Crenolanib besylate, a type I pan-FLT3 inhibitor, demonstrates clinical activity in multiply relapsed FLT3-ITD and D835 AML

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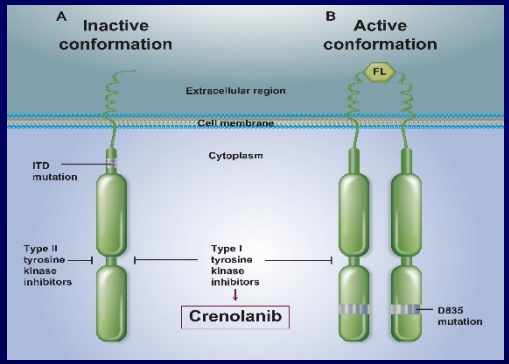
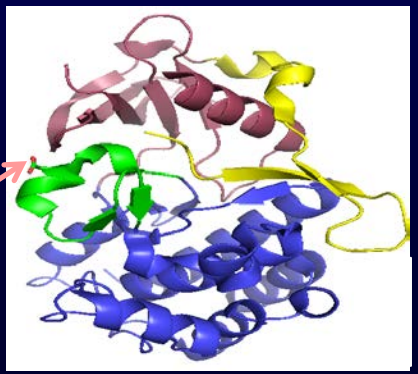
Crenolanib

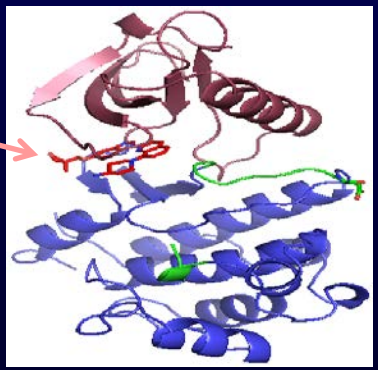
- Crenolanib inhibits both FLT3-ITD and FLT3-TKD mutations in the active conformation
- FLT3 is stabilized in an activated state by substitution of Asp835 with a hydrophobic AA
- Crenolanib binds to the active conformation of FLT3



