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Safety Study of Salvage Chemotherapy and Type I FLT3-TKI Crenolanib in First Relapsed/Primary Refractory AML

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Background

- Treatment of newly diagnosed AML with standard chemotherapy regimens can lead to high complete remission rates (60-70%). Unfortunately, the majority of these patients will relapse.
- Upon relapse, the prognosis in these patients significantly worsens.
- Several combinations have been suggested for patients with R/R AML:
  - HAM: high-dose cytarabine combined with mitoxantrone
  - FLAG-Ida: fludarabine, cytarabine, G-CSF and idarubicin
  - MEC: mitoxantrone, etoposide, and cytarabine
- A TKI that can show significant clinical benefit and can be safely administered in combination with salvage chemotherapy is desirable.

Crenolanib is a type I pan-FLT3 inhibitor

- Single agent activity in R/R FLT3+ AML.
- Active against FLT3-ITD, FLT3-D835 and FLT3-ITD+D835.
- Anti-leukemic activity in FLT3-AML patients who progressed on sorafenib, midostaurin, quizartinib, and/or gilteritinib.
- No activity against cKIT at clinically achievable levels.

Relative activity against FLT3 and cKIT, and myelosuppressive activity of tyrosine kinase inhibitors

TKI	pFLT3 IC_{50} plasma	pcKIT IC_{50} plasma	Steady-state plasma levels	*In vivo* cKIT inhibition	Myelo-suppression
Crenolanib	48 nM	2.0 µM	384 nM	No	No

Adapted from Galanis A and Levis M, Haematologica 2015; ;100(3):e77-9.

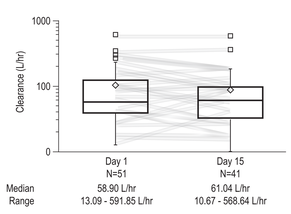
Crenolanib has a favorable toxicity profile

- Common side effects include GI toxicities (N/V/D), majority being grade 1/2 in severity and well managed with anti-emetics and anti-diarrheals.
- No evidence of QTc prolongation.
- Ability to administer concomitantly with anti-fungal azoles.

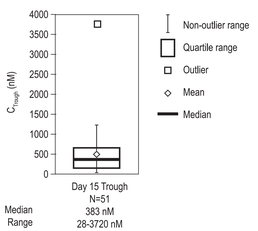
Crenolanib has a favorable pharmacokinetic profile

- 6-7h half-life with no accumulation after chronic dosing

Comparison of Clearance of Day 1 and Day 15



Trough Level at Steady State on Day 15



Study design

First relapsed/ primary refractory AML

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Salvage chemotherapy + crenolanib

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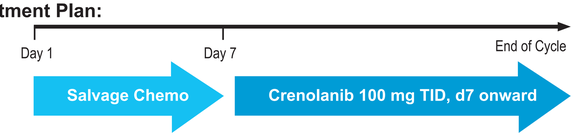
Follow-up

Key Eligibility:
- Age ≥18 years
- First relapsed or primary refractory AML
- Secondary AML allowed
- FLT3 wild type or mutant AML

Primary Objective:
- Safety and tolerability

Secondary Objectives:
- PK
- Clinical efficacy

Treatment Plan:



Salvage Chemotherapy Options (up to 2 Cycles)		
HAM, pts ≤ 60 yrs	Mitoxantrone Cytarabine	10 mg/m²/d, d1-3 1000 mg/m² IV over 3h, d16
Lower dose HAM, pts > 60y, or h/o prior HSCT, or requiring reinduction	Mitoxantrone Cytarabine	8 mg/m²/d, d1-3 500 mg/m²,IV over 3h, d1-6
FLAG-Ida	Fludarabine Cytarabine Idarubicin G-CSF	30 mg/m²/d, d1-5 2 g/m² IV over 2h, d1-5 8 mg/m², d1-3 d6- neutrophil recovery
Crenolanib Schedule		
Crenolanib	100 mg TID, from d7 – d49 or until 72 hrs before next chemotherapy regimen	

Demographics

Characteristics, n (%)	HAM (n=9)	FLAG-Ida (n=5)	Combined (n=14)
Age, yrs	65 [36 – 78]	64 [46-68]	64 [36-78]
≥60	7 (78%)	3 (60%)	10 (71%)
Sex, male	5 (56%)	4 (80%)	9 (64%)
Response to Frontline Treatment			
Relapsed	6 (67%)	4 (80%)	10 (71%)
Refractory	3 (33%)	1 (20%)	4 (29%)
Prior SCT	0 (0%)	1 (20%)	1 (7%)
FLT3 Mutations			
FLT3-WT	4 (44%)	5 (100%)	9 (64%)
FLT3-mutant	4 (44%)	0 (0%)	4 (29%)
unknown	1 (11%)	0 (0%)	1 (7%)

Crenolanib can be administered at single agent full dose (100 mg TID) following HAM

Age/ Sex	Cytarabine Doses (Total)	Crenolanib Doses	Dose Modification	DLT
36/F	6 g/m²	100 mg TID	No	No
55/M	6 g/m²	100 mg TID	No	No
60/F	3 g/m²	100 mg TID	No	No
64/F	3 g/m²	100 mg TID	No	No
65/F	3 g/m²	100 mg TID	No	No
73/M	3 g/m²	100 mg TID	No	No
74/M	3 g/m²	100 mg TID	No	No
75/M	3 g/m²	100 mg TID	No	No
78/M	3 g/m²	100 mg TID	No	No

Crenolanib can be administered at single agent full dose (100 mg TID) following FLAG-Ida

Age/ Sex	Crenolanib Doses	Dose Modification	DLT
46/M	100 mg TID	No	No
52/F	100 mg TID	No	No
64/M	100 mg TID	No	No
67/M	100 mg TID	No	No
68/M	100 mg TID	No	No

- Crenolanib 100 mg TID is well tolerated in relapsed/refractory AML patients and can be safely administered sequentially following HAM or FLAG-Ida.

Overall response

Response	FLT3 Mutant (n=4)	FLT3 WT/unknown (n=10)	Total (n=14)
CR	2	1	3
CRi	1	4	5
PR	1	0	1
Overall Response (CR/CRi+ PR)	**4 (100%)**	**5 (50%)**	**9 (64%)**

4/4 FLT3+ AML patients remain in remission

- 4 patients with FLT3+ AML were treated with crenolanib following salvage chemotheraphy.
  - 2 patients who had FLT3 clearance performed on study achieved FLT3 negativity.
  - All 4 patients are currently in remission.

Age/ Sex	FLT3	Cytogenetics	Chemo Regimen	Response	FLT3 Clearance	Status
75/M	ITD	t(6;9), +8	HAM	CR	Not done	Leukemia free for 7+ months
74/M	ITD	+8,+11	HAM	CRi	Not done	Leukemia free for 2+ months
60/F	TKD	normal	HAM	CR	FLT3 negative	Leukemia free for 4+ months
36/F	ITD	normal	HAM	10% blasts	FLT3 negative	post SCT In remission

Conclusion/current status

- Full doses of crenolanib (100 mg TID) can be safely combined with HAM or FLAG-Ida in patients with first relapsed/ primary refractory AML.
- All patients with FLT3 mutant AML are currently in remission.
- This trial has been expanded to allow combination of full dose crenolanib with 3 choices of salvage chemotherapies per physician's discretion: HAM, FLAG-IDA, and MEC (mitoxantrone, etoposide, cytarabine).
- A phase III study of crenolanib in combination with salvage chemotherapy is being initiated (NCT02298166; EudraCT number: 2014-000460-18).

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