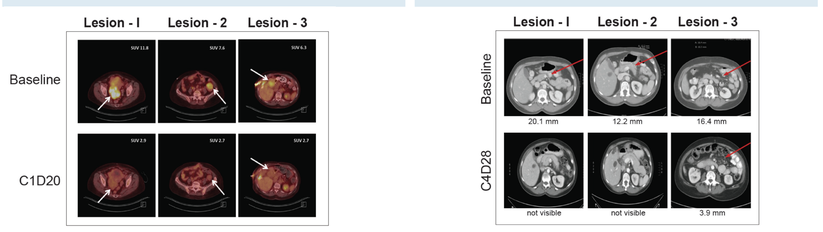
Crenolanib showed 32% clinical benefit in patients with PDGFRA^{D842V} GIST

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

Evaluable Patients (N=16)		
Response	**Number**	**Percentage (%)**
Partial Response (PR)	2	13
Stable Disease (SD)	3	19
Overall clinical benefit (PR+SD)	5	32

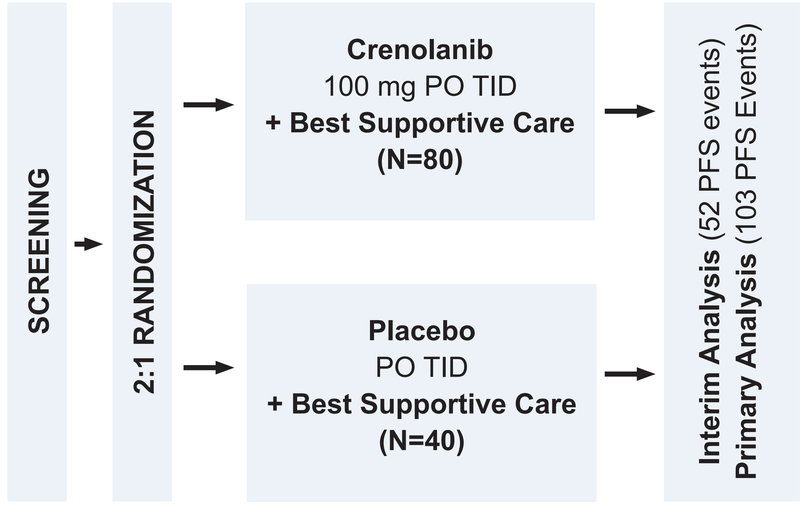
Strong metabolic response in GIST D842V patient following 20 days of crenolanib therapy

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



von Mehren et al., ASCO 2016

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 *PDGFRA* Gene

Study Endpoints:

Primary
- Progression-free survival (PFS)

Secondary
- Overall survival (OS)
- Objective response rate (ORR; based on RECIST 1.1)

Safety
- Subject incidence of treatment-emergent adverse events
- Changes in laboratory values

Pharmacokinetic
- Pharmacokinetic profile of crenolanib

Study Overview

This randomized phase III study is enrolling adult subjects with histologically or cytologically confirmed advanced or metastatic GIST with a PDGFRA^{D842V} 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 opened in Germany, Italy, UK and Asia.

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

Patient Population

Key Inclusion Criteria:
- Histologically confirmed advanced or metastatic GIST with a **D842V mutation in the *PDGFRA* 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

Genomic Testing

Genomic Panel via Knight Diagnostic Laboratories
- Screening for mutations in 23 genes commonly involved in GIST, using the GeneTrails® GIST Panel

Knight Diagnostic Laboratories
OHSU

GeneTrails®: GIST panel

AKT1	BRAF	KRAS	PDGFRA	SDHA	SDHC
AKT2	CDKN2A	MAP2K1	PIK3CA	SDHAF1	SDHD
AKT3	HRAS	NF1	PTEN	SDHAF2	TP53
ATM	KIT	NRAS	PTPN11	SDHB	

Study Status

- This phase III study is actively enrolling.
- Please contact info.012@davacro.com or visit http://clinicaltrials.gov if you would like more information about this trial or if you have a patient who may be interested in participating.
- 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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