Phase I-II Study of Crenolanib Combined with Standard Salvage Chemotherapy and Crenolanib Combined with 5-Azacitidine in Acute Myeloid Leukemia Patients with FLT3 Activating Mutations

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Abstract

Background: Crenolanib is a type I oral pan-FLT3 inhibitor with high potency and selectivity against FLT3-ITD and FLT3-tyrosine kinase domain (TKD) mutations. Crenolanib has demonstrated a clinical activity as a single agent in heavily treated acute myeloid leukemia (AML) patients (pts). Preclinical studies have shown an antileukemic synergistic effect of the combination of crenolanib with cytotoxic agents. We report here the final analysis of an open label, dose escalation, two-arm, phase I/II trial of crenolanib combined with standard chemotherapy in pts with relapsed/refractory (R/R) FLT3 mutant AML.

Methods: Adult pts with a diagnosis of R/R FLT3 mutant AML were enrolled. Pts were assigned per physician's choice to either crenolanib in combination with higher intensity salvage chemotherapy (Arm1) or crenolanib with 5-azacitidine (Arm2). Higher intensity chemotherapy options consisted of either IA (Idarubicin (Ida) 12 mg/m^2 for 3 days (d) with cytarabine (AraC) 1.5 g/m^2 for 4 d (3 d if age > 60 yrs)). On a later amendment two other options were added: FLAG-Ida (Fludarabine 30 mg/m^2, AraC 2g/m^2 each for 5 d, and Ida 8 mg/m^2 for 3 d), or MEC (Mitoxantrone 8 mg/m^2, etoposide 100 mg/m^2, AraC 1g/m^2 all for 5 d). 5-azacitidine was given at 75 mg/m^2/d for 7d each cycle. 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). Crenolanib was given continuously starting at the end of chemotherapy, and discontinued 3d before the next cycle. Responding pts were eligible to proceed to allogeneic hematopoietic cell transplant (alloHCT) or consolidation with AraC (750 mg/m^2 for 3d) and Ida (8 mg/m^2 for 2d) followed by crenolanib up to 6 cycles. Pts could continue on maintenance with single-agent crenolanib up to 1 year. Pts on Arm2 could continue combination therapy until progression or unacceptable toxicity. The primary objective was to determine the dose limiting toxicity (DLT) and maximal tolerated dose of crenolanib-based combinations, as well as overall response rates (ORR), including complete remission (CR), CR with incomplete blood count recovery (CRi), and partial remission (PR). Secondary objectives are duration of response, relapse free survival, and overall survival.

Results: Total 28 pts were treated. Baseline characteristics are summarized in Table 1. All 3 dose escalation cohorts have been completed. 20 pts received crenolanib in combination with salvage chemotherapy, and 8 with 5-azacitidine. 16 (57%) pts had received prior FLT3 inhibitors including sorafenib (n=11), quizartinib (n=3), E6201 (n=2). The median number of cycles received was 1 (range, 1-14). No DLTs were observed at any of the dose levels explored. Non-hematologic adverse events possibly related to crenolanib were all grade 1 or 2 in severity, including nausea (n=1), vomiting (n=2), fatigue (n=2), diarrhea (n=1), abdominal pain (n=1), muscular weakness (n=1), hypotension (n=1). No deaths were attributed to crenolanib. The ORR in 24 pts evaluable for response was 11 (46%) including CR (n=3), CRi (n=7), and PR (n=1). Three (11%) pts had hematologic improvement with bone marrow blast count reduction of at least 50%. Four pts were not evaluable for response due to early death (3 from infection, 1 stopped therapy early for unrelated reasons). The median time to response was 29 days (range, 19-116). Among responders, 4 (36%) pts achieved negative minimal residual disease by flow cytometry after a median of 3.2 mo (range, 0.7-3.7). Five pts received consolidation with alloHCT, and 2 other pts had alloHCT after subsequent salvage therapy. One pt received crenolanib maintenance after transplant. The median OS (mOS) was 4.7 (0.4-27) mo (Figure 1); median RFS was 4 (1-23) mo. Of 18 pts who received one or 2 prior therapies, 9 (50%) pts achieved CR/CRi (including 3 of 9 pts with prior exposure to FLT3 inhibitors) and 5 (28%) received subsequent alloHCT. The mOS for pts who received ≤ 2 prior therapies was 6.2 mo versus 1.5 mo for pts who received ≥ 3 prior therapies (p=0.0002). OS by treatment arm and prior therapies is shown in Figure 2.

Conclusion: Full dose crenolanib (100 mg TID) can be safely combined with chemotherapy in R/R FLT3 mutant AML. ORR can reach up to 50% with the combination, even with prior exposure to FLT3 inhibitors, and particularly among Arm 1 pts with ≤ 2 prior therapies (mOS=8.6 mo). The study was terminated at the sponsor's request.

