Safety Analysis of Intra-Patient Dose-Study of Crenolanib Maintenance Therapy in Patients with FLT3 Mutant AML Following Allogeneic Hematopoietic Stem Cell Transplant

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Abstract

Background: FLT3 inhibitors (like sorafenib and midostaurin) have been administered as maintenance therapy post allogeneic stem cell transplantation (SCT) to reduce persistent relapse risks in FLT3-mutant AML patients. Reduced doses of both sorafenib and midostaurin have been found to be tolerable in the post-HSCT setting. Crenolanib is a highly potent and selective FLT3-targeted TKI that has activity as a single-agent and combined with chemotherapy in patients with FLT3-ITD and/or FLT3-TKD mutations. We here report the outcomes of safety and tolerability of crenolanib maintenance in FLT3 mutant AML patients after allo-HSCT (NCT02400255).

Methods: To assess the tolerability of crenolanib maintenance in post-SCT AML patients and evaluate the appropriate dose for such patient population, a clinical trial of crenolanib maintenance therapy was performed in patients (age ≥ 18) with FLT3 mutant AML who had undergone SCT. Enrollment criteria included patients with FLT3-ITD, or FLT3-TKD positive disease at any point prior to SCT, having first SCT, with ≥ 50% T cell donor chimerism, adequate engraftment with complete remission (CR) at post-SCT evaluations. Patients needed to enroll between 42 and 90 days post-transplant without uncontrolled infection and graft versus host disease (GvHD).

Initially, the study was designed for patients to be treated with crenolanib 80 mg TID (240 mg daily. Due to initial tolerability in the first patients (n=4), the design was changed to an intra-patient dose-escalation, in which patients received crenolanib starting at a dose of 60 mg BID for a month and then escalated to 80 mg BID and finally 80 mg TID as tolerated.
As of July 2018, 24 patients, median age 53.5 years (range 31-74) have been enrolled and received crenolanib maintenance therapy. Disease status at SCT was CR (n=10, 42%), CR without count recovery (CRi, n=12, 50%), and active disease (n=2, 8%). The minimal residual disease (MRD) by multicolor flow cytometry was evaluable in 22 CR/CRi patients at SCT and was deemed to positive in 5 (23%). Conditioning regimen was myeloablative (20, 83%) or reduced intensity (4, 17%). Donors were matched related (n=11, 46%), matched unrelated (n=11, 46%) or haploidentical (n=2, 8%).

After 4 patients enrolled, the trial design was altered to allow for intra-patient dose escalation. Ten patients were never able to escalate above 60mg BID, one patient stayed at 60 mg TID, 12 patients escalated to 80 mg BID, of those 12, 7 were able to escalate to 80 mg TID.

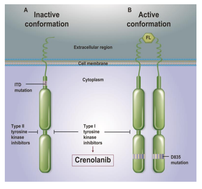
The median days on crenolanib was 474 days (4-728 days) and median number of cycles was 17.5 cycles (1-26 cycles). Of the 21 patients no longer on study, 6 were due to relapse with median time to progression of 17 days (7-76 days) after first dose of crenolanib. Of the 6 relapses, four patients were positive for MRD prior to transplant and two had active disease. Two patients came off study due to noncompliance with study procedures, two were due to withdrawal of consent, 7 were patient decision due to side effects, one was due to suicidal ideation, and one was for insurance non-payment. Only one patient completed the planned 24 cycles of treatment with crenolanib 60 mg BID. Currently, four patients remain on study.

Observed side effects were predominantly grade 1 and 2 with the most common (regardless of attribution) being nausea (62%), vomiting (38%), and diarrhea (33%), 13 adverse events that were grade 3 were reported likely attributable to crenolanib, no grade 4 side effects reported. There were two grade 2 GVHD-AEs, one grade 1 and one ungraded GVHD-AEs reported. One patient had a grade 3 rash that was confirmed as GVHD.

