Efficacy of a Type I FLT3 Inhibitor, Crenolanib, with Idarubicin and High-Dose Ara-C in Multiply Relapsed/Refractory FLT3 Mutant AML

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Abstract

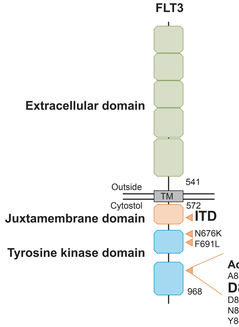
Background: Crenolanib is a novel, type I, oral pan-FLT3 inhibitor with *in vitro* activity against FLT3-ITD and FLT3-tyrosine kinase domain (TKD) mutations. Crenolanib has a half-life of 6-8 hrs and does not accumulate after chronic dosing. As a single agent, an overall response rate (ORR) of 30% (CR/CRi 19%, PR 12%) has been reported among patients (pts) with multiply relapsed/refractory (R/R) AML pts with FLT3 mutations despite sixty-five percent of the patients having prior exposure to FLT3 inhibitors. We report data from the first 13 pts with R/R FLT3+ AML treated with salvage idarubicin (Ida) and high-dose ara-C (HiDAC) followed by crenolanib. Design: Pts received Ida (12 mg/m^2 for 3d) with HiDAC (1.5 g/m^2/d over 3 hrs for 4d or for 3d if >60y), followed by crenolanib starting on d5 and continued until 72 hrs prior to next chemotherapy regimen. Standard rolling-6 design was implemented with dose escalation of crenolanib as follows: 60 mg TID (dose level 1), 80 mg TID (dose level 2), and 100 mg TID (dose level 3). Responding pts were eligible to proceed to allogeneic stem cell transplant (allo-SCT) or receive consolidation with ara-C (750 mg/m^2 for 3d) and Ida (8 mg/m^2 for 2d) followed by crenolanib at the same dose received during induction. Patients could then continue on maintenance with crenolanib. Post-SCT crenolanib maintenance therapy was not allowed.

Results: To date, all 3 dose escalation cohorts have been completed, which included 13 pts (11 males, 2 female) with a median age of 51 yrs (range 19-73). All pts had R/R FLT3+ AML. 6/13 pts had relapsed after 1 or 2 prior AML therapies, with the remaining 7 pts having 3-8 prior AML therapies (allo-SCT in 3). Nine pts had received prior FLT3 inhibitors including sorafenib (n=7), quizartinib (n=2), and E6201 (n=2). Nine pts had a FLT3-D835 kinase domain mutation, of which 4 pts also had FLT3-ITD; the remaining 4 pts had FLT3-ITD alone. Conventional cytogenetic testing included: normal karyotype (n=4; 31%), miscellaneous (n=5; 36%), and complex (n=4; 31%). Besides FLT3, multiple other leukemia-associated mutations were present at baseline: NPM1 (36%), DNMT3A (36%), NRAS/KRAS (27%), WT1 (18%), TET2 (18%), RUNX1 (18%), IDH1 (9%), IDH2 (9%), and ASXL1 (9%). No dose-limiting toxicities were observed at any of the dose levels explored and there were no dose reductions required. Non-hematologic adverse events assessed as possibly or probably related to crenolanib were all grade 1 in severity, including: nausea (n=2), vomiting (n=2), diarrhea (n=1), and abdominal pain (n=1). No deaths were attributed to crenolanib. The ORR in 11 pts evaluable for response was 36% (1 CR, 3 CRi; 2 not evaluable because of early discontinuation of therapy). Among 6 pts who received ≤2 prior AML therapies, 4 pts (67%) achieved a CR/CRi (including 2 pts with prior exposure to FLT3 inhibitors). These remissions occurred in pts with FLT3-ITD (n=2), FLT3-D835 (n=1) and FLT3-ITD+FLT3-D835 (n=1) (Table 1). No CRs were seen in the 5 pts who had 3 or more prior therapies (including 3/5 who had received prior FLT3 inhibitors) before coming on study. Three CRi pts have undergone allo-SCT: 1 pt (43/F) achieved CRi (with persistent FLT3-ITD) after 1 cycle and maintained remission with FLT3-ITD negativity for 6 months post allo-SCT, 1 pt (67/M) achieved CRi with FLT3-D835 negativity after 2 cycles and maintained remission for 3 months post allo-SCT, and 1 pt (58/M) achieved CRi after 1 cycle and relapsed 1.5 months post allo-SCT. One pt (73/M) achieved a full CR with FLT3 negativity and count recovery and is currently receiving crenolanib maintenance. The median OS for all patients was 259d; median OS by prior therapies was 259d for pts with ≤ 2 prior therapies, and 53d for pts with ≥ 3 prior therapies.

Conclusions: Full doses of crenolanib (100 mg TID) can be safely combined with idarubicin and HiDAC in multiply relapsed/refractory FLT3+ AML. There is suggestion of clinical efficacy particularly among pts with only 1-2 prior therapies. This trial is being expanded to allow combination of full dose crenolanib with other standard salvage chemotherapies, including MEC (mitoxantrone, etoposide, cytarabine) and FLA(G)-IDA (fludarabine, cytarabine, idarubicin w/ or w/o G-CSF).