Background

- Crenolanib is a type I pan-FLT3 inhibitor
- Single agent activity in R/R FLT3 mutant AML
- High potency and selectivity against FLT3-ITD and FLT3-TKD
- 6-7 hour half-life with no accumulation after chronic dosing
- Crenolanib does not inhibit c-KIT at clinical achievable levels allowing for hematological count recovery
- Preclinical synergy in combination with cytarabine and daunorubicin, and with hypomethylating agents

Objectives

Primary objectives:

Phase I:

- To determine the dose limiting toxicity (DLT) and maximal tolerated dose (MTD) of the combination of crenolanib with standard salvage chemotherapy (Arm 1) or with 5-azacytidine (Arm 2) in patients with R/R AML or high-risk MDS with FLT3 mutations
- To determine the safety of the combination of crenolanib with chemotherapy (Arm 1) or with 5-azacytidine (Arm 2) in patients with R/R FLT3 mutant AML or high-risk MDS

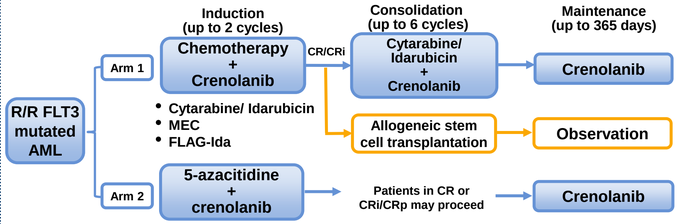
Phase II:

- To determine the response rate (including the rates of complete remission (CR), CR with incomplete blood count recovery (CRi), and partial remission (PR)) with crenolanib-based combinations in patients with AML with activating FLT3 mutations

Secondary objectives: Response rate, duration of response, progression -free survival, overall survival, pharmacokinetics and pharmacodynamics of crenolanib with chemotherapy

Study Design

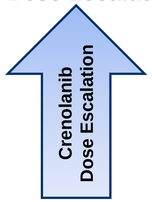
- Non- randomized, open label, dose escalation, two-arm, phase I-II trial
- Treatment assignment by physician's choice



Arm 1 Induction Regimens			
Ida/AraC	Idarubicin	12 mg/m2	Days 1-3
	Cytarabine	1.5 g/m2	Days 1-4 (≤ 60 yrs) Days 1-3 (> 60 yrs)
	Crenolanib*	TID	Day 5 → continuously
MEC	Mitoxantrone	8 mg/m²	Days 1-5
	Etoposide	100 mg/m2	Days 1-5
	Cytarabine	1000 mg/m²	Days 1-5
	Crenolanib*	TID	Day 6 → continuously
FLAG-Ida	Fludarabine	30 mg/m2	Days 1-5
	Cytarabine	2 g/m2	Days 1-5
	Idarubicin	8 mg/m2	Days 1-3
	G-CSF	300 ug sc	Day 6 → neutrophil recovery
	Crenolanib*	TID	Day 6 → continuously
Arm 1 Consolidation Regimen			
Idarubicin		8 mg/m2	Days 1-2
Cytarabine		0.75 g/m2	Days 1-3
Crenolanib*		TID	Day 5 → continuously
Arm 2 Induction / Consolidation			
5-azacitidine		75 mg/m2	Days 1-7
Crenolanib		TID	Day 1 → continuously
Maintenance (Both Arms)			
Crenolanib		TID	Up to 365 days

*Crenolanib to be stopped 72 hours before the start of the next cycle of chemotherapy

Dose Escalation



Dose level 3 100 mg TID, N=3 to 6
Dose level 2 80 mg TID, N= 3 to 6
Dose level 1 (Starting dose) 60 mg TID, N= 3 to 6
Dose level 0 60 mg BID

Rolling-6 Design:

- Dose-Finding Cohort:

  3 dose levels of crenolanib
- Dose Expansion Cohort:

  Crenolanib administered at maximum tolerated dose or the maximum feasible dose

Baseline Characteristics

Characteristics	N (percent), or median [range]		
	Total N=28	Arm 1 N= 20*	Arm 2 N= 8
Age, years	60 [20-82]	59 [20-78]	65 [27-82]
Male	15 (54)	13 (65)	2 (25)
Diagnosis			
De-novo AML	17 (61)	14 (70)	3 (37)
Secondary AML	11 (39)	6 (30)	5 (63)
Cytogenetics			
Diploid	16 (57)	10 (50)	6 (75)
Complex	4 (14)	2 (10)	2 (25)
Miscellaneous	8 (29)	8 (40)	0 (0)
FLT3 status			
FLT3 ITD	12 (43)	7 (35)	5 (63)
FLT3 D835	8 (29)	6 (30)	2 (25)
FLT3 ITD / FLT3 D835	8 (29)	7 (35)	1 (12)
Molecular profile			
NPM1	11 (39)	8 (40)	3 (37)
IDH1/IDH2	4 (14)	3 (15)	1 (12)
DNMT3A	7 (25)	6 (30)	1 (12)
Treatment category			
Refractory to 1st induction	4 (14)	4 (20)	0 (0)
1st Relapse	5 (18)	3 (15)	2 (25)
≥ 2nd Relapse	6 (22)	3 (15)	3 (37)
Refractory to >1 line of therapy	13 (46)	10 (50)	3 (37)
No. prior AML therapies**	2 [1-8]	2 [1-8]	2 [1-2]
Prior SCT	6 (22)	4 (20)	2 (25)
Prior FLT3 inhibitor			
Sorafenib	11 (39)	9 (45)	2 (25)
Quizartinib	3 (11)	2 (10)	1 (12)
E6201	2 (7)	2 (10)	0 (0)
None	12 (43)	7 (35)	5 (63)

