INTRA-PATIENT DOSE-ESCALATION STUDY OF CRENOLANIB MAINTENANCE THERAPY IN PATIENTS WITH FLT3 MUTANT AML WHO HAD UNDERGONE ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT

B. Oran* [1], S. Ciurea[1], D. Marin[1], J. McCarty[1], Q. Bashir[1], S. Ahmed[1], A. Olson[1], U. Popat[1], Y. Nieto[1], P. Kebriaei[1], E. Shpall[1], T. Agrawal[2], R. Champlin[1]

1Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston,

2AROG Pharmaceuticals, Inc., Dallas, United States

STOCKHOLM 23RD CONGRESS JUNE 14 - 17 | 2018 European Hematology Association

ABSTRACT

Background: FLT3 inhibitors (like sorafenib and midostaurin) have been administered as maintenance therapy post allo-HSCT to reduce persistent relapse risks in FLT3-mutant AML patients. Recent studies suggest that inhibition of FLT3 can downregulate dendritic cell proliferation and increase cytotoxic CD8+ T-cell function in allo-HSCT recipients thus increasing graft-versus-leukemia (GvL) effect (Lau et al. J. Exp. Med, 2016). Some FLT3 inhibitors including crenolanib have shown increased IL-15 production resulting in elevated GVL activity, thus reducing the risk of post-transplant relapse (Mathew et al. Nat Med, 2018).

Only 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. Given the favorable safety profile of crenolanib at 100 mg TID (300 mg daily) and promising clinical benefits in AML patients, crenolanib has been used as maintenance therapy in the post-transplant setting. We here report the outcomes of safety and tolerability of crenolanib maintenance in FLT3 mutant AML patients with prior allo-HSCT (NCT02400255).

Aims: To assess the tolerability of crenolanib maintenance in the post allo-HSCT AML patients and evaluate the appropriate dose for such patient population.

Methods: A study of crenolanib maintenance therapy was performed in patients (age ≥ 18) with FLT3 mutant AML who had undergone HSCT. Initially, patients were treated with 80 mg TID (240 mg daily) which was subsequently 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. Regular assessment of chemistry and hematologic laboratory values were performed to ensure safety of crenolanib in this patient population.

Results: 21 patients, who received a variety of prior treatments and graft sources, have been enrolled to date. 4 patients received an initial dose of 80 mg TID, but due to early tolerability issues dosing was changed to an intra-patient escalation, after which crenolanib was well tolerated at the initial dose of 60 mg BID as well as the next dose level of 80 mg BID. 16 patients have discontinued treatment: 7 due to patient choice, 5 due to disease progression and 4 due to investigator decision. Of 5 progressions, 4 were MRD positive prior to HSCT and 2 had received haplo transplant, with a median time to progression of 17 days.

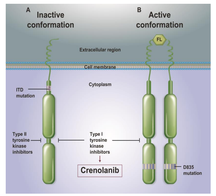
Side effects were predominantly grade 1 and 2 with the most common (regardless of attribution) being nausea (62%), vomiting (38%), and diarrhea (33%). Of the 6 patients escalated to 80 mg TID, 4 tolerated multiple cycles. Currently, five patients remain on treatment and the median duration of survival follow-up is 433 days.

Conclusion/Summary: These interim results suggest that crenolanib can be safely given at a dose of 160 mg to 240 mg total daily in the post-HSCT 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). Based on these results, post HSCT crenolanib maintenance will be offered at 100 mg BID (200 mg daily) in both trials.

INTRODUCTION

CRENOLANIB IS A POTENT TYPE I PAN-FLT3 INHIBITOR

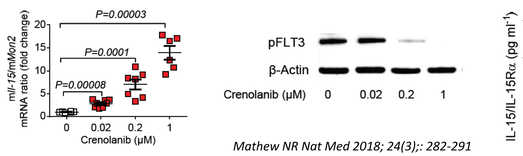
- Crenolanib inhibits both active and inactive conformations of FLT3-ITD and FLT3-TKD mutations
- Has activities as single-agent in both newly diagnosed and R/R FLT3+ AML as well as combined with chemotherapy in patients with FLT3-ITD and/or FLT3-TKD mutations
- 7-8h half-life with no accumulation after chronic dosing; no increase in QTc intervals
- Well-tolerated and safely given as single-agent and at full doses (100 mg TID) in combination with chemotherapy



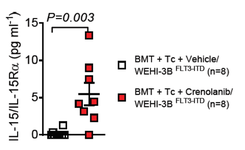
Fathi AT Blood. 2013;122(22):3547-8

FLT3 INHIBITORS ADMINISTERED POST TRANSPLANT CAN POTENTIALLY CAUSE GVL EFFECTS

- Inhibition of FLT3 can downregulate dendritic cell proliferation and increase cytotoxic CD8+ T-cell function thus increasing graft-versus-leukemia (GvL) effect to eliminate residual leukemic cells after allogeneic BM transplantation.
- Crenolanib as well as some other FLT3 inhibitors has shown increased IL-15 production in FLT3-ITD$^+$ AML cells, suggesting its potential to contribute to an immune-mediated cure of FLT3-ITD-mutant AML relapse after allo-HSCT.



