#3937

A Phase I Study of Crenolanib Plus Sorafenib as a Salvage Therapy for Pediatric Patients with FLT3-ITD+ AML

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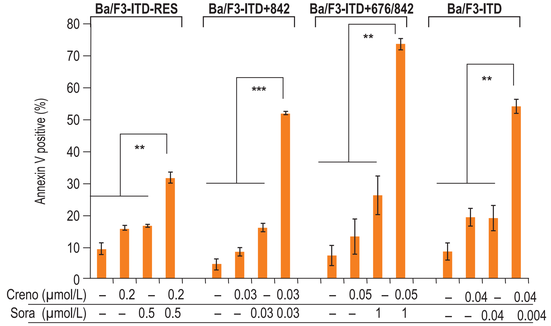
Background/Rationale

- *FLT3* mutations are found in about 30% of adult AML patients and about 20% of pediatric AML patients and are associated with a poor prognosis [1-2].
- Sorafenib is a Type 2 TKI that has shown efficacy in AML patients with *FLT3*-ITD (internal tandem duplication) mutations, but eventually most patients relapse or develop resistance [1].
- Acquired secondary mutations in the *FLT3* tyrosine kinase domain (TKD) is one mechanism of sorafenib resistance [1-5].
- Crenolanib is a novel Type 1 TKI that can inhibit both ITD and TKD FLT3 mutants, including known FLT3-TKD mutants associated with sorafenib resistance [3-5].
- Preclinical research has demonstrated enhanced anti-leukemic activity both *in vitro* and *in vivo* by combining crenolanib and sorafenib treatment [4-5].

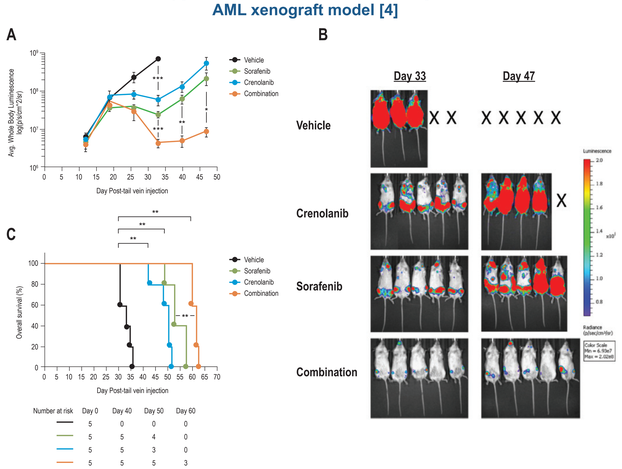
Crenolanib can target sorafenib resistant *FLT3* mutants [5]

	Crenolanib K_d, nM	Sorafenib K_d, nM
FLT3 variant		
FLT3	0.15	13†
FLT3 (ITD)	0.26	95
FLT3 (D835H)	0.16	11
FLT3 (D835Y)	0.14	24
FLT3 (D835V)	3.3	140
FLT3 (ITD, D835V)	3.6	630
FLT3 (ITD, F691L)	22	860

Combination treatment provides additive/synergistic apoptotic effects on *FLT3* mutant cell lines [3]



Combination therapy enhances anti-leukemic activity in mouse FLT3-ITD AML xenograft model [4]



Objectives

Primary Objectives
- Safety and tolerability
- AE profile

Secondary Objectives
- Pharmacokinetics
- Anti-leukemia activity

Treatment Schema

Key Eligibility Criteria
- **Ages 1-18 years old**
- **R/R AML**
- **FLT3-ITD +**
- **Any # prior therapies**
- **CNS leukemia allowed**

Crenolanib continuous dosing starting on C1D1

Sorafenib continuous dosing starting on C1D8

Day 8, IT

Until disease progression, or unacceptable toxicity

Dose Level	Crenolanib (per day × 28 days)	Sorafenib (per dose × 28 days)	Maximum dose of Sorafenib
1	66.7 mg/m² divided into 3 doses*	150 mg/m² QD	300 mg
2	66.7 mg/m² divided into 3 doses*	200 mg/m² QD	400 mg
-1	66.7 mg/m² divided into 3 doses*	200 mg/m² QOD	400 mg

*Total daily dose is rounded to nearest 20mg then divided TID.

Intrathecal Chemotherapy			
Patient age	**Methotrexate**	**Hydrocortisone**	**Cytarabine**
1-2 years	8 mg	16 mg	24 mg
2-3 years	10 mg	20 mg	30 mg
> 3 years	12 mg	24 mg	36 mg