Background

- Crenolanib is a benzimidazole, type I, pan-FLT3 inhibitor.
- Single agent activity in R/R FLT3+ AML
- Active against FLT3-ITD, FLT3-TKD, and FLT3-ITD+TKD
- 6-7h half-life with no accumulation after chronic dosing
- Crenolanib does not inhibit c-KIT at clinical achievable levels, allowing for hematological count recovery.



Known FLT3 activating mutations:

- Juxtamembrane mutation: **ITD**
- Kinase domain 1: **N676K, F691L**
- Activation loop mutations: **A833S, D835V/Y/H/R, D839Y/G, N841K**

Multiple FLT3 activating mutations can be seen in the same patient at time of diagnosis or at relapse.

Smith et al. PNAS. 2014; 111(14):5319-24
Huang et al. Ann Hematol. 2016; 95(5):783-91
Zhang et al. Blood 2015;126(23):2468

Objectives

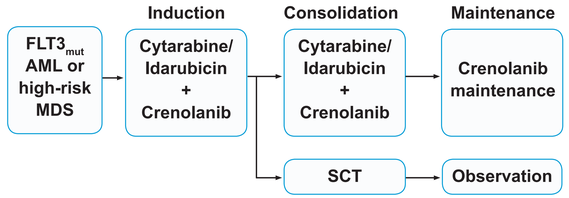
Phase I:

a. To determine the dose limiting toxicity (DLT) and maximal tolerated dose (MTD) of the combination of crenolanib + idarubicin and ara-C in patients with refractory/relapsed AML with FLT3 mutations.
b. To determine the safety of the combination of crenolanib + idarubicin and ara-C in patients with refractory/ relapsed AML with FLT3 mutations.

Phase II:

To determine the response rate (including the rates of complete remission (CR), CR with incomplete blood count recovery (CRi), and partial remission (PR)) with the combination of crenolanib + idarubicin and ara-C in refractory/relapsed AML with activating FLT3 mutations.

Dose-escalating Study



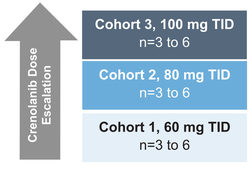
Key Eligibility

- FLT3 activating mutations w/ no restriction on FLT3 burden
- Relapsed/refractory AML w/ no restriction on prior therapies*
- Secondary AML (MDS, MPN, and MDS/MPN) are eligible
- Adequate hepatic and renal function required

*protocol was amended to allow a maximum of 3 prior therapies in June 2016

Regimen:

Induction		
Cytarabine	1.5 g/m^2/d over 3h	Days 1-4 (≤ 60 yrs) Days 1-3 (> 60 yrs)
Idarubicin	12 mg/m^2	Days 1-3
Crenolanib	TID	Day 5 onward until 72 h prior to subsequent chemotherapy regimen
Consolidation		
Cytarabine	0.75 g/m^2/day over 1.5 h	Days 1-3
Idarubicin	8 mg/m^2	Days 1-2
Crenolanib	TID	Day 5 onward until 72 h prior to subsequent chemotherapy regimen
Maintenance		
Crenolanib	TID	Up to 365 days



Rolling-6 Design:

- Dose-Finding Cohort:
  - 3 dose levels of crenolanib
- Dose Expansion Cohort:
  - Crenolanib will be administered at MTD or the maximum feasible dose

Table 1. Patient Characteristics

Characteristics, n (%)	Total (n=18)
Age (yrs), median [range]	54 [19 - 77]
≥ 60 yrs	6 (33%)
Sex, male	11 (61%)
Antecedent hematological disorder (AHD)	5 (28%)
Number of therapies, median [range]	3 [1 - 9]
Prior allogeneic SCT	4 (22%)
Prior FLT3 TKI	13 (72%)
Sorafenib	11 (61%)
Quizartinib	2 (11%)
E6201	3 (17%)
FLT3 Status	
ITD	4 (22%)
TKD (D835)	7 (39%)
ITD + TKD	7 (39%)
Conventional Cytogenetics	
Normal Karyotype	5 (28 %)
Miscellaneous*	8 (44 %)
Complex	5 (28 %)

*Including 1pt with t(8;21) and 1 with trisomy 8

Table 2. Dose Finding Cohort: Safety

Age/ Sex	Dosing Cohort	Re-induction	Dose Modification	DLTs
Cohort 1: 3 Pts treated at 60 mg TID, no DLTs seen				
43/F	60 mg TID	No	No	No
67/M	60 mg TID	Yes	No	No
21/M	60 mg TID	No	No	No
Cohort 2: 5 Pts treated at 80 mg TID, no DLTs seen				
31/M	80 mg TID	No	No	No
51/M	80 mg TID	No	No	No
30/M	80 mg TID	No	No	No
58/M	80 mg TID	No	No	No
57/M	80 mg TID	No	No	No
Cohort 3: 4 Pts treated at 100 mg TID, no DLTs seen				
70/M	100 mg TID	No	No	No
19/M	100 mg TID	Yes	No	No
24/M	100 mg TID	No	No	No
59/F	100 mg TID	No	No	No

- In all 3 dosing cohorts, no dose reduction/modification were required (including the 2 patients that received re-induction).