Mathew NR Nat Med 2018; 24(3);: 282-291



DEMOGRAPHICS

Patient Characteristics

Gender	n = 21
Male, N	11
Female, N	10
Age	
median (range)	54 (31-74)
Disease status prior to HSCT	
CR	7
CRi	11
Residual disease	2
Unknown	1
Conditioning regimen	
Myeloablative	15
Reduced intensity	5
Unknown	1
Donor type	
Match-related donor	9
Match-unrelated donor	10
Haploidentical	2
Crenolanib start date post-HSCT	
Days, median (range)	80 (50-98)
Duration of treatment	
Days, median (range)	208 (4-728*)

* Updated information as of May 17, 2018.

FLT3 Mutation Status at Baseline

FLT3 Status (ITD or TKD)	N=19*
ITD with low allelic ratio	8
ITD with high allelic ratio	5
ITD burden unavailable	6
TKD (exclude ITD)	4

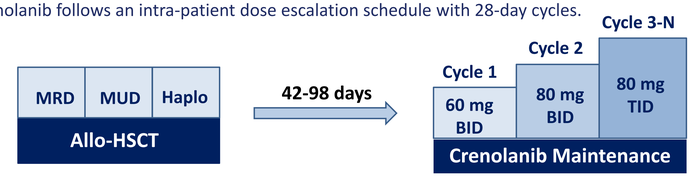
Concurrent Mutations at Baseline

Other mutations	N=13*
NMP1	11 (85%)
IDH1	1 (8%)
IDH2	4 (31%)
NRAS	2 (15%)
PTPN11	1 (8%)
TET2	2 (15%)
DNMT3A	4 (31%)
ABL1	1 (8%)
EGFR	1 (8%)
WT1	1 (8%)
RUNX1	3 (23%)

* Some patient data is not available.

TREATMENT SCHEMA

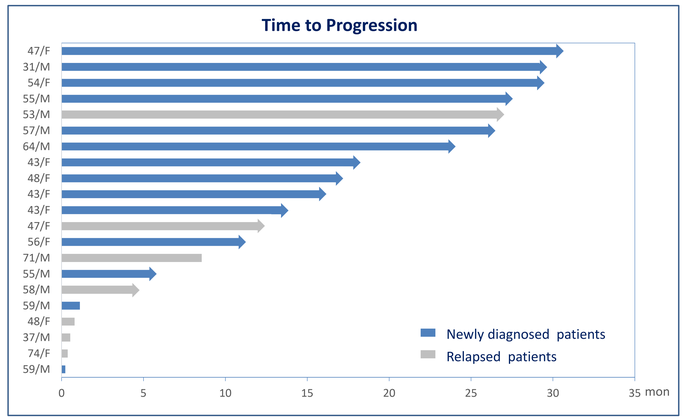
Crenolanib maintenance therapy starts between 42-98 days after allo-HSCT. Dosing regimen of crenolanib follows an intra-patient dose escalation schedule with 28-day cycles.



CRENOLANIB IS WELL TOLERATED IN POST-HSCT SETTING

	Maximum TEAE Grade by Patient							
	Preferred Term	Total AEs	Percent	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
All TEAEs regardless of causality	Nausea	13	61.9%	2	9	0	0	0
	Diarrhea	8	38.1%	1	4	2	0	0
	Vomiting	7	33.3%	5	2	0	0	0
	Platelet count decreased	4	19.0%	0	1	2	1	0
	Oedema peripheral	3	14.3%	3	0	0	0	0
	Periorbital oedema	3	14.3%	2	1	0	0	0
	Rash	3	14.3%	1	2	0	0	0
	Upper respiratory tract infection	3	14.3%	0	3	0	0	0
TEAEs with attribution to Crenolanib	Nausea	10	47.6%	2	8	0	0	0
	Diarrhea	7	33.3%	1	4	2	0	0
	Vomiting	7	33.3%	5	2	0	0	0
	Oedema peripheral	3	14.3%	3	0	0	0	0
	Periorbital oedema	3	14.3%	2	1	0	0	0

RESULTS



- In this population of newly diagnosed as well as relapsed FLT3 mutant AML patients, 16 out of 21 patients remain free of leukemia with a median follow up of 17.4 months as of May 17, 2018.
- Of these 16 patients in remission, four had received allo-HSCT as salvage therapy after a prior relapse.

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 or mycophenolic acid and antifungal agents such as posaconazole. Crenolanib's increased tolerability at a reduced dose is consistent with other FLT3 TKIs given as post-transplant maintenance, such as sorafenib and midostuarin. No liver enzyme elevations, GI bleeds or respiratory failure events were observed; additionally, no patients experienced Grade 4 or 5 adverse events which were attributed to crenolanib.

Based on these results, post-HSCT crenolanib maintenance will be offered at a convenient dose of 100 mg BID (200 mg daily) 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, EudraCT 2017-001600-29; NCT03258931).

REFERENCES

1. **Lau C-M et al**. Leukemia-associated activating mutation of Flt3 expands dendritic cells and alters T cell responses. *J of Exp Med 2016; 213(3);: 415-431*

2. **Mathew N-R et al**. Sorafenib promotes graft-versus-leukemia activity in mice and humans through IL-15 production in FLT3-ITDmutant leukemia cells. *Nat Med 2018; 24(3);: 282-291*

3. **Fathi A-T** Emergence of crenolanib for FLT3-mutant AML. *Blood 2013;122(22):3547-3548*

CONTACT INFORMATION

Corresponding author: Betul Oran, boran@mdanderson.org