#7027

Clinical activity of Crenolanib in patients with D835 mutant FLT3-positive relapsed/refractory acute myeloid leukemia (AML)

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Abstract #7027

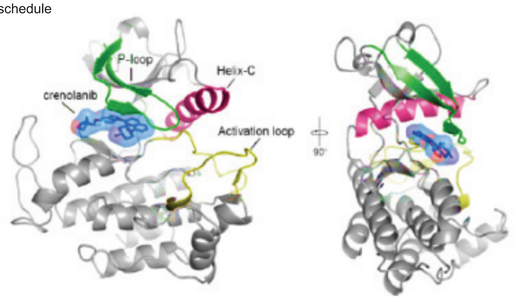
Background: Development of D835 is a common mechanism of resistance to most FLT3 inhibitors. Crenolanib, a type I FLT3 tyrosine kinase inhibitor, has *in vitro* activity against FLT3 ITD and FLT3 D835. Crenolanib trials in relapsed/refractory FLT3 mutant AML (FLT3 ITD, FLT3 D835, FLT3 ITD/D835) are ongoing (NCT01522469, NCT01657682). Methods: Clinical data on the first 22 patients (9M, 13F) with a median age of 50 years (21-87) are currently available; 6 patients were refractory and 9 had relapsed within 6 months of induction therapy. Four had undergone prior allogeneic transplant. 15/22 had progressed after exposure to ≥1 prior FLT3 TKI (11 Sorafenib, 6 AC220, 2 PLX3397, 1 PKC412,); 3 had received ≥ 2 prior FLT3 TKIs. Initially, crenolanib was given at a fixed dose of 100 mg PO TID but the dose was subsequently individualized to 200 mg/m^2/d given in 3 divided doses. Results: Crenolanib had a Tmax of 1.5-2 hours and a T1/2 of 8-9 hours. Median day 15 trough levels (from 11 patients) ranged from 136-785 nM (median 473nM). Commonly observed side effects included nausea and vomiting and transaminase elevations (primarily grade 1, 2). No patients went off study due to toxicity. One patient each required crenolanib dose reduction due to grade 3 nausea and transaminitis, respectively. No QT prolongations on EKG were observed in any patient. Twenty-two patients are currently evaluable for response. 1 patient achieved a rapid molecular and clinical CR with full count recovery. 5 patients achieved a CR with incomplete count recovery (CRi). An additional 3 patients had a partial response. 4 patients were bridged to transplant. Conclusions: Crenolanib is a FLT3 TKI that is showing preliminary clinical activity in a heavily pretreated population with both FLT3 D835 and compound FLT3 ITD/D835 mutant AML. Importantly, crenolanib is also the first agent to demonstrate clinical activity in patients refractory to other FLT3 TKIs via the major clinical resistance mechanism. Trials of crenolanib in newly diagnosed as well as first relapsed AML patients are being initiated.

FLT3-D835 mutation in AML

- D835 is an activating mutation in the kinase domain of FLT3
- Incidence of 5%-7% in newly diagnosed AML
- Resistant to currently available FLT3 TKIs
- D835 is the most commonly reported resistance mutation to sorafenib and quizartinib[1]

Crenolanib Besylate, Type I FLT3 inhibitor

- Benzimidazole moiety provided as besylate salt
- Type I inhibitor
- Binds to the active FLT3 conformation
- Orally bioavailable
- Rapidly absorbed, with half life of 6-9 hrs.
- TID schedule

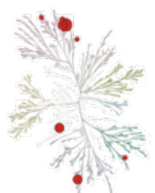


Modeling of FLT-3 crenolanib interactions. Cartoon presentation of modeled FLT3 KD in an active conformation.[1]

Crenolanib inhibits FLT3-ITD, FLT3-D835, and compound mutations[1]

Mutation	IC_{50} nM
FLT3-ITD	9.1 ± 3.8
D835V	2.9 ± 0.5
D835Y	5.3 ± 2.7
FLT3-ITD/F691L	55.4 ± 14.4
FLT3-ITD/D835V	13.1 ± 4.8
FLT3-ITD/D835Y	12.3 ± 2.5
FLT3-ITD/D835F	16.5 ± 0.4
FLT3-ITD/Y842C	15.4 ± 4.8
FLT3-ITD/Y842H	17.9 ± 2.0

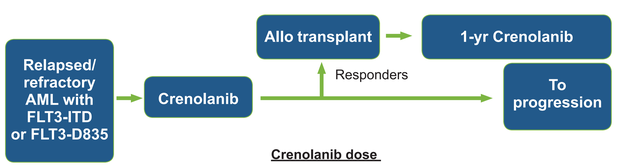
Selective for FLT3 with ~25 fold less KIT inhibition[2,3]



