Younger Patients with Newly Diagnosed FLT3-Mutant AML Treated with Crenolanib Plus Chemotherapy Achieve Durable Remissions

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Abstract

We have previously reported that cytarabine/daunorubicin as well cytarabine/idarubicin can be safely combined with crenolanib at the full monotherapy dose (100mg TID) and administered throughout induction, consolidation and maintenance in newly diagnosed FLT3-mutated AML (Walter et al., EHA 2018). We hypothesize that crenolanib plasma levels might correlate with long term outcome in these patients.

Methods: Twenty-seven newly diagnosed AML patients with FLT3 mutations, aged 18-60 years old enrolled in a phase II study of crenolanib combined with chemotherapy (NCT02283177) were included in this analysis. Patients received 7+3 induction with cytarabine 100 mg/m^2 for 7 days and either daunorubicin 90 mg/m^2 (n=16) or idarubicin 12 mg/m^2 (n=11) for 3 days. Crenolanib 100 mg TID was administered continuously starting 24-48 hours after induction until 72 hours prior to the next chemotherapy cycle. Consolidation could consist of up to four cycles of high-dose cytarabine (HiDAC): 3 g/m^2 for < 60 years and 1 g/m^2 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 up to 12 cycles.

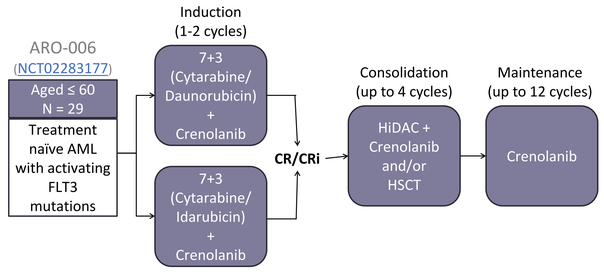
Crenolanib levels (total and free) were measured 2-4 hours following the first dose of crenolanib and after two weeks of continuous crenolanib administration. Crenolanib levels were also measured on first day of crenolanib treatment following HiDAC consolidation. Free crenolanib was measured by rapid equilibrium dialysis. Durability of clinical remissions were documented by routine follow up every 3-4 months (as per institutional practice).

Results: As of July 2019, all patients have completed all protocol therapy (one patient has continued crenolanib maintenance for 25 months per patient request). Twenty-three of 27 patients (85%) achieved complete remission, all of whom required only 1 cycle of induction chemotherapy. Nineteen of 27 patients remain alive and free of disease with a median follow-up of 29.3 months. Three relapses have occurred, all within the first year of treatment and no relapses have occurred in patients who completed at least 1 cycle of crenolanib maintenance. Seven patients received HiDAC consolidation along with crenolanib but did not receive HSCT. Six of these patients remain in long term remission. While the number of patients is small, we observed similar overall survival and cumulative incidence of relapse in patients who underwent HSCT as compared to those who did not.

Pharmacokinetic studies demonstrate that despite increases in acute phase reactants and AGP levels, both total and free crenolanib rapidly achieve sufficient levels to provide the continuous inhibition required to eradicate FLT3-ITD, FLT3-D835, and other FLT3 mutations including FLT3-N841, A680, V592, V491, and D839. Total levels of crenolanib exceeded 500 nM at steady state, and the majority of patients showed clearance of FLT3 mutations after combination therapy.

Summary/Conclusion: These pharmacokinetic data show that crenolanib when given with chemotherapy can achieve sufficient levels to inhibit multiple FLT3 mutations, despite rises in FLT3 ligand and acute phase reactants. These clinical data suggest that this combination might improve outcomes in younger patients with newly diagnosed FLT3-mutant AML. With 29 months median follow up, median overall survival (OS), event-free survival (EFS), and cumulative incidence of relapse (CIR) have not been reached. No relapses have been observed in patients after completing crenolanib maintenance. A phase III randomized multicenter trial has been initiated to compare the efficacy of crenolanib versus midostaurin combined with standard chemotherapy for newly diagnosed patients with FLT3-mutant AML (NCT03258931).

Study Design



Induction:	Cytarabine 100mg/m^2/CIV for 7 days Anthracycline: Daunorubicin 90mg/m^2 or Idarubicin 12 mg/m^2 x 3 days Crenolanib 100mg TID starting day 9
Consolidation:	Cytarabine 3g/m^2 q12h x 6 doses Crenolanib 100mg TID starting day 7
Maintenance:	Crenolanib 100mg TID continuously

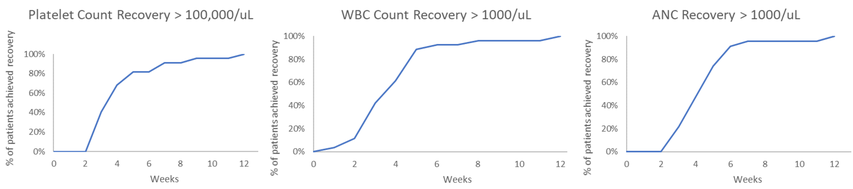
High Rates of Clinical Complete Remission with Full Count Recovery After Single Induction Cycle

