Addition of Crenolanib to Standard Induction and Consolidation Therapy Improves Long-Term Outcomes in Newly Diagnosed FLT3-Mutant AML Patients ≤ 60 Years Old

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Abstract

Background: The mult-ikinase inhibitor midostaurin was recently approved in combination with chemotherapy based on a survival benefit (2yr OS: 60% midostaurin vs 51% placebo) demonstrated by the RATIFY trial of younger patients with treatment-naïve FLT3-mutant AML. We hypothesized that a more selective FLT3-targeted agent such as crenolanib, a potent and specific FLT3 tyrosine kinase inhibitor (TKI) which inhibits both FLT3ITD and FLT3TKD mutations, would further improve patient outcomes when combined with chemotherapy. We here report an analysis of patients treated with crenolanib combined with chemotherapy similar to the population studied in the RATIFY trial, and to be studied in a phase III trial of chemotherapy combined with crenolanib or midostaurin in newly diagnosed FLT3-mutant AML (NCT03258931).

Aims: To assess the outcomes of a sub-group of newly diagnosed FLT3-mutant AML patients treated with crenolanib and standard chemotherapy to be targeted in a pivotal phase III trial comparing crenolanib with midostaurin.

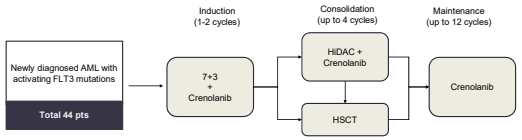
Methods: Twenty-seven of 29 consecutive patients ≤ 60 years old enrolled in a phase II study of crenolanib combined with chemotherapy in newly diagnosed FLT3-mutant AML (NCT02283177) were included in this analysis. Two patients were excluded due to 1) prior treatment for a myeloproliferative disorder and 2) pre-existing liver cirrhosis. Patients received 7+3 induction with cytarabine 100 mg/m² for 7 days and either daunorubicin 90 mg/m² (n=16) or idarubicin 12 mg/m² (n=11) for 3 days. Crenolanib 100 mg TID was administered continuously starting 24 hours after chemotherapy until 72 hours prior to the next chemotherapy cycle.

Consolidation consisted of up to four cycles of high-dose cytarabine (HiDAC: 3 g/m² for < 60 years and 1 g/m² for 60 years) q12 hours on days 1, 3, and 5 with crenolanib starting 24 hours after the final HiDAC dose in each cycle. Eligible patients proceeded to allogeneic hematopoietic stem cell transplant (HSCT). Maintenance crenolanib at 100mg TID was started after HiDAC or 30-90 days after HSCT for a maximum of 12 cycles.

Results: Patients included in the analysis were generally older (median 51 vs. 47 years for RATIFY) and most patients (85%) had FLT3-ITD mutations. Six patients had concurrent NPM1 and DNMT3A mutations, a constellation associated with poor prognosis. Only 4 (15%) patients had more favorable FLT3-TKD mutations compared with 23% in the RATIFY study.

As of February 2018, 22/27 (81%) patients are alive with a median follow-up of 20.8 months. Median overall survival (OS), event-free survival (EFS), and cumulative incidence of relapse (CIR) have not been reached. Fourteen patients received HSCT of which 11 are alive free of disease. Seven patients were consolidated with HiDAC and did not undergo HSCT. Only one of these seven patients has relapsed and the other six remain alive free of disease, suggesting that standard chemotherapy plus crenolanib can provide durable remissions without HSCT. 4/6 (67%) patients with high-risk concomitant mutations in FLT3-ITD, DNMT3A and NPM1 are alive free of disease. Overall, only 3/21 patients have relapsed, none of whom received > 1 week of crenolanib maintenance.

Study Design



Key Features:
- FLT3-ITD or FLT3-TKD
- Any FLT3 allelic burden
- Physician's choice of anthracycline
- High doses of daunorubicin (90 mg/m²) allowed in younger patients

Induction	Cytarabine 100mg/m²/CIV, d1-d7 Dnr 90mg/m² (<60y) or Ida 12 mg/m², d1-d3 Crenolanib 100mg TID starting d9
Consolidation	Cytarabine 3g/m² (<60y) or 1g/m² (60y), q12h, 6 doses Crenolanib 100mg TID starting d7
Maintenance	Crenolanib 100mg TID continuously

References

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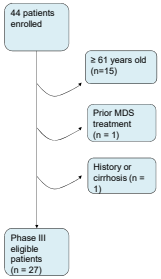
3. Smith, C.C., et al., Crenolanib is a selective type I pan-FLT3 inhibitor. Proceedings of the National Academy of Sciences of the United States of America, 2014. 111(14): p. 531924.
4. Zimmerman, E.I., et al., Crenolanib is active against models of drug-resistant FLT3-ITDpositive acute myeloid leukemia. Blood, 2013. 122(22): p. 3607-15.

