#7016

Effect of Cytarabine/Anthracycline/Crenolanib Induction on Minimal Residual Disease (MRD) in Newly Diagnosed FLT3 Mutant AML

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Abstract

Background: Baseline characteristics such as age ≥60, WBC≥100,000/µL and *FLT3/NPM1/DNMT3A*+ve are known to be associated with a poor prognosis in AML. Ivey et al. (NEJM 2016) reported that *FLT3-ITD*+ve patients (pts) who were MRD+ve after 2 cycles of induction chemotherapy were more likely to relapse as compared to those who became MRD-ve (92% vs 35%). Eradication of *FLT3*+ve clones may lead to reduced relapse rates. Crenolanib is a type I FLT3 tyrosine kinase inhibitor (TKI), which inhibits both *FLT3*- ITD and TKD mutations. We here report that a single induction cycle of cytarabine/anthracycline / crenolanib leads to MRD negativity by multi-parameter flow cytometry (MPF), and low rate of early relapse in pts with newly diagnosed *FLT3*+ve AML.

Methods: This abstract includes 29 consecutively treated, newly diagnosed, *FLT3*+ve AML pts, who achieved CR1 after one course of cytarabine/anthracycline/crenolanib. Pts received 7+3 induction with cytarabine 100 mg/m^2/d for 7d and either daunorubicin (<60 y: 90 mg/m^2; ≥60 y: 60 mg/m^2) or idarubicin 12 mg/m^2 for 3d. Crenolanib (100 mg TID) was started on day 9 until 72 h prior to next chemotherapy.

Results: 29 pts (15M, 14F), median age 55y (10pts ≥60y) are included. MRD at time of count recovery was assessed by MPF in 25/29 pts. 20/25 (80%) became MRD–ve. With a median follow up of 7mth, 4/25 pts have relapsed (2/5 MRD+ve, 2/20 MRD-ve). Age ≥60 was a risk factor for MRD+ve and relapse. All 4 pts with WBC≥ 100,000/µL as well as 5 pts with *FLT3/NPM1/DNMT3A*+ve AML became MRD-ve after one induction cycle.

Conclusions: These data suggest, in the context of an ongoing trial (NCT02283177), crenolanib in combination with standard induction is associated with a high rate of achieving an MRD negative state by MPF and a low rate of relapse in previously untreated adults with mutant *FLT3*. Longer follow-up and comparison of MRD data with similar pts treated with standard chemo alone will be necessary to reach more definitive conclusions.

Background

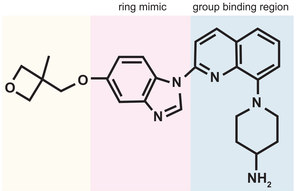
Crenolanib is a Type I FLT3 Tyrosine Kinase Inhibitor

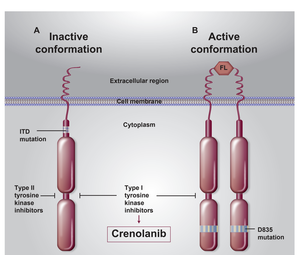
- Inhibits both FLT3-ITD and FLT-TKD mutations

Crenolanib is a unique chemotype (benzimidazole moiety)

FLT3 K_d = 0.74nM

Non-binding region	Kinase binding region	
Metabolism only	Adenosine ring mimic	Binds at the phosphate group binding region





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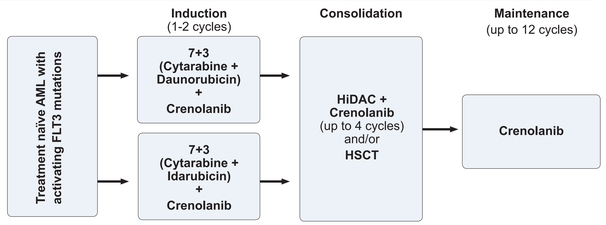
Measurable Residual Disease (MRD)

- Current induction chemotherapy for FLT3+ve AML leads to CR rate of about 60%; however, relapse after CR remains a significant problem. *(Stone et al., ASH 2015)*
- Patients with MRD have higher relapse rate as compared to patients without MRD. *(Ivey et al., NEJM 2016)*
- Patients who require multiple chemotherapy courses to achieve MRD-ve state remain at high risk of relapse, suggesting the importance of achieving MRD negativity early in induction. *(Loken et al., Blood 2012)*
- This *post hoc* analysis aims to understand whether cytarabine/anthracycline/crenolanib can result in a deep remission, manifested by complete remission with MRD negativity as determined by multi-parameter flow cytometry.

Study Design



Induction:	Cytarabine 100mg/m^2/CIV for 7 days Anthracycline: Daunorubicin 90mg/m^2 (<60y) or 60mg/m^2 (≥60y) or Idarubicin 12 mg/m^2 x 3 days Crenolanib 100mg TID starting day 9
Consolidation:	Cytarabine 3g/m^2 (<60y) or 1g/m^2 (≥60y), q12h x 6 doses Crenolanib 100mg TID starting day 7
Maintenance:	Crenolanib 100mg TID continuously

Response Rate

Induction Chemotherapy Regimen	CR after Induction 1	Overall Complete Response
Cytarabine/Daunorubicin/Crenolanib (n=23)	17/23 (75%)	19/23 (83%)
Cytarabine/Idarubicin/Crenolanib (n=9)	9/9 (100%)	9/9 (100%)
Total Evaluable Patients (n=32)	26/32 (81%)	28/32 (88%)

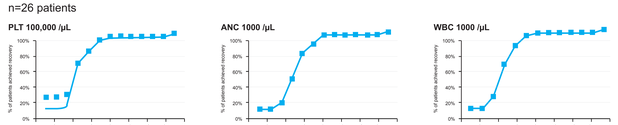
- 26 (81%) patients achieved CR/CRi after first induction.
- 2 (6%) patients achieved PR after first induction and CR after second.
- 4 (13%) patients were non-responders.
- 16 (42%) patients were bridged to transplant.