Demographics/ Prior History

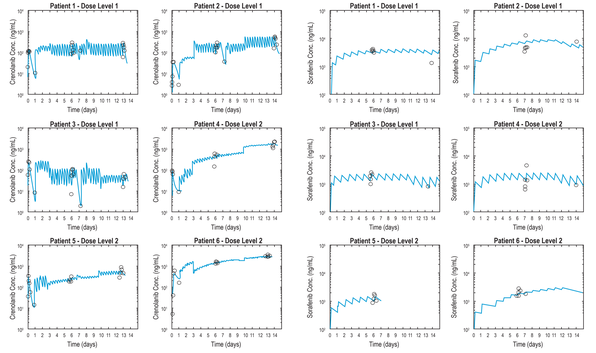
Characteristics	Total (N=9)
Age (yrs), median [range]	9.7 [5.7 – 17.8]
Sex, male	5 (55%)
Baseline Bone Marrow Blasts (%), median [range]	71% [0-98%]
Number of Prior Therapies, median [range]	3 [1–6]
Prior sorafenib	6 (67%)
Prior SCT	4 (45%)
Disease Status	
CNS leukemia	3 (43%)
Extramedullary AML	1 (11%)
FLT3-ITD +	9 (100%)

*2 cases did not have CSF examination

Pharmacokinetic Analysis

- Crenolanib steady-state concentrations were adequate to inhibit both wild-type and mutant FLT3 molecules
- Crenolanib steady-state concentrations were not altered by the addition of sorafenib 150mg/m² QD on day 8

Crenolanib PK **Sorafenib PK**



Safety Analysis

- No DLTs were reported at either sorafenib dose levels.
- 68% of AEs were grade 1 or 2 in severity.
- No QTc prolongation >500ms was observed.

Selected Treatment Emergent AEs- Regardless of Attribution	Total AEs	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Gastrointestinal disorders						
Diarrhea	4	2	2	0	0	0
Nausea	6	5	1	0	0	0
Vomiting	5	4	1	0	0	0
General disorders and administration site conditions						
Edema face	2	1	1	0	0	0
Edema limbs	2	1	1	0	0	0
Infections and infestations						
Enterocolitis infectious	3	0	0	3	0	0
Lung infection	1	0	0	1	0	0
Otitis media	1	0	0	1	0	1
Sepsis	1	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders						
Bronchopulmonary hemorrhage	1	0	0	0	0	1
Respiratory failure	1	0	0	0	0	1
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodyses thesia syndrome	1	0	1	0	0	0
Pruritus	2	2	0	0	0	0
Rash maculo-papular	6	4	1	1	0	0
Urticaria	1	0	1	0	0	0
Vascular disorders						
Hypertension	1	1	0	0	0	0
Hypotension	1	0	0	1	0	0
Liver Function Tests						
Alanine aminotransferase increased	8	2	2	4	0	0
Alkaline phosphatase increased	1	0	0	1	0	0
Aspartate aminotransferase increased	8	3	3	2	0	0
Blood bilirubin increased	4	1	2	1	0	0
GGT increased	4	1	1	1	1	0

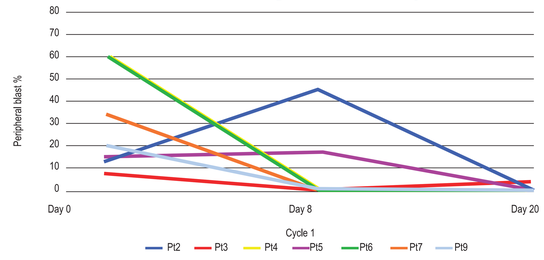
Two deaths occurred on study
- Pancytopenia with Enterobacter sepsis
- Pancytopenia with E.coli bacteremia and pulmonary hemorrhage (post intubation)

Efficacy Evaluations

Patient ID	Dose Level	Disease	Best Response
1*	1	AML#	CR
2*	1	AML	RDCB
3*	1	AML#	PR
4	2	AML	CRi
5	2	AML	RDCB
6*	2	AML with CNS Involvement	NR
7	2	AML with CNS Involvement	NR
8*	2†	EMD AML#	NE†
9*	2	AML with CNS Involvement#	CR

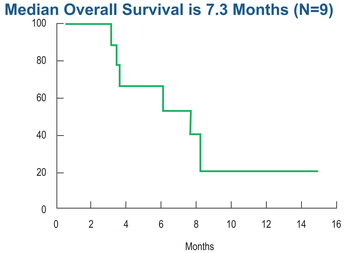
* Patients who received prior sorafenib therapy # Patients who received prior hematopoietic stem cell transplantation †Patient not evaluable due to development of graft-versus-host disease but had near complete disappearnce of EMD. CNS: Central nervous system, EMD: Extramedullary disease, CR: Complete Response, RDCB: Resistant disease with clinical benefit (no peripheral or CNS blasts), PR: Partial Response, NR: no response, NE: not evaluable

Reduction in Circulating AML Blasts on Cycle 1



Note: All but 1 patient had disappearance of peripheral blasts. Patients 1 and 8 did not have detectable peripheral blasts at enrollemnt.

Median Overall Survival is 7.3 Months (N=9)



Conclusions

- Crenolanib 66.7 mg/m2 TID can be safely combined with sorafenib at 150 mg/m² QD and 200 mg/m² QD in pediatric patients with relapsed/refractory FLT3+ AML.
- Even in patients with prior exposure to sorafenib, this combination showed clinical benefit for AML patients, represented by rapid reduction of bone marrow and peripheral blasts on cycle 1 of study.
- The response seemed favorable for patients who had prior hematopoietic stem cell transplantation.
- Future crenolanib trials in pediatric patients are planned.

References

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