Expansion Cohort:

- In the expansion cohort, patients were treated at full does crenolanib (100 mg TID) with no dose reduction/ modification required.

Table 3. TEAEs Reported in ≥ 5 Patients

(Lab Abnormalities Not Included)

Event Name	# of Patients (Max Grade) n=18				
	All Grade		Grade 3	Grade 4	Grade 5
Cough	12	67%	0	0	0
Nausea	11	61%	0	0	0
Pneumonia*	11	61%	8	0	0
Diarrhea	10	56%	0	0	0
Anemia	8	44%	7	0	0
Pyrexia	8	44%	3	0	0
Hypotension	8	44%	1	0	0
Febrile neutropenia	7	39%	6	0	0
Tachycardia	7	39%	0	0	0
Chills	7	39%	0	0	0
Alanine aminotransferase increased	7	39%	1	0	0
Blood alkaline phosphatase increased	7	39%	0	0	0
Blood bilirubin increased	7	39%	1	1	0
Edema peripheral	6	33%	0	0	0
Headache	6	33%	0	0	0
Dyspnea	6	33%	1	0	0
Constipation	5	28%	0	0	0

*Pneumonia includes pneumonia, pneumonia bacterial, pneumonia RSV, pneumonia fungal

Table 4. Overall Responses

Response	Evaluable* (n=15)	Relapsed after 1-2 prior therapies (n=5)	Relapsed AML (h/o AHD) (n=5)	Relapsed after ≥ 3 prior therapies (n=5)
CR/CRi	6 (40%)	5 (100%)	1 (20%)	0 (0%)
PR	1 (7%)	0 (0%)	1 (20%)	0 (0%)
ORR (CR/CRi+PR)	7 (47%)	5 (100%)	2 (40%)	0 (0%)

*3 non-evaluable: 2 had no assessment; 1 never received crenolanib

- 3 patients received subsequent SCT
- Overall response rate for patients treated at 100 mg TID: 44% (4/9) with 3 CR/CRi and 1 PR

Table 5. Summary of CR/CRi Patients

Age/ Sex	Prior Treatment	FLT3 Status	Karyotype	Response	Post Remission Therapy	DoR (Months)
43 F	3+4 (AraC+ Ida); decitabine + sorafenib	ITD	complex	CRi	SCT	7.3
67 M	7+3 and HiDAC	TKD	inv(1)	CRi	SCT	5.0
73 M	CPX-351; CIA	ITD	normal	CR	Crenolanib	In remission 6.3+
62 F	7+3 w/ sorafenib→ 5+3 w/ sorafenib→ sorafenib (maintenance)	ITD + TKD	normal	CRi	Remains in off-therapy remission	In remission 3.5+
42 F	7+3	TKD	t(8;21), del(11),+22	CR	Consol.	In remission 0.9+
57 M	Aza (MDS); 7+3 and HiDAC; quizartinib	ITD+ TKD	t(6;9)	CRi	SCT	2.4

Table 6. Response by FLT3 Mutations

Evaluable for Response	FLT3-ITD (n=3)	FLT3-TKD (n=6)	FLT3-ITD + FLT3-TKD (n=6)
CR/CRi	2 (67%)	2 (33%)	2 (33%)
PR	0 (0%)	1 (17%)	0 (0%)
ORR (CR/CRi+PR)	2 (67%)	3 (50%)	2 (33%)

Figure 1. Overall Survival

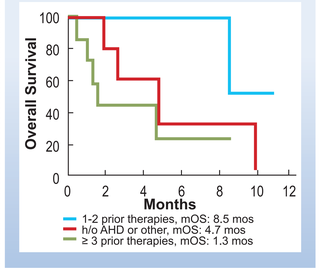
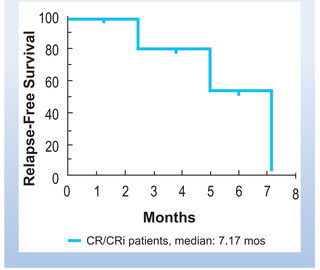


Figure 2. Relapse-Free Survival



Conclusion/Current Status

- Full dose of crenolanib (100 mg TID) can be safely combined with idarubicin and high dose ara-C in multiply relapsed/refractory FLT3+ AML.
- High complete response rate was seen in patients who had relapsed after no more than 2 prior therapies.
- This trial has been expanded to allow combination of full dose crenolanib with other standard salvage chemotherapies, including MEC (mitoxantrone, etoposide, cytarabine) and FLA(G)-IDA (fludarabine, cytarabine, idarubicin w/ or w/o G-CSF).
- A phase III study of crenolanib in combination with salvage chemotherapy is being initiated (NCT02298166; EudraCT number: 2014-000460-18).

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Disclosures

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