Wang et al. Blood. 2016; 128(22): 1071

Hematologic Reconstitution After Induction

	Platelet count recovery >20,000 /µL	Platelet count recovery >100,000 /µL	WBC count recovery >1000 /µL	Absolute neutrophil count recovery >500 /µL	Absolute neutrophil count recovery >1000 /µL
Median (days)	22	27	27	27	30

n=26 patients



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Methods

Multi-parameter Flow Cytometry to Assess MRD

- MRD assessment was performed by multi-parameter flow cytometry.
- Bone marrow samples at count recovery were assessed.
- Patients had to be in CR/CRi after one cycle of cytarabine/anthracycline/crenolanib.
- MRD data was available in 24 *de novo* AML patients.
- Flow markers varied among centers, as shown below.

	HLA-DR	CD2	CD3	CD4	CD5	CD7	CD8	CD10	CD11b	CD11c	CD13	CD14	CD15	CD16	CD19	CD20	CD22	CD24	CD25	CD32	CD33	CD34	CD36	CD38	CD41	CD45	CD56	CD57	CD64	CD71	CD117	CD123	CD138	CD163	pK	pλ
UTSW	√	√	√	√	√	√	√	√	√		√	√	√	√	√	√	√				√	√	√	√		√	√		√		√				√	√
RPCI	√	√	√	√	√	√		√	√		√	√	√	√	√	√		√			√	√	√	√	√	√	√	√	√	√	√			√		
FH	√	√		√	√	√		√	√		√	√	√	√	√	√	√				√	√		√	√	√			√	√	√	√	√		√	√
MSK	√	√		√	√	√			√		√	√	√	√	√	√			√		√	√		√	√	√			√	√	√	√				
DFCI	√						√		√		√	√	√		√						√	√			√	√			√		√	√				
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UTSW, University of Texas at Southwestern Medical Center; RPCI, Roswell Park Cancer Institute; FH, Fred Hutchinson Cancer Research Center; MSK, Memorial Sloan Kettering Cancer Center; DFCI: Dana-Farber Cancer Institute; CoH, City of Hope National Medical Center; flow markers assessed and sensitivities of MRD assays may vary among patients.

Patient Demographics

CR/CRi patients with MRD assessment (n=24)

Characteristic	No.	%
Age, years		
Median, [range]	55	[22 - 70]
Sex		
Female	13	54%
Male	11	46%
Chemotherapy regimen		
Idarubicin	10	42%
Daunorubicin 60	6	25%
Daunorubicin 90	8	33%
Response after induction 1		
CR	21	88%
CRi	3	13%

Results

20/24 CR/CRi Patients became MRD–ve by Flow

	Overall	MRD-ve	MRD+ve
CR after induction 1	24	20 (83%)	4 (17%)

- 24 *de novo* AML patients who achieved CR1 had MRD assessment by multi-parameter flow cytometry using bone marrow samples at count recovery.
- 20/24 (83%) patients achieved CR/CRi with MRD negativity.
- Only 4 patients remained MRD+ve.

Achievement of MRD-ve CR was associated with a lower relapse rate

	MRD-ve N=20	MRD+ve N=4
Relapse Free	16 (80%)	2 (50%)

- Median follow-up of 8.2 months
- 16/20 CR_{MRD-} (80%) patients remain relapse-free.
  - Only 4 patients have relapsed (6.7, 8.2, 8.4, 11.2 months after treatment).
    - 2 patients have had bone-marrow relapse; one patient was FLT3-ve (N-*RAS* and *JAK3* +ve) at the time of relapse.
    - 2 patients have had an isolated CNS relapse.

Age <60y was associated with higher MRD-ve CR and lower relapse rate

Sub-group	MRD-ve	Relapse free
<60y	14/15 (93%)	14/15 (93%)
≥60y	6/9 (67%)	4/9 (44%)

- 93% younger adults (<60y) achieved CR_{MRD-} with only one cycle of cytarabine/anthracycline/crenolanib.
- At a median follow up of 8.2 months, only 1/15 patients <60y have relapsed.

All CR patients with high WBC counts at baseline achieved MRD negativity

Sub-group	MRD-ve	Relapse free
WBC ≥100,000/µL	4/4 (100%)	3/4 (75%)

- Baseline WBC count of >100,000/µL is known to be associated with a poor prognosis in AML.
- 4 patients achieved a CR with MRD-ve after 1 cycle of induction.

All CR patients with *FLT3/NPM1/DNMT3A* mutations achieved MRD negativity

Sub-group	MRD-ve	Relapse free
FLT3/NPM1/DNMT3A	6/6 (100%)	5/6 (83%)

- *FLT3/NPM1/DNMT3A*+ve is known to be associated with a poor prognosis in AML.
- All 6 patients who achieved CR were also MRD-ve.

Conclusions

1. Crenolanib in combination with standard induction chemotherapy is associated with a high rate of complete remission with an MRD-ve state.
2. Patients who achieved CR_{MRD-} have lower relapse rates as compared to CR_{MRD+}.
3. 93% patients achieved MRD-ve in younger adults (< 60y), and significant lower relapse rates were seen in this population.
4. Even patients who were at high risk (WBC ≥100,000/µL or *FLT3/NPM1/DNMT3A*+ve) can achieved MRD-ve with only one cycle of cytarabine/anthracycline/crenolanib.
5. As MRD techniques were not standardized and sensitivities varied among different labs, a standardized central MRD test will be required to achieve more definitive conclusions in future studies.

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