Crenolanib Besylate, a Type I FLT3 TKI, can be Safely Combined with Cytarabine and Anthracycline Induction Chemotherapy and Results in High Response Rates in Patients with Newly Diagnosed FLT3 mutant Acute Myeloid Leukemia (AML)

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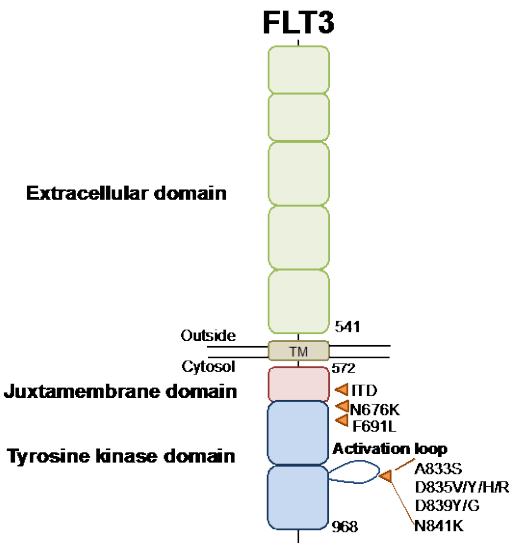
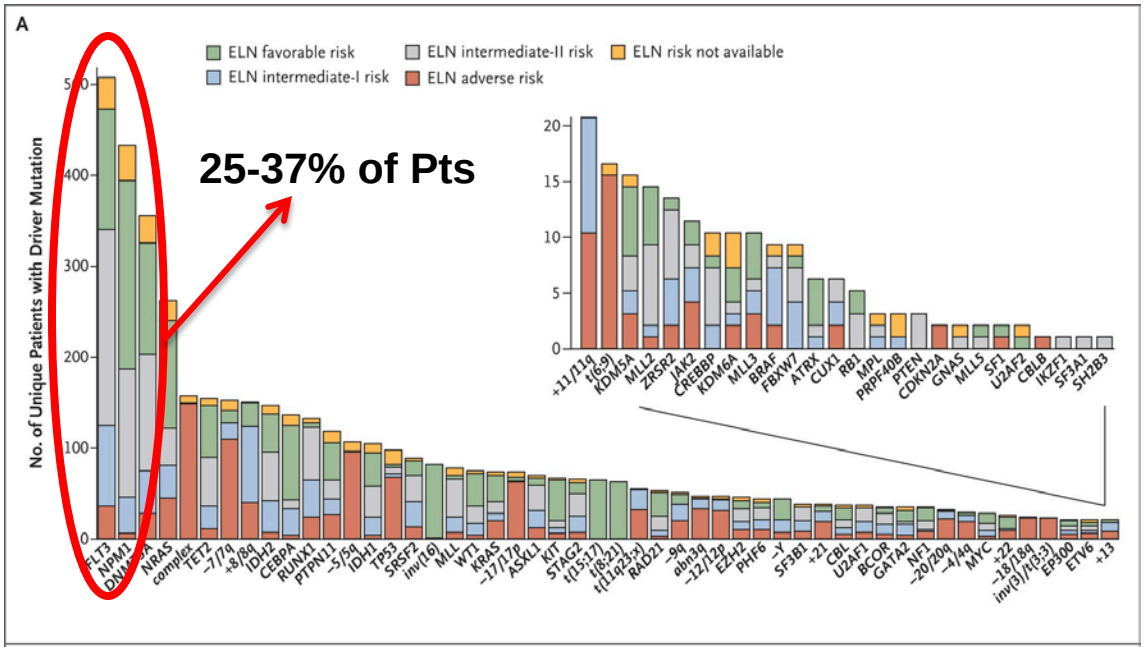
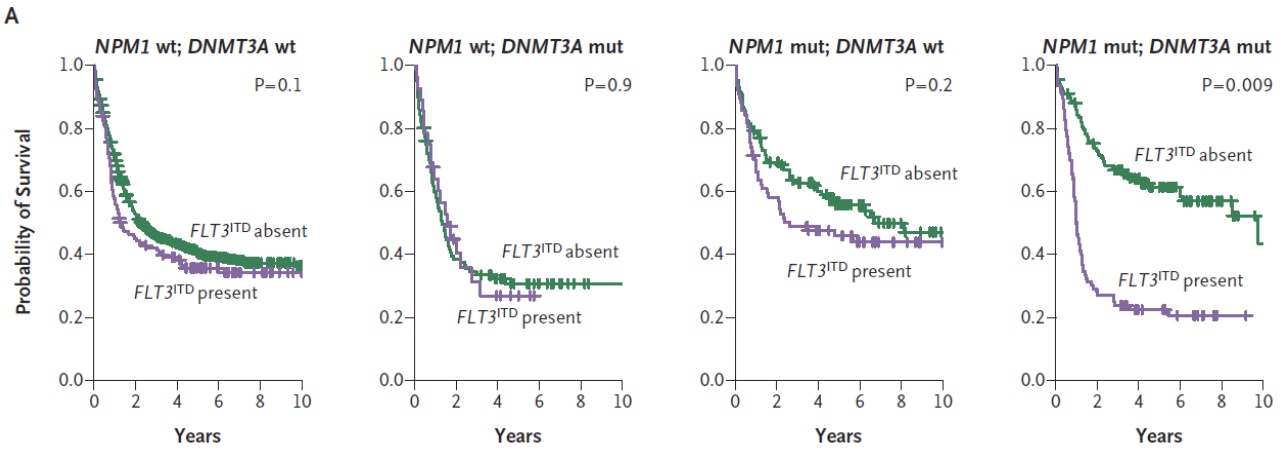
FLT3 Mutations are common and connote poor prognosis in AML