Patient Demographics

Characteristics	Phase III eligible (n=27)	Total (n=44)
Age (years), median [range]	51 [19 – 60]	57 [19 – 75]
Sex, male	13 (48%)	22 (50%)
AML classification		
De novo	27 (100%)	40 (91%)
sAML	0	4 (9%)
WBC count/µL, median [range]	33,010 [2,300 – 248,800]	32,520 [2,270 – 248,800]
≥100,000	6 (21%)	7 (16%)
≥200,000	1 (3%)	2 (5%)
Platelets/µL, median [range]	71,000 [21,000 – 619,000]	68,000 [10,000 – 619,000]
Cytogenetic risk classification		
Intermediate	24 (89%)	39 (89%)
Adverse	2 (7%)	3 (7%)
Not available	1 (3%)	2 (5%)
FLT3 mutations		
ITD	21 (78%)	33 (75%)
TKD	4 (15%)	8 (18%)
ITD and TKD	2 (7%)	3 (7%)
FLT3 +NPM1 + DNMT3A	6 (21%)	9 (21%)



Crenolanib can be safely administered at full dose with standard chemotherapy

Daunorubicin 90 mg/m²

Age/Gender	Starting Crenolanib Dose	Dose Reductions
19/M	100mg TID	No
23/F	100mg TID	No
24/M	100mg TID	No
34/F	100mg TID	No
36/M	100mg TID	No
36/F	100mg TID	No
44/F	100mg TID	Yes, 80 TID
47/F	100mg TID	No
48/M	100mg TID	No
50/F	100mg TID	No
51/M	100mg TID	No
54/M	100mg TID	No
54/F	100mg TID	No
58/F	100mg TID	Yes, 80 TID
58/M	100mg TID	No
59/F	100mg TID	No

Idarubicin 12mg/m²

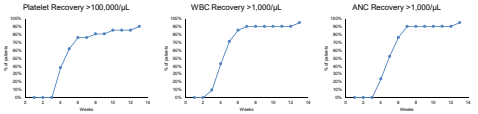
Age/Gender	Starting Crenolanib Dose	Dose Reductions
22/F	100mg TID	Yes, 80 TID
44/F	100mg TID	No
47/M	100mg TID	No
52/M	100mg TID	No
54/F	100mg TID	No
55/M	100mg TID	No
55/M	100mg TID	No
57/M	100mg TID	No
59/M	100mg TID	No
60/F	100mg TID	No
60/F	100mg TID	No

- 89% of the patients were able to continue on crenolanib 100 mg TID during induction.
- No dose reductions were required for induction chemotherapy
  16 pts received daunorubicin (90 mg/m²)
  11 pts received idarubicin (12 mg/m²)

Patients are able to achieve full count recovery following induction + crenolanib

	Platelet count recovery >20,000 /µL	Platelet count recovery >100,000 /µL	WBC count recovery >1000 /µL	Absolute neutrophil count recovery >500 /µL	Absolute neutrophil count recovery >1000 /µL
Median (days)	23	29	30	30	34

n = 21 evaluable patients

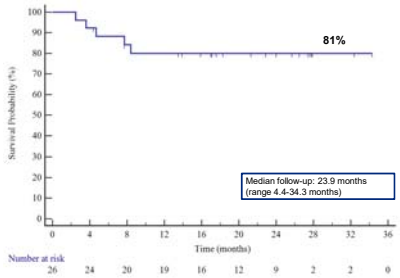


Continuous administration of full dose crenolanib can be safely combined with cytarabine/daunorubicin or cytarabine/idarubicin induction chemotherapy.

High rates of deep remission with single induction cycle

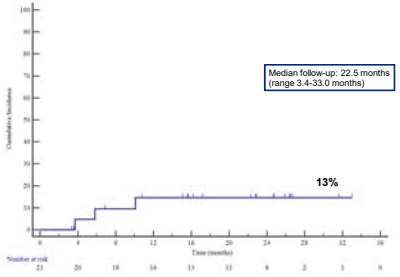
23/27 (85%) achieved complete remissions per protocol therapy
MRD testing after first induction showed that **15/16 (94%) of patients were MRD negative** and of those **93% remain relapse free**
FLT3 mutation after first induction demonstrated that **16/17 (94%) of patients became FLT3 negative**

81% overall survival with 24 month median follow up



- Total of 5 deaths: 2 refractory, 2 relapsed pts (both received <1 week of crenolanib maintenance), and 1 from transplant-related complications

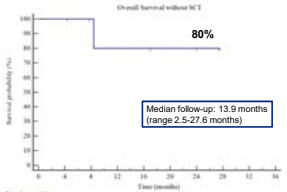
Low relapse rates (13%) with 22.5 months median follow up

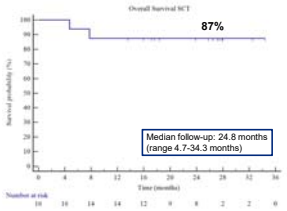


Cumulative incidence of relapse (CIR) is 13%
Only 3 patients have relapsed , none of whom received a full cycle of maintenance
In the RATIFY trial, the 2 year CIR was roughly 40%.
Six patients have completed 12 cycles of maintenance therapy. One patient remains on maintenance.

Similar survival following HSCT vs. HiDAC consolidation

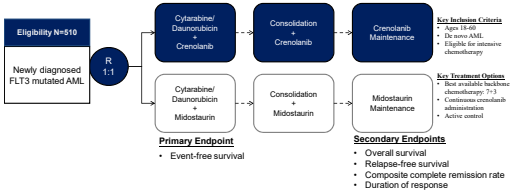
Patients either had HiDAC + crenolanib (n=7), HiDAC + crenolanib + HSCT (n=12) or HSCT (n=4)
13 patients then proceeded to crenolanib maintenance





- **Combination of crenolanib with chemotherapy results in high rates of durable remissions in patients with FLT3 ITD and TKD mutations.**
- **With a follow-up of 24 months, the overall survival remains at 81%.**
- **Patients who received HiDAC + crenolanib demonstrate comparable overall survival compared to those who received allo-HSCT + crenolanib.**
- **Based on these results Arog has initiated a global Phase 3 randomized trial to compare the efficacy of crenolanib versus midostaurin combined with standard chemotherapy (ARO-021, NCT03258931)**

ARO-021, NCT03258931



Please contact info@arogpharma.com or visit https://clinicaltrials.gov if you would like more information about this trial or if you have a patient who may be interested in participating.