*18 IA, 1 FLAG-Ida, 1 MEC

**Prior therapies for MDS and/or MPN not included. 8 patients received prior hypomethylating agents for MDS and/or MPN (Arm1, n=5; Arm2, n=3)

Results

- All dose escalation cohorts completed. No DLTs observed at any dose level
- In the expansion cohort, patients were treated at full does crenolanib (100 mg TID) with no dose reduction/modification required

Crenolanib Dose Levels	Arm 1 N= 20		Arm 2 N= 8	
	N. of cycles	N. of patients	N. of cycles	N. of patients
60 mg TID	4	3	8	5
80 mg TID	5	5	8	3
100 mg TID	19	12	0	0

Responses

- Median time to response: 29 days (range, 19-116 days)
- Among responders, 4 (36%) patients achieved negative measurable residual disease by flow cytometry after a median of 3.2 months (range, 0.7-3.7 months)
- Five patients had consolidation with alloHCT, and 2 other alloHCT after subsequent salvage therapy. One patient received crenolanib maintenance after transplant

Responses	Arm 1 N (%)		Arm 2 N (%)	
	All patients N=20	1-2 prior therapies N=11	All patients N=8	1-2 prior therapies N=7
CR/CRi	7 (35)	6 (55)	3 (38)	3 (43)
PR	1 (5)	1 (9)	0 (0)	0 (0)
HiB	2 (10)	0 (0)	1 (13)	1 (14)
ORR (CR/CRi + PR)	8 (40)	7 (64)	3 (38)	3 (43)
Early death*	3 (15)	1 (9)	1 (13)	1 (14)

*Four patients died early (3 from infections, 1 stopped therapy early and died 2 weeks later with progressive disease and infection); "CR: Complete remission; CRi: CR with incomplete count recovery; PR: Partial remission; HiB: Hematologic improvement in blasts defined as reduction in BM blasts at least 50%.

Treatment-related Adverse Events

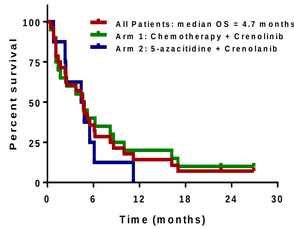
Total AE = 515 (all grades)	Number of patients			
	Arm 1		Arm 2	
	All grades	Grades 3-5	All grades	Grade 3-5
All adverse events	405	81	110	25
Anemia	9	7	2	2
Stomatitis	3	0	3	0
Nausea	11	0	5	0
Abdominal pain	3	0	4	0
Diarrhea	10	0	2	1
Cough	12	0	3	0
Dyspnea	6	1	3	1
Pneumonia	11	8	4	4
Respiratory failure	4	4	2	2
Febrile neutropenia	7	5	0	0
Septic shock	2	1	0	0
Hypotension	8	1	3	1
Hyponatremia	11	2	4	0
Hypokalemia	12	5	4	1
Hypomagnesemia	6	0	4	0
Hypophosphatemia	7	2	1	0
Alkaline phosphatase increased	7	0	3	0
Hypoalbuminemia	11	4	3	0
Muscular weakness	2	1	0	0

No deaths were attributed to crenolanib

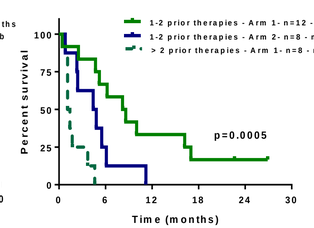
Survival Endpoints

- Median OS for all patients: 4.7 (0.4-27) months
- Median RFS for all patients: 4 (1-23) months
- Median response duration for all patients: 3.8 (1-23.1) months
- Median OS for all patients who had received ≤2 prior therapies: 6.2 months vs. 1.5 months for patients who received ≥3 prior therapies (p=0.0002)

By Arm of treatment



By N. of prior AML therapies



Conclusions

- Full dose crenolanib (100 mg TID) can be safely combined with both standard chemotherapy and with 5-azacitidine in R/R FLT3 mutated AML
- Significant clinical efficacy even with prior exposure to FLT3 inhibitors, particularly among Arm 1 pts with ≤2 prior therapies (mOS=8.4 months)
- A phase III study of crenolanib in combination with salvage chemotherapy is being initiated (NCT02298166)

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Disclosures

Dr. Jorge Cortes is a Consultant for Astellas, Daiichi, Novartis, and Pfizer, and has received research support (for institution) by Astellas, Daiichi, Novartis, Pfizer and Arog. Dr. Iman Abou Dalle has no disclosures.