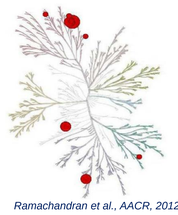
Conclusion: These interim results suggest that crenolanib can be safely given at a dose of 160 mg to 240 mg total daily in the post-SCT setting. Two randomized phase III trials have been initiated to investigate the efficacy of crenolanib with chemotherapy vs chemotherapy alone in R/R FLT3 mutated AML as well as crenolanib vs midostaurin following chemotherapy in newly diagnosed FLT3 mutated AML (NCT03250338, EudraCT 2017-001600-29; NCT03258931). Post HSCT crenolanib maintenance will be offered at 100 mg BID (200 mg daily) in both trials.

Crenolanib is a Highly Selective FLT3 Inhibitor

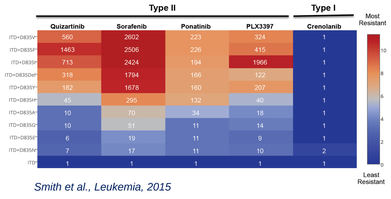
Crenolanib is a potent Type I pan-FLT3 inhibitor
- Inhibits both active and inactive conformations of FLT3 mutations
- Highly selective: no KIT inhibition at clinical achievable levels permits count recovery and limits hair depigmentation
- Active against novel variant FLT3 mutations
- Well-tolerated and safely given as single-agent and at full doses in combination with chemotherapy



Fathi AT Blood. 2013;122(22):3547-8

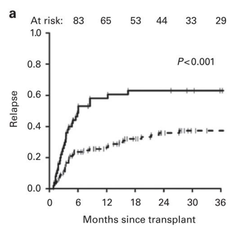


Ramachandran et al., AACR, 2012



Smith et al., Leukemia, 2015

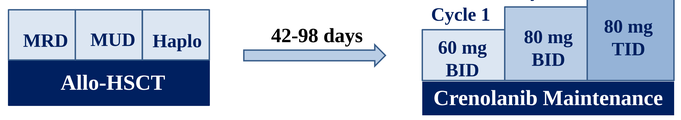
FLT3 mutation predicts for increased risk of relapse after Allo-HSCT
- Graph (right) shows three year cumulative incidence of relapse by FLT3 mutation status



Song Y, Bone Marrow Transplant. 2016

Treatment Schema

Crenolanib maintenance therapy starts between 42 and 98 days after allo-HSCT. Dosing regimen of crenolanib follows an intra-patient dose escalation schedule with 28-day cycles.



33% of Patients had R/R AML

Gender	n=24
Male, N	12
Female, N	12
Age	
median (range)	53 (31-74)
≤60 years	20
>60 years	4
AML Diagnosis	
Primary	21
MDS	2
CMML	1
Response to Prior Therapy	
CR 1	16
CR 2	5
CR 3+	1
PR	1
RD	1
Previous Therapies	
TKI Naïve	9
TKI Pretreated	15
Sorafenib	13
Quizartinib	1
Midostaurin	1

Many patients had a high risk of relapse
- 33% of patients had a history of relapsed or refractory AML
  - 2 patients had not achieved CR at time of HSCT
- 60% of patients had been previously treated with a FLT3 TKI
- 2 patients had history of CNS leukemia
- 3 patients had AML secondary to antecedent hematological disorders

25% of Patients Were MRD+ at Time of Transplant

Disease Status Prior to HSCT	n=24
CR	12
CRi	10
Residual Disease	2
MRD Status Prior to HSCT	
Active Disease	2
MRD +	4
MRD -	18

25% of patients were not in molecular remission at time of transplant
- 2 patients had active disease prior to HSCT
- 4 patients had measurable residual disease prior to HSCT

42% of patients did not receive consolidation therapy prior to HSCT
- 4 patients received reduced intensity conditioning regiments in preparation for HSCT
- 2 patients received transplants from haploidentical donors

	n=24
Direct to Tranpslant	10
≥1 Cycle of Consolidation	14
Conditioning regimen	
Myeloablative	20
Reduced Intensity	4
Donor type	
Match-related donor	10
Match-unrelated donor	12
Haploidentical	2
Time to Maintenance	
Days, median (range)	80 (51-96)