Papaemmanuil E et al. N Engl J Med 2016;374:2209-2221

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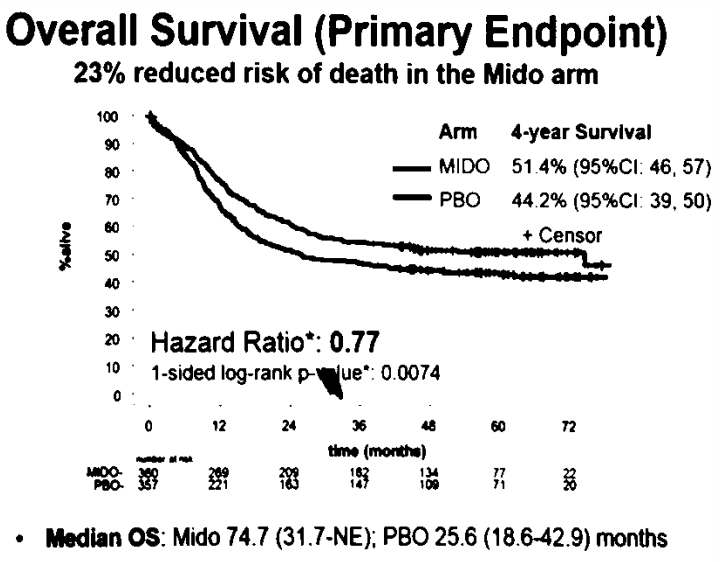
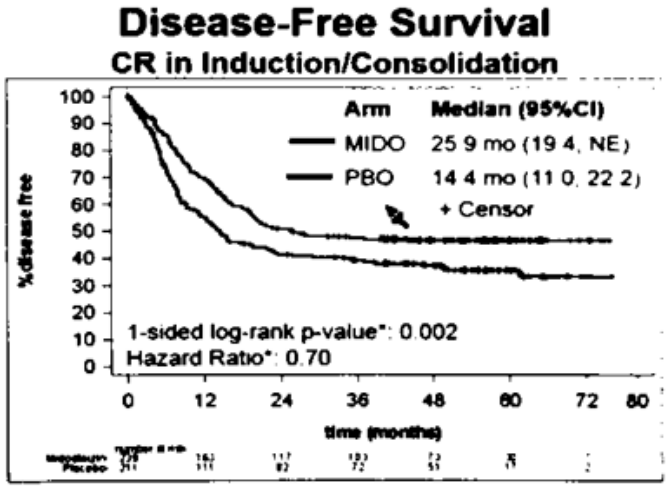
Midostaurin plus 7+3 Improves Survival in FLT3 mutant AML



- **Median OS**: Mido 74.7 (31.7-NE); PBO 25.6 (18.6-42.9) months



- **4 year DFS rate: MIDO 46.4% vs. PBO 37.4%**
- **Event: first of relapse or death among CR**

7.2% absolute improvement in overall survival at 4 year with addition of midostaurin to chemotherapy

4 year DFS rate in patients who achieved CR was 46.4% suggesting an ongoing risk of relapse, especially during the first year

Stone et al, ASH, 2015, Abstract #6

Wang et al., Proc. ASH: 2016. abstract 1071

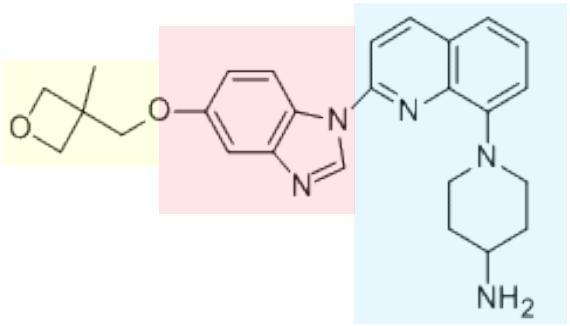
Crenolanib is a Type I Tyrosine Kinase Inhibitor