Inactive FLT3 Conformation

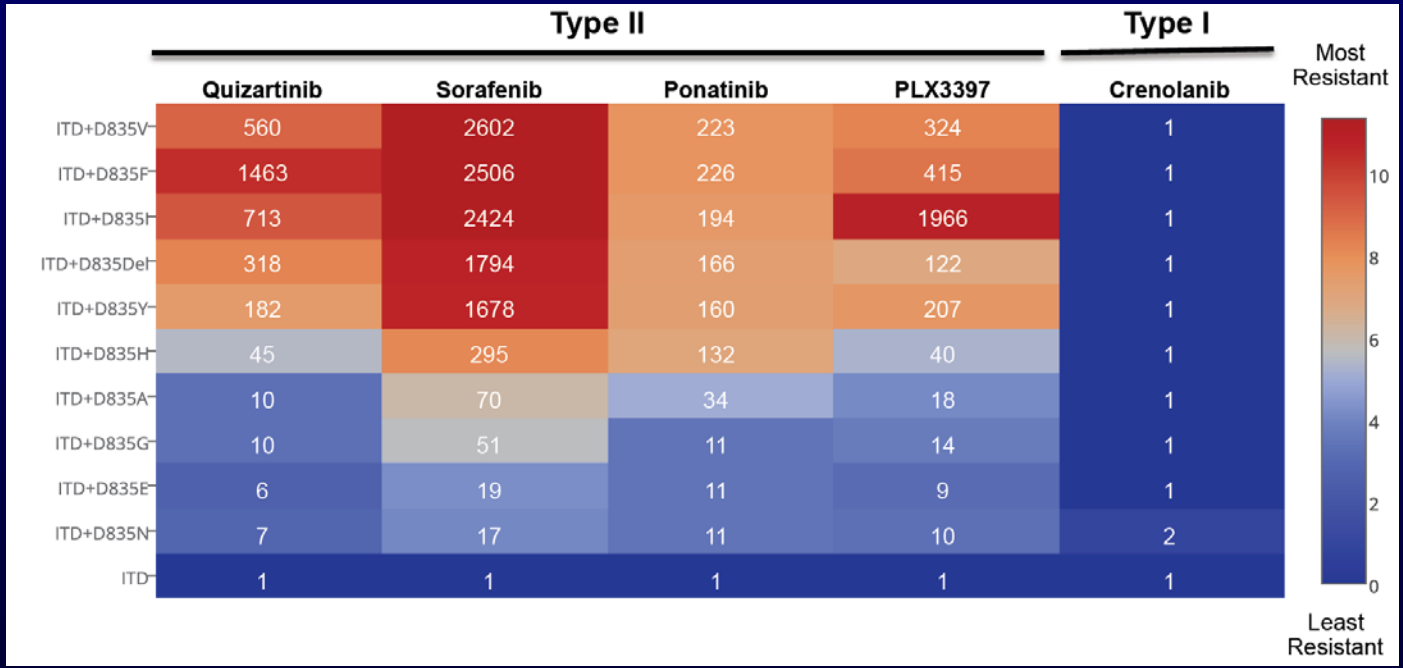


Active FLT3 Conformation



Fathi AT et al. Blood 2013; 122: 3547-8; Gajiwala et al. (2016) Personal communication

Relative Efficacy of FLT3 Inhibitors Against FLT3 Mutations Compared to FLT3-ITD



- **Substitution of D835 in the activation loop with increasingly hydrophobic amino acids like valine, isoleucine and phenylalanine results in increasing resistance to type II FLT3-TKIs**

Smith et al. Leukemia 2015; 29: 2390-2.

Crenolanib Phase 2 in FLT3-Mutated R/R AML Study design

- **69 patients enrolled (Aug 2012-Aug 2015) in two parallel trials:**
  - **MDACC (NCT01657682) (N=56)**
  - **UT Southwestern (NCT01522469) (N=13)**
- **Patient Population:** Refractory/Relapsed AML in 3 cohorts:
  - ***Cohort 1****:* No prior exposure to FLT3-TKI
  - ***Cohort 2****:* Prior exposure to FLT3-TKI
  - ***Cohort 3****:* Secondary AML
- **Primary Objective:** Response Rate, Safety/Tolerability
- **Dosing Schedule**
  - 100 mg TID (43 patients)
  - 66 mg/m^2 TID (26 patients)
  - Continuous oral dosing

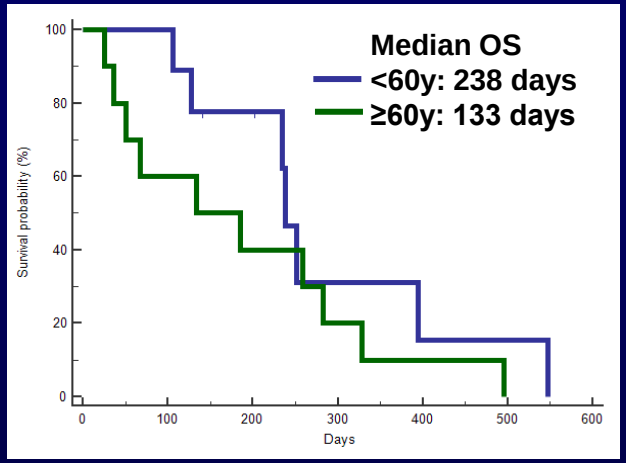
Crenolanib Phase 2 in FLT3-Mutated R/R AML