Induction Chemotherapy Regimen	Complete Remission after Induction 1	Overall Remission
Cytarabine + Daunorubicin (n=16)	11/16 (69%)	13/16 (81%)
Cytarabine + Idarubicin (n=11)	10/11 (91%)	10/11 (91%)
Total (n=27)	21/27 (78%)	23/27 (85%)

- **21/27 (78%) achieved complete remission after one cycle of chemotherapy**
  - Spares patients from addition anthracycline/cytarabine toxicities
  - 2 patients (7%) required re-induction to achieve remission
- **23/27 (85%) achieved complete remissions** per protocol therapy

Full Count Recovery Is Possible While Taking Crenolanib

Patients achieved full count recovery while taking crenolanib after induction chemotherapy, with a median time to full recovery of 30 days



	Platelet count recovery >20,000 /µL	Platelet count recovery >100,000 /µL	WBC count recovery >1000 /µL	ANC recovery >500 /µL	ANC recovery >1000 /µL
Median (days)	22	27	27	27	30

High Rates of MRD Negativity With Crenolanib Combination Therapy

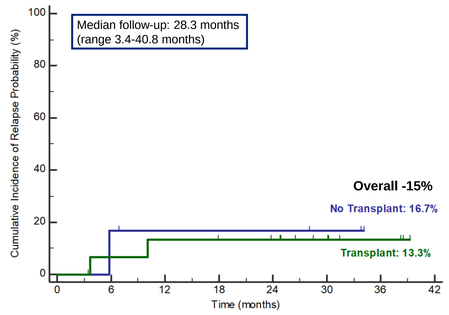
Multi-parameter Flow Cytometry to Assess MRD

- MRD assessment was performed by multi-parameter flow cytometry using bone marrow samples obtained at count recovery
- Patients in CR/CRi after a single cycle of chemotherapy/crenolanib treatment were assessed
- Flow markers used varied between center. Common markers included: HLA-DR, CD7, CD13, CD15, CD19, CD33, CD34, CD45, CD56, CD64, and CD117
- FLT3 status was determined by local testing, either PCR based or NGS panels

Status at CR1	Number of Patients (n=17)	Relapse Free
MRD Negative	16 (94%)	15 (94%)
MRD Positive	1 (6%)	1 (100%)
FLT3 Negative	16 (94%)	15 (94%)
FLT3 Positive	1 (6%)	1 (100%)

- MRD testing after first induction showed that **15/16 (94%) of patients were MRD negative** and of those **94% remain relapse free**
- FLT3 mutation after first induction demonstrated that **16/17 (94%) of patients became FLT3 negative**

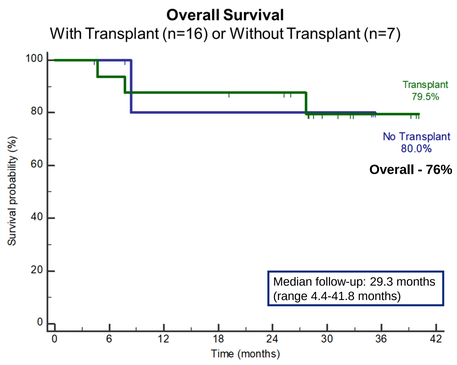
Low Relapse Rates Observed



Cumulative incidence of relapse (CIR) is 15%.

- All 3 relapses occurred in the first 12 months.
  - 1 relapsed patient had a CNS relapse with no evidence of bone marrow relapse
- No relapses have been observed in patients who completed at least one cycle of crenolanib maintenance.

76% Patients Alive and Free of Disease with 29 Months Follow-up



Overall Survival is 76% with median follow up of 29.3 months.

There have been a total of 6 deaths:

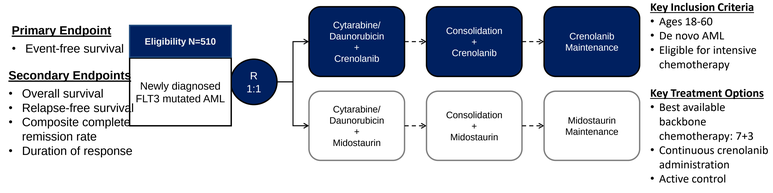
- 2 patients were refractory
- 3 relapsed
- 1 death due to complications post transplant

Similar survival rates have been seen regardless of transplant for patients receiving post-consolidation maintenance

Conclusions

- **23/27 patients (85%) achieved complete remission after induction chemotherapy followed by crenolanib, with only 2 patients (7%) requiring a second cycle of induction**
- **Median event-free survival has not been reached in 29+ months**
  - **Overall survival is 76%**
- **Patients who did not receive allo-HSCT show similar survival and relapse rates compared to patients who underwent transplant**
- **Based on these results Arog has initiated a global Phase 3 randomized head-to-head 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.