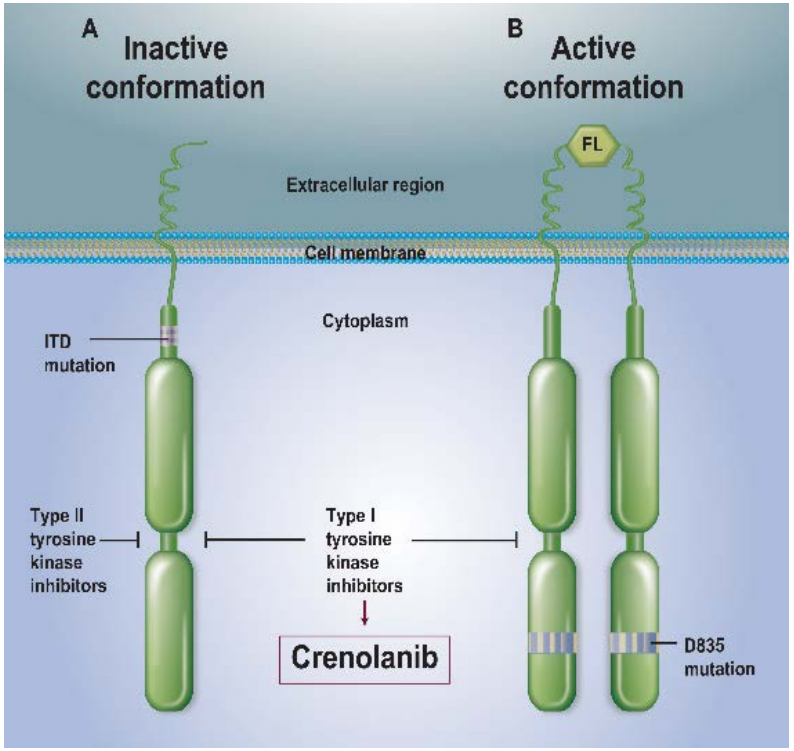
Activity Against Both Active and Inactive Conformations of FLT3-ITD and TKD Mutations

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





Inhibits both FLT3-ITD and FLT3-TKD mutations in the active conformation

Fathi AT Blood. 2013;122(22):3547-8.

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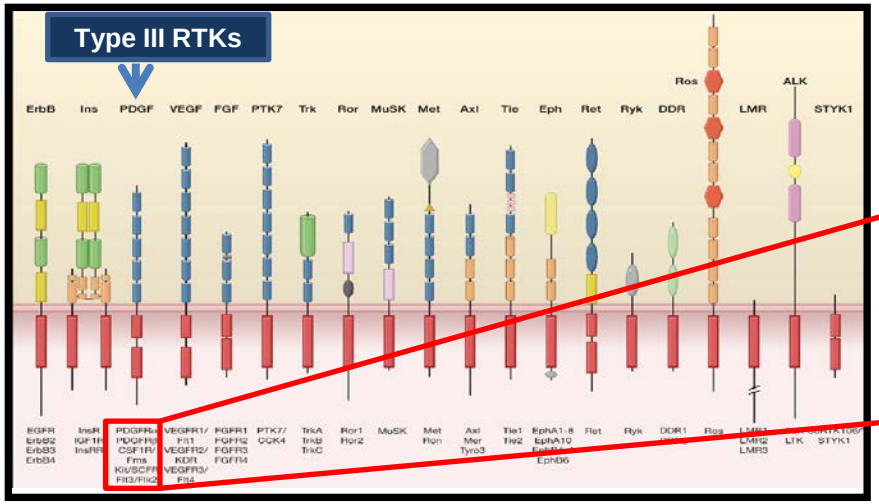
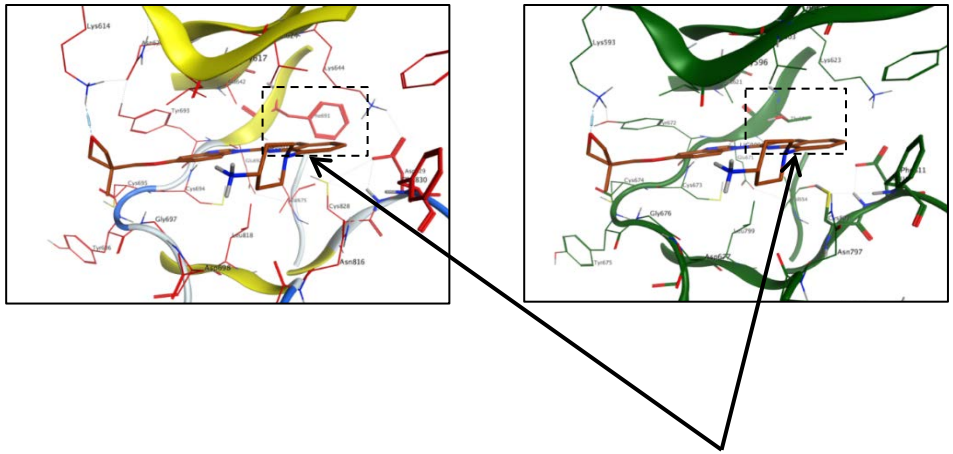
Crenolanib is Highly Selective for FLT3