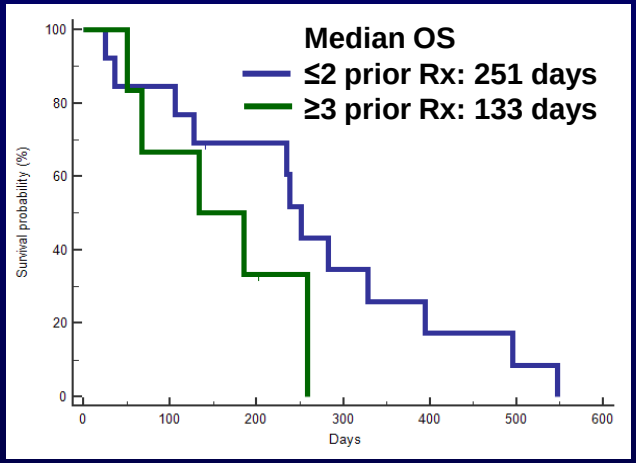
Demographics

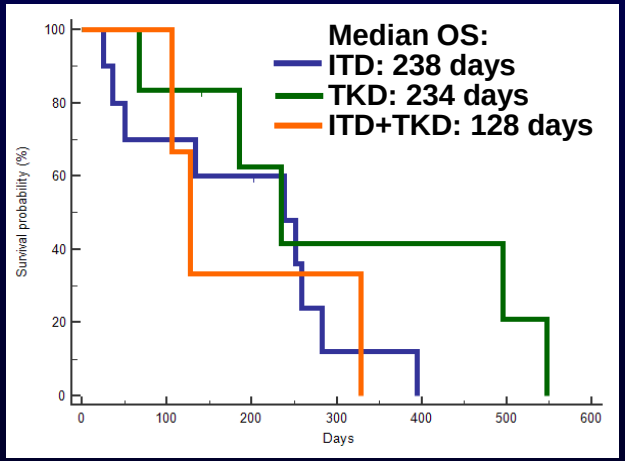
Characteristics	Median [range], or n (%)			
	Total (n=69)	TKI naïve (n=19)	Prior TKI (n=39)	Secondary AML (n=11)
Age, y	60 [21-87]	63 [37-81]	55 [21-87]	74 [38-83]
Sex, male	30 (43)	7 (37)	18 (46)	5 (45)
Prior Therapies				
1 – 2	31 (45)	13 (68)	13 (33)	5 (45)
≥3	38 (55)	6 (32)	26 (67)	6 (55)
FLT3 Status				
ITD	29 (42)	10 (53)	16 (41)	3 (27)
D835	11 (16)	6 (32)	2 (5)	3 (27)
ITD + D835	29 (42)	3 (16)	21 (54)	5 (45)
Treatment Duration, wks	7 [1-36]	8 [2-36]	6 [1-33]	5 [3-16]
Bridged to SCT	6 (9)	3 (16)	3 (8)	0 (0)

Crenolanib Phase 2 in FLT3-Mutated R/R AML

OS by age, prior Rx and FLT3 Mutation - TKI naïve







Crenolanib Phase 2 in FLT3-Mutated R/R AML
Prior TKI – Cohort 2

Prior TKIs		N=39
1 TKI (n=29)	Sorafenib only	21
	Quizartinib only	5
	Pexidartinib only	2
	Midostaurin only	1
2 TKIs (N=7)	Sorafenib → Gilteritinib	2
	Quizartinib → Sorafenib	2
	Sorafenib → Quizartinib → Sorafenib	1
	Sorafenib → Midostaurin	1
	FLX925 → Sorafenib	1
3TKIs (n=3)	Quizartinib → Sorafenib → Pexidartinib	2
	Sorafenib → Midostaurin → Quizartinib → Sorafenib	1

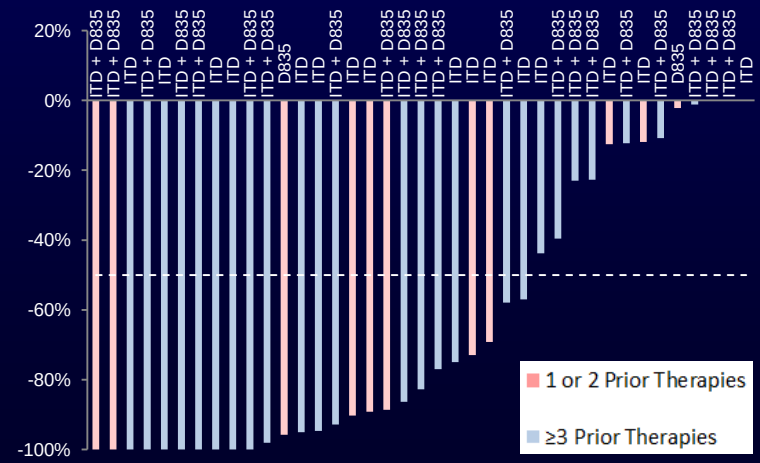
Crenolanib Phase 2 in FLT3-Mutated R/R AML

Response rate and overall survival – Prior TKI

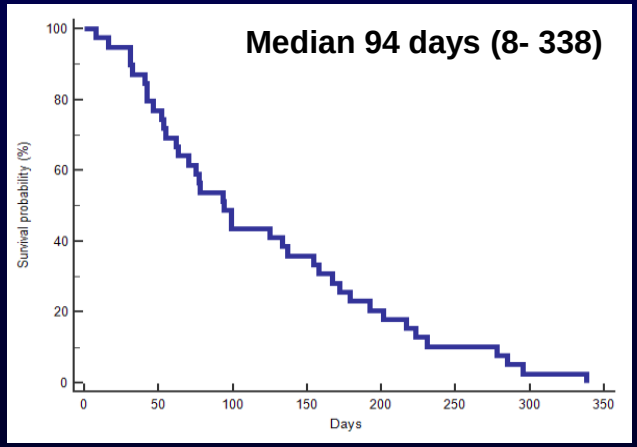
Response (n=39)	n (%)
CR/CRi	6 (15)
PR	5 (13)
ORR (CR+PR)	11 (28)
Blast Response	15 (38)
Clinical Benefit (CR +PR+HI)	26 (67)
RD	13 (33)
Duration of CR/CRi: 47.5 days (17 - 189)*	