Crenolanib is Well Tolerated in the Post-HSCT Setting

Maximum TEAE Grade by Patient							
Preferred Term	Total AEs	Percent	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nausea	16	67%	4	12	0	0	0
Vomiting	11	46%	8	3	0	0	0
Diarrhea	10	42%	3	5	2	0	0
Fatigue	4	17%	2	2	0	0	0
Alanine aminotransferase increased	3	13%	2	0	1	0	0
Oedema peripheral	3	13%	3	0	0	0	0
Periorbital oedema	3	13%	2	1	0	0	0

Crenolanib Caused Limited Myelosuppression

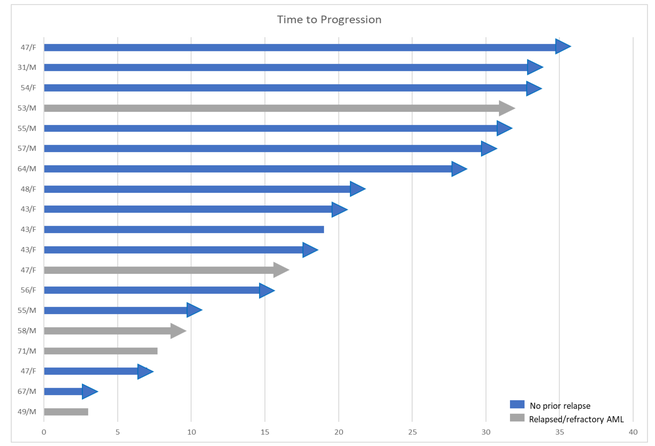
There was one instance of myelosuppression related AEs attributed to crenolanib
- One patient had reported grade 3 decreased platelet count attributed to crenolanib, which recovered after treatment discontinuation

Crenolanib was Tolerable as Long-Term Post-HSCT Maintenance

Duration of Treament	n=24
Days, median (range)	101 (4-728)*
Completed ≥6 months maintenance	5
On-study	4
*As of October 10. 2018	

33% of patients have completed at least 6 months of treatment
- 4 patients are still on study
  - 3 have completed >6 months of maintenance therapy
- 1 patient completed a full 2 years of maintenance therapy

90% of Patients Evaluable for Efficacy are Leukemia Free



90% of patients receiving >1 cycle of crenolanib are leukemia free
- Of the 24 patients enrolled to date, 6 have relapsed
  - 5 of these patients progressed in the first 30 days of treatment (not included in graph)
  - 2 patients have died after removal from study
  - The remaining 17 patients are alive and disease free with a median follow up of 20 months (as of October 10, 2018)

Conclusions

- The interim results suggest that crenolanib can be safely administered post-HSCT at a daily dose of 160 mg to 240 mg, even in patients receiving concomitant immunosuppressive medications such as tacrolimus and antifungal agents
- No GI bleeds or respiratory failure events were observed; additionally no patients experience Grade 4 or 5 adverse events which were attributed to crenolanib
- Patients must be kept motivated to stay on treatment during the initial two cycles of maintenance, at which point tolerability improves
- Based on these results, post-HST crenolanib maintenance will be offered at 100 mg BID in two recently initiated randomized phase III trials investigating the efficacy of crenolanib with chemotherapy in newly diagnosed and R/R FLT3 mutated AML patients, respectively (NCT03250338, EduraCT 2017-001600-29; NCT03258931)

References

Fathi A-T Emergence of crenolanib for FLT3-mutant AML. *Blood 2013;122(22):3547-3548*
Ramachandran A Crenolanib, a novel Type I, mutant-specific inhibitor of Class III receptor tyrosine kinases, preferentially binds to phosphorylated kinases. *AACR 2012*
Smith C-C FLT3 D835 mutations confer differential resistance to type II FLT3 inhibitors. *Leukemia 2015;29(12):2390-92*
Song Y FLT3 mutational status is an independent risk factor for adverse outcomes after allogenic transplantation in AML. *Bone Marrow Transplant 2016; 51(4):511-20*

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.