RTK	Crenolanib K_d (nM)
FLT3	0.74 nM
PDGFRβ	2.1 nM
PDGFRα	3.2 nM
CSF1R	30 nM
KIT	78 nM



Quinoline ring that interacts with F691 in FLT3 but not in KIT

High selectivity with lack of binding to cKIT:

- Reduces potential for myelosuppression
- Reduced time to count recovery following chemotherapy in AML patients

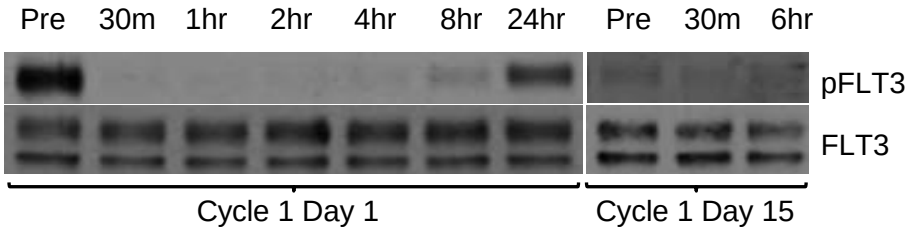
Gajiwala et al. "Molecular Mechanism of Crenolanib Recognition by FLT3." Data on file.

Wang et al., Proc. ASH: 2016. abstract 1071

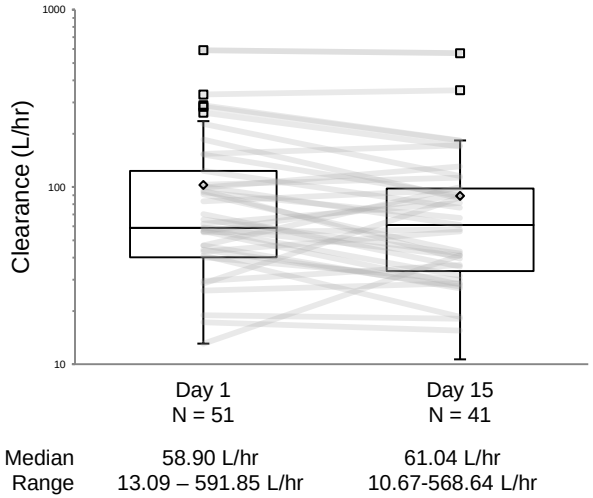
Crenolanib has a 6-8 Hour Half-Life

Rapid FLT3 Inhibition and No Accumulation with Chronic Dosing

Rapid pFLT3 inhibition achieved by crenolanib



Comparison of clearance of day 1 and day 15



- Rapid absorption: T_{max} 1.5-2 hr
- Maximal FLT3 inhibition seen within 2-3 hr
- Half-life: 6-8 hr, eliminated within two days of stopping crenolanib

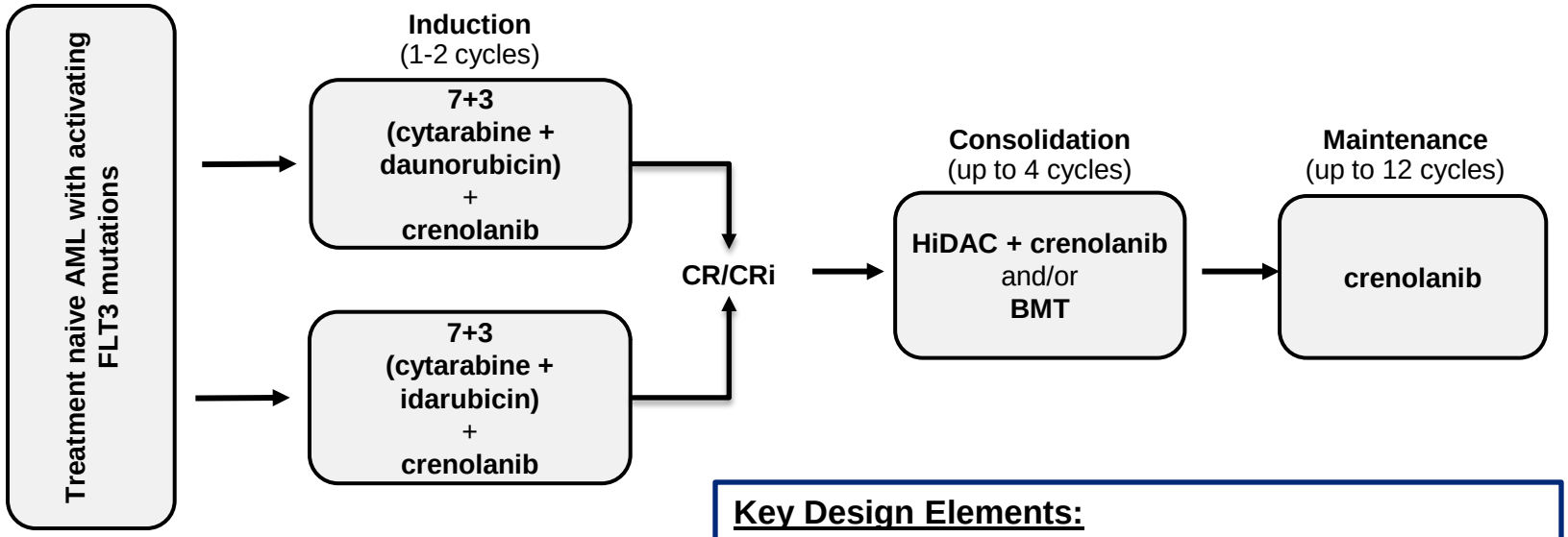
- Consistent PK on days 1 and 15 (with no drug accumulation)
- Median trough level adequate to inhibit FLT3 was 384nM