* 2 patients bridged to SCT, 2 came off study while in CR/CRi

Peripheral Blast Reduction

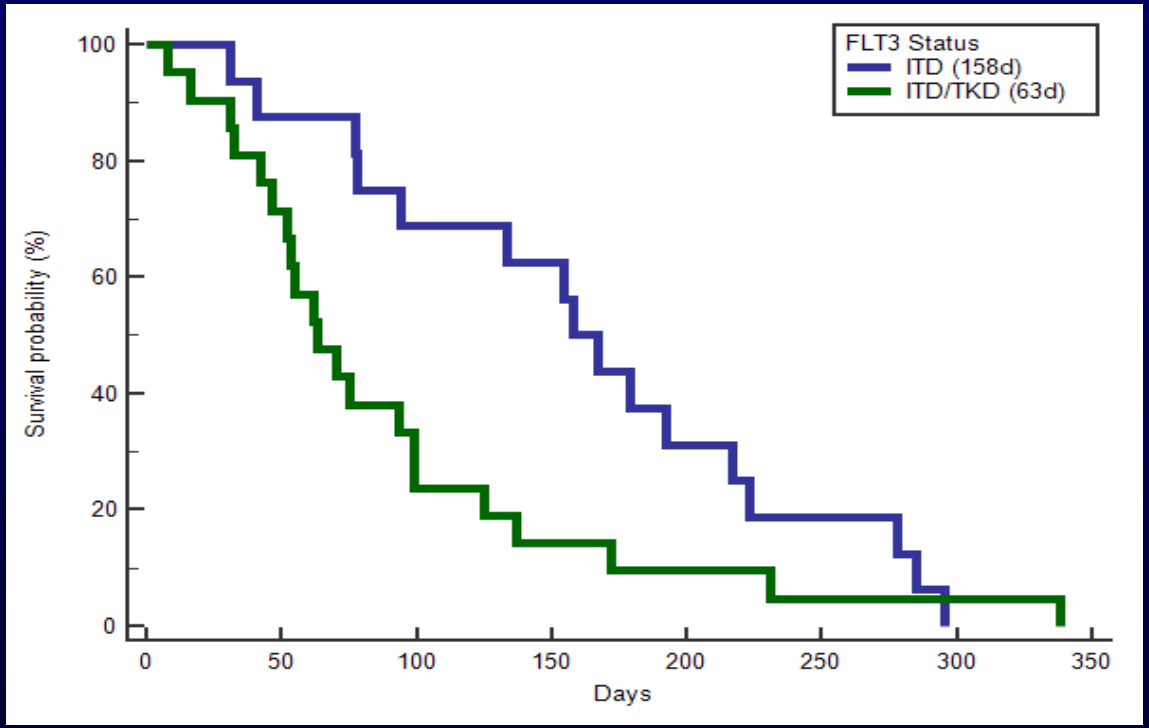


Overall Survival



Crenolanib Phase 2 in FLT3-Mutated R/R AML

OS by FLT3 Mutational Status – Cohort 2: Prior TKI



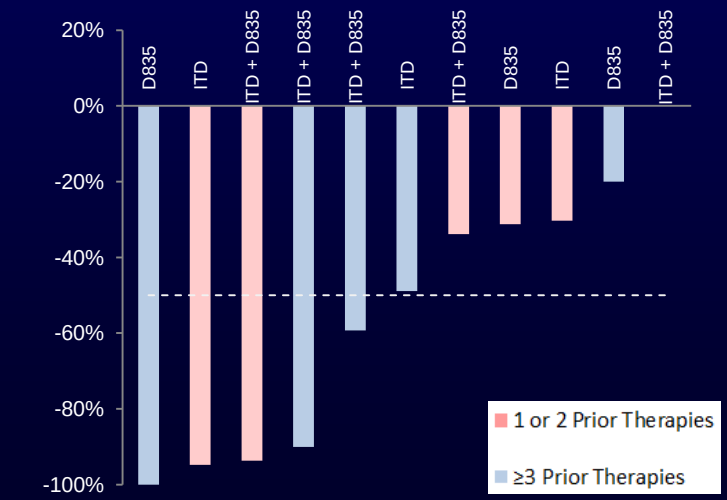
- **The 2 patients with TKD only had OS of 42 and 201 days, respectively**