Crenolanib	IC_{50}
p-FLT3 IC_{50}	2.65 nM
p-cKit IC_{50}	67 nM

Single agent data on first 22 D835 pts. enrolled on two single agent phase II studies

- Key eligibility criteria:
  - R/R FLT3-D835 +ve AML
  - ECOG performance status between 0-2
  - Age ≥18 (no upper limit)
  - Prior allogeneic transplants allowed
- Ten pts. treated at UTSW and 12 pts. at MD Anderson



Crenolanib dose

- First 15 patients: 100 mg, TID (flat dosing)
- All subsequent patients: 200 mg/m^2/day in 3 divided doses

Heavily pretreated patient population with a median of 3 prior therapies

	N=22
Gender	13F/9M
Median (range) age, years	50 (21-87)
≥60 years	9
≥80 years	2
FLT3 status	
FLT3-ITD and FLT3-D835	17
FLT3-D835 only	5
Median (range) prior systemic therapies	3 (1-6)
Prior allogeneic transplant	4

2/3rd of patients had progressed after treatment with other FLT3 TKIs

	N=22
Prior FLT3 TKI exposure	15
Sorafenib only	7
Sorafenib followed by quizartinib	2
Sorafenib → quizartinib → PLX3397	1
Sorafenib → midostaurin (PKC412)	1
Quizartinib only	3
PLX3397 only	1
No prior FLT3 TKI exposure	7

Higher response rates in patients with ≤3 prior therapies

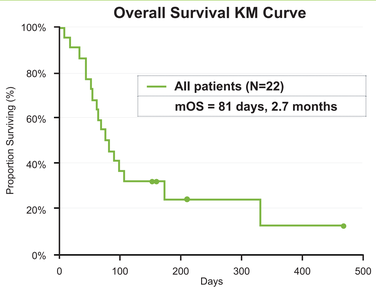
Crenolanib	N	CR/CRi	PR	Blast Response	Overall Clinical Benefit
Overall	22	6 (27%)	3 (14%)	2 (9%)	11 (50%)
≤3	14	6 (43%)	2 (14%)	2 (14%)	10 (71%)
≥4	8	0	1 (12%)	0	1 (12%)

One patient achieved rapid CR with full count recovery and was transfusion independent

Response Definitions[4]:

- CR: Bone marrow blasts <5%; neutrophil count >1.0 x 10^9/L; platelet count >100×10^9/L; independent of red cell transfusion
- CRp: CR with incomplete platelet recovery: <100×10^9/L
- CRi: CR with incomplete hematologic recovery: neutrophil count <1.0 x 10^9/L with or without platelet count <100×10^9/L; not required to be transfusion-independent
- Partial response (PR): same criteria as CRi, except bone marrow blast count between 5%-25% and represents a ≥50% decrease from baseline
- Blast response (BR)/peripheral blast response (PBR): Baseline peripheral blasts of >5%, and peripheral blast count decreased by ≥50%

Median overall survival was 81 days on intent to treat basis



- Includes all patients that received at least 1 day of crenolanib
- 4 patients were bridged to transplant
- Survival at 6 months was 24%

Common toxicities were GI and transaminase elevations

AEs, N=18	Total	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Fatigue	12	7	4	1	0
Nausea	12	5	5	2	0
Vomiting	10	7	1	2	0
Diarrhea	9	6	2	1	0
Neutropenic fever	3	0	0	1	2
ALT	2	1	0	0	1
ALP	2	1	1	0	0

- Full toxicity data available only for first 18 patients
- No patients discontinued drug due to toxicity
- No QT prolongation was observed
- Sweet Syndrome was observed in one patient

Summary and conclusion

- Crenolanib is a type-1 FLT3 inhibitor that inhibits both FLT3-ITD and TKD mutations
- Crenolanib has demonstrated preliminary clinical activity in R/R AML patients with FLT3-ITD(+) or FLT3-D835(+), or compound mutation (CR/CRi rate of 27%)
- CR/CRi rate improved to 43% in patients with 3 or less prior therapies
- Common side effects were gastrointestinal (nausea & diarrhea) and transaminase elevations
- Trials testing crenolanib in combination with chemotherapy earlier in the course of disease are planned

References

1. Smith CC, et al. Proc Natl Acad Sci USA. 2014; 111(14): 5319-24.
2. Galanis et al. AACR 2012. Abstract #3660.
3. Galanis A, Levis M. ASH. 2013. Abstract #3846.
4. Cortes et al. J Clin Oncol. 2013; 31(29): 3681-7.