Panetta et al., ASH Annual Meeting:2015. abstract 3695

Wang et al., Proc. ASH: 2016. abstract 1071

Phase II Trial in Newly Diagnosed FLT3 mutant AML

Goal: To assess the tolerability and efficacy of crenolanib when administered sequentially with standard induction chemotherapy in patients with newly diagnosed FLT3 mutant AML



Key Design Elements:

2 cohorts:

A. Daunorubicin/cytarabine + crenolanib 100 mg TID

B. Idarubicin/cytarabine + crenolanib 100 mg TID

Eligibility criteria:

- No upper age limit
- Secondary AML (post MDS) included
- Any FLT3 allelic burden

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Demographics (n=38)

Characteristics	≤ 60 yrs (n=23)	> 60 yrs (n=15)	Total (n=38)
Age (yr), median [range]	48 [19– 60]	68 [61– 75]	58 [19– 75]
Sex, male	10 (43%)	8 (53%)	18 (47%)
AML			
De novo	21 (91%)	12 (80%)	33 (87%)
sAML	2 (9%)	3 (20%)	5 (13%)
WBC count (unit/μL), median [range]	41,350 [3,770–248,800]	26,460 [2,270–241,100]	32,500 [2,270–248,800]
≥100,000	5 (22%)	1 (7%)	6 (16%)
≥200,000	2 (5%)	1 (3%)	3 (8%)
Platelets (unit/μL), median [range]	84,304 [1,000 – 208,000]	80,214 [16,000 – 242,000]	82,757 [1,000 – 242,000]
ELN risk classification			
Favorable	1 (4%)	1 (7%)	2 (5%)
Intermediate	19 (83%)	14 (93%)	33 (87%)
Adverse	3 (13%)	0 (0%)	3 (8%)
Mutations			
FLT3 + ITD	18 (78%)	10 (67%)	28 (74%)
FLT3 + TKD	3 (13%)	4 (27%)	7 (18%)
FLT3 + ITD and TKD	2 (9%)	1 (7%)	3 (8%)

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Patients

- **All 38 patients received induction followed by crenolanib.**
  - **14 patients < 60 yo received daunorubicin (90 mg/m^2)**
  - **12 patients ≥ 60 yo received daunorubicin (60 mg/m^2)**
  - **12 patients received idarubicin (12 mg/m^2)**
- **20 patients received 28 cycles of HiDAC consolidation administered with crenolanib.**
- **32 evaluable patients for response**
- **16 patients (42%) were bridged to transplant in CR1.**

Tolerability of Crenolanib Following Induction

Daunorubicin 90 mg/m²

Age/ Gender	Starting Crenolanib Dose	Dose Reductions
19/M	100mg TID	No
23/F	100mg TID	No
24/M	100mg TID	No
34/F	100mg TID	No
36/F	100mg TID	No
36/M	100mg TID	No
44/F	100mg TID	No
48/M	100mg TID	No
50/F	100mg TID	No
51/M	100mg TID	No
54/F	100mg TID	No
58/F	100mg TID	Yes, 80mg TID
58/M	100mg TID	No
59/F	100mg TID	No

Daunorubicin 60 mg/m²

Age/ Gender	Starting Crenolanib Dose	Dose Reductions
60/F	100mg TID	No
61/F	100mg TID	Yes, 80mg TID
61/M	100mg TID	No
65/F	100mg TID	Yes, 80mg TID
65/M	100mg TID	No
66/F	100mg TID	Yes, 80mg TID
68/F	100mg TID	No
68/M	100mg TID	No
68/M	100mg TID	No
69/M	100mg TID	Yes, 80mg TID
70/M	100mg TID	No
74/F	100mg TID	No
75/M	100mg TID	No