Crenolanib Phase 2 in FLT3-Mutated R/R AML

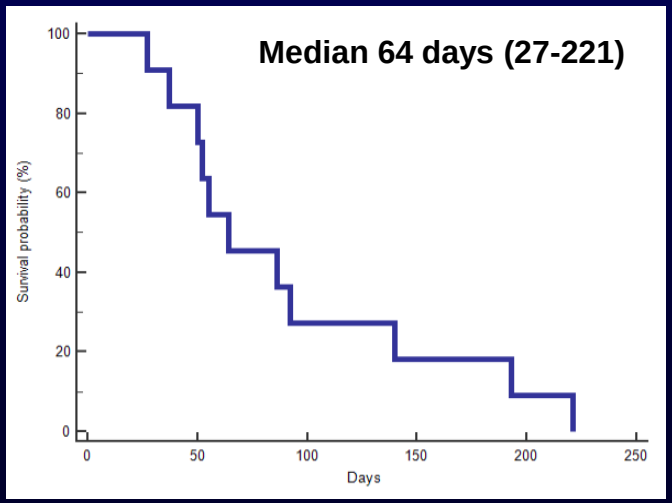
Response rate and overall survival – Secondary AML

Response (n=11)	n (%)
CR/CRi	0 (0)
PR	1 (9)
ORR (CR+PR)	1 (9)
Blast Response	4 (36)
Clinical Benefit (CR +PR+HI)	5 (45)
RD	6 (55)

Peripheral Blast Reduction



Overall Survival



Crenolanib Phase 2 in FLT3-Mutated R/R AML
Response rate and overall survival – Secondary AML

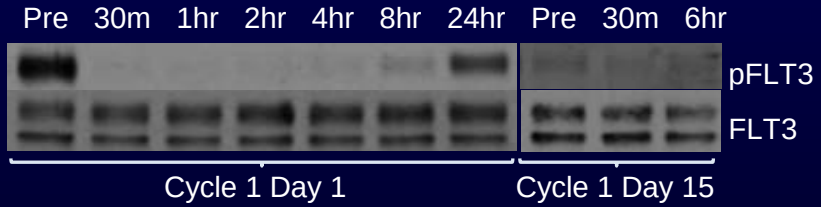
- Exons 17 and 20 ultra-deep sequencing in 17 paired samples
  - No acquisition of TKD mutations in 6/6 patients with FLT3-ITD/no TKD at baseline
  - 1/20 patients acquired F691L at time of relapse
  - A833S, D839Y/G and N841K at baseline in pts → eliminated on crenolanib
- Whole exome sequencing in 42 patients
  - Three novel mutations (L601F, K429E and D200N) at relapse; 2 present at baseline
  - 3/42 developed F691L at time of resistance
  - Increased frequency of WT1, NRAS, SF3B1, STAG2, ASXL1, IDH2, TET1 & CCND3 mutations at relapse

Zhang et al. ASH 2015. Abstract 2468

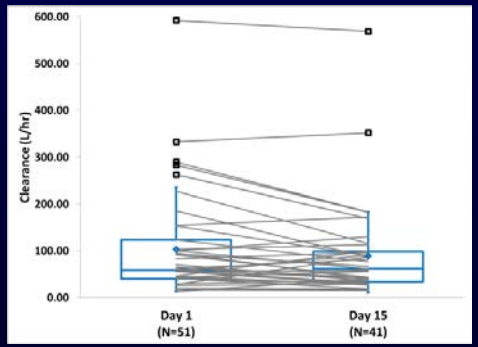
Crenolanib Phase 2 in FLT3-Mutated R/R AML PK/PD

- **Rapid absorption: T_{max} 1.5-2 hr**
- **Maximal FLT3 inhibition within 2-3 hr**
- **$t_{1/2}$ 6-8 hr**
- **Consistent PK on day 1 and day 15 (no accumulation)**
- **Trough levels adequate to inhibit FLT3: median 384nM (IC_{50} of pFLT3 inhibition in plasma: 34 nM)**

pFLT3 inhibition



D1 and D15 Clearance



	Day 1 (N=51)	Day 15 (N=41)
Median	58.90 L/hr	61.04 L/hr
Range	13.09 – 591.85 L/hr	10.67-568.64 L/hr

Panetta et al. ASH 2015. Abstract 3695

Crenolanib Phase 2 in FLT3-Mutated R/R AML

Treatment-emergent AE (regardless of attribution)

Event Name	Percentage	
	All Grade	Grade 3-4
Nausea	70	9
Vomiting	58	9
Diarrhea	56	2
Fatigue	36	11
Febrile neutropenia	35	35
Pneumonia	32	23
Peripheral Edema	30	2
Pleural effusion	21	8
Dyspnea	20	5
Epistaxis	20	8

TEAEs (all grades) reported in ≥ 20% subjects

Crenolanib Phase 2 in FLT3-Mutated R/R AML