Idarubicin 12mg/m²

Age/ Gender	Starting Crenolanib Dose	Dose Reductions
22/F	100mg TID	Yes, 80 TID
42/M	100mg TID	No
44/F	100mg TID	No
47/M	100mg TID	No
54/F	100mg TID	No
55/M	100mg TID	No
55/M	100mg TID	No
57/F	100mg TID	No
62/F	100mg TID	No
66/M	100mg TID	No
74/F	100mg TID	No

- 84% of the patients were able to continue on crenolanib 100 mg TID during induction.
- 6 dose reductions needed (4 were in patients > 60 years)

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Treatment-Emergent AE During Induction (≥ 10%)

Non-Hematologic and Regardless of Attribution to Crenolanib

Event Name	N=32 patients					
	All Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	13 41%	4	7	2	0	0
Nausea	12 38%	6	5	1	0	0
Rash*	12 38%	5	3	4	0	0
Edema%	11 34%	9	1	1	0	0
Pyrexia	9 28%	6	2	1	0	0
Vomiting	8 25%	7	1	0	0	0
Decreased appetite	8 25%	3	3	2	0	0
Constipation	6 19%	2	4	0	0	0
Aspartate aminotransferase increased	6 19%	5	1	0	0	0
Stomatitis	5 16%	2	3	0	0	0
Cough	5 16%	5	0	0	0	0
Pneumonia	4 13%	0	1	3	0	0
Alanine aminotransferase increased	4 13%	3	0	1	0	0
Blood alkaline phosphatase increased	4 13%	2	2	0	0	0
Dehydration	4 13%	1	0	3	0	0
Depression	4 13%	2	2	0	0	0
Insomnia	4 13%	1	3	0	0	0
Acute kidney injury	4 13%	1	1	2	0	0

*Rash includes rash maculo-papular, rash erythematous, rash pruritus, rash papular, erythema multiform and urticaria
%Edema includes peripheral, localized, periorbital, and face

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Selected Adverse Events During Induction

Regardless of Attribution to Crenolanib

Event Name	N=32 patients						
	All Grade		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
AST elevation	6	19%	5	1	0	0	0
ALT elevation	4	13%	4	0	1	0	0
Bilirubin elevation	3	9%	1	0	2	0	0
Respiratory failure*	2	6%	0	0	0	2	0
Hypoxia	1	3%	0	0	1	0	0
Pneumonia	4	13%	0	1	3	0	0
Sepsis**	2	6%	0	0	0	2	0
Upper gastrointestinal hemorrhage	3	9%	1	0	2	0	0
Lower gastrointestinal hemorrhage	3	9%	1	1	1	0	0
Acute kidney injury	4	13%	1	1	2	0	0
Dehydration	4	13%	1	0	3	0	0

* Both patients with respiratory failure recovered and continued on crenolanib.
** Both patients with sepsis recovered and were able to continue on study.

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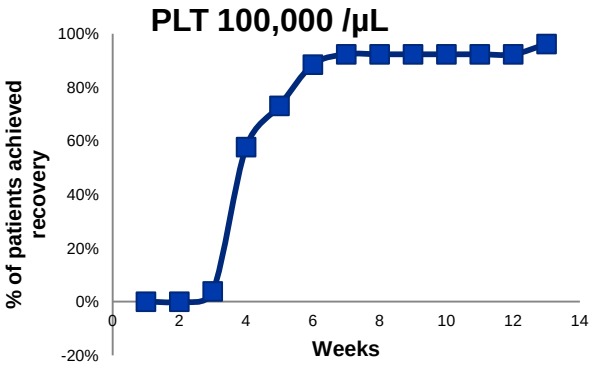
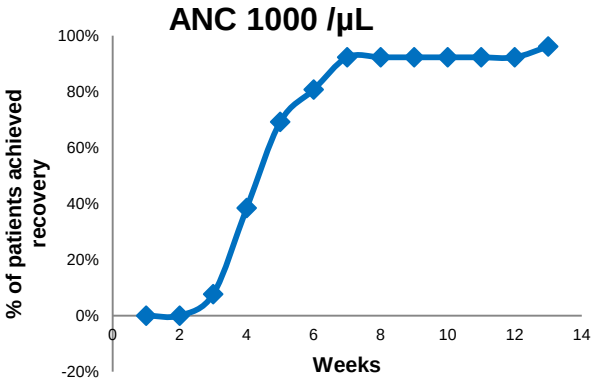
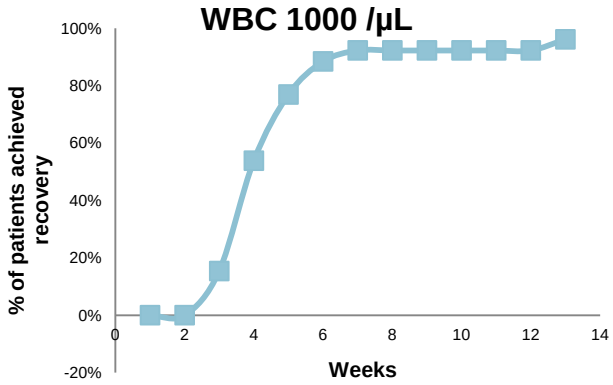
Hematologic Reconstitution After Induction in CR/CRi Pts

n = 26 patients

	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







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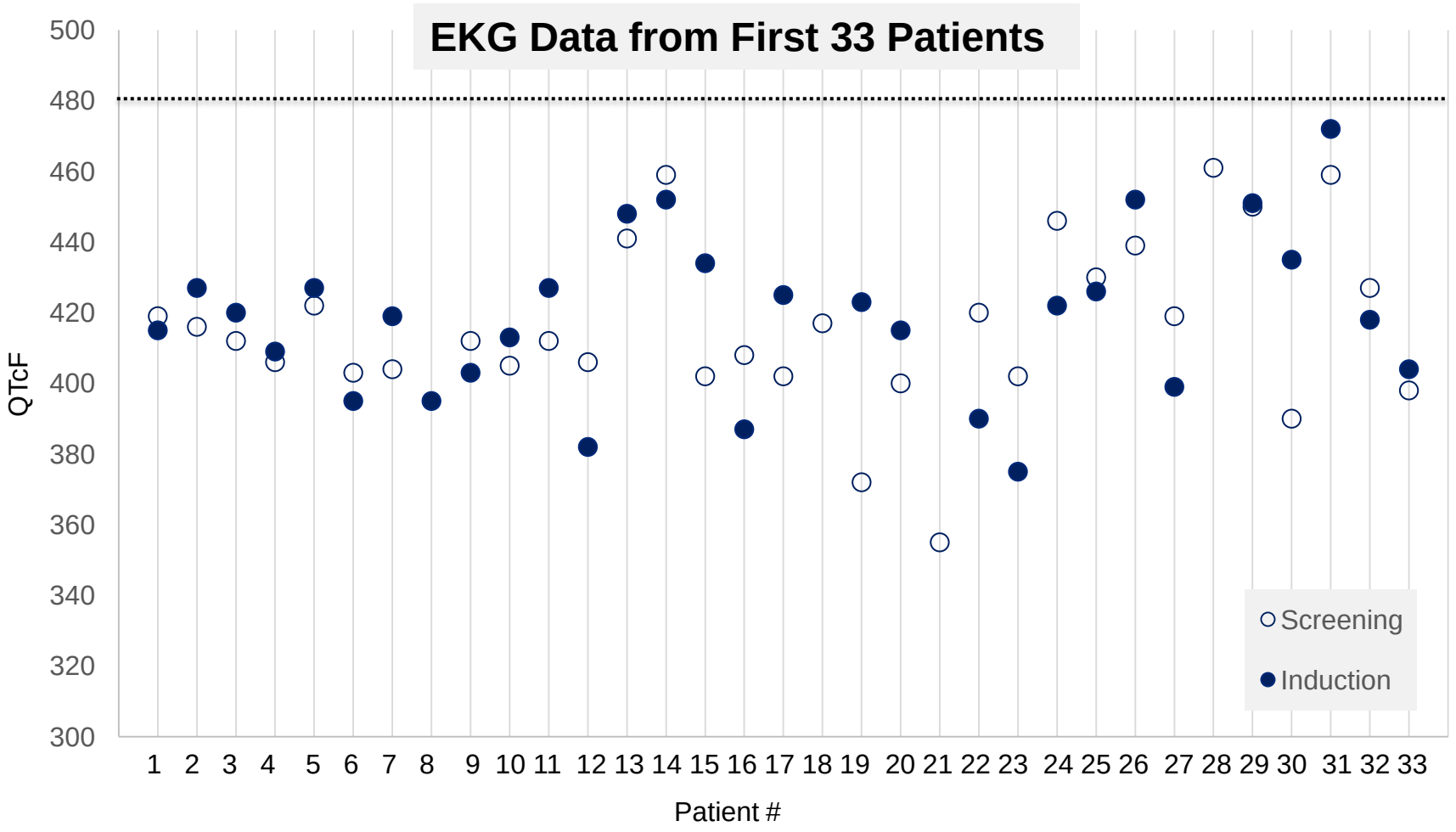
Crenolanib Does Not Affect QTc interval



- No QTc above 480 during induction

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Clinical Response Rate in 32 Evaluable Patients

Induction Chemotherapy Regimen	CR after Induction 1	Overall Complete Response
Cytarabine + Daunorubicin (n=23)	17/23 (75%)	19/23 (83%)
Cytarabine + Idarubicin (n=9)	9*/9 (100%)	9/9 (100%)
Total (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.

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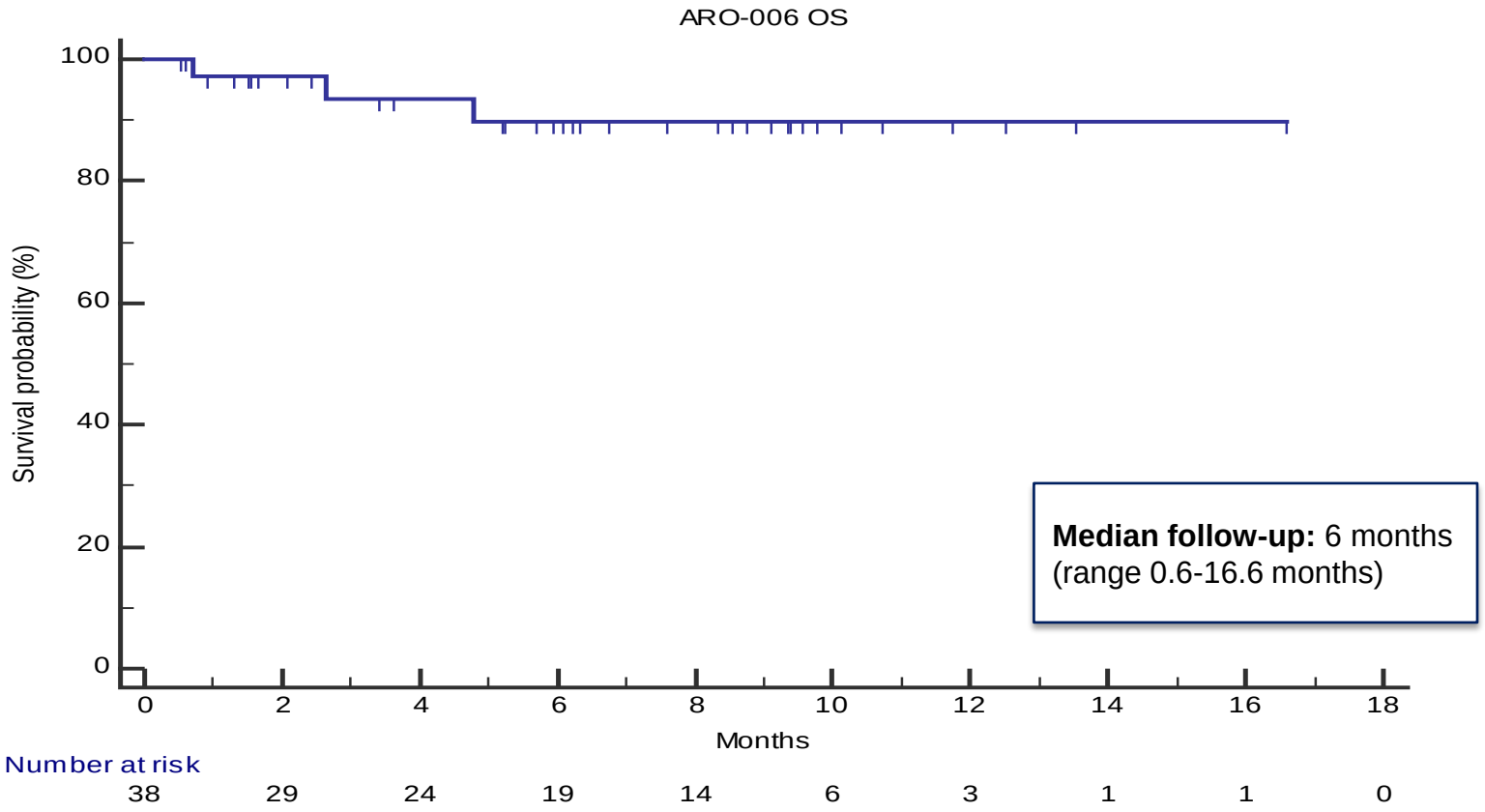
Overall Survival (n=38)



Median follow-up: 6 months (range 0.6-16.6 months)

No leukemia related deaths on study to-date

- Causes of Death:
  - Died in hospice care, withdrew consent day 19
  - Died in remission, h/o cirrhosis with portal hypertension, hepatic insufficiency
  - Died in remission, day 35 post allo HSCT (multi-organ failure)

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Conclusions

- **Crenolanib can be safely combined at full doses with cytarabine/daunorubicin or cytarabine/idarubicin induction and HiDAC consolidation chemotherapy.**
- **Overall CR rate of 88% reported with 81% achieving remission following first induction.**
- **Median survival follow-up at 6 months shows no leukemia-related deaths.**
- **The trial continues to accrue to the 7+3 (Ida) cohort. Plans are underway for a confirmatory, multi-center, pivotal trial.**

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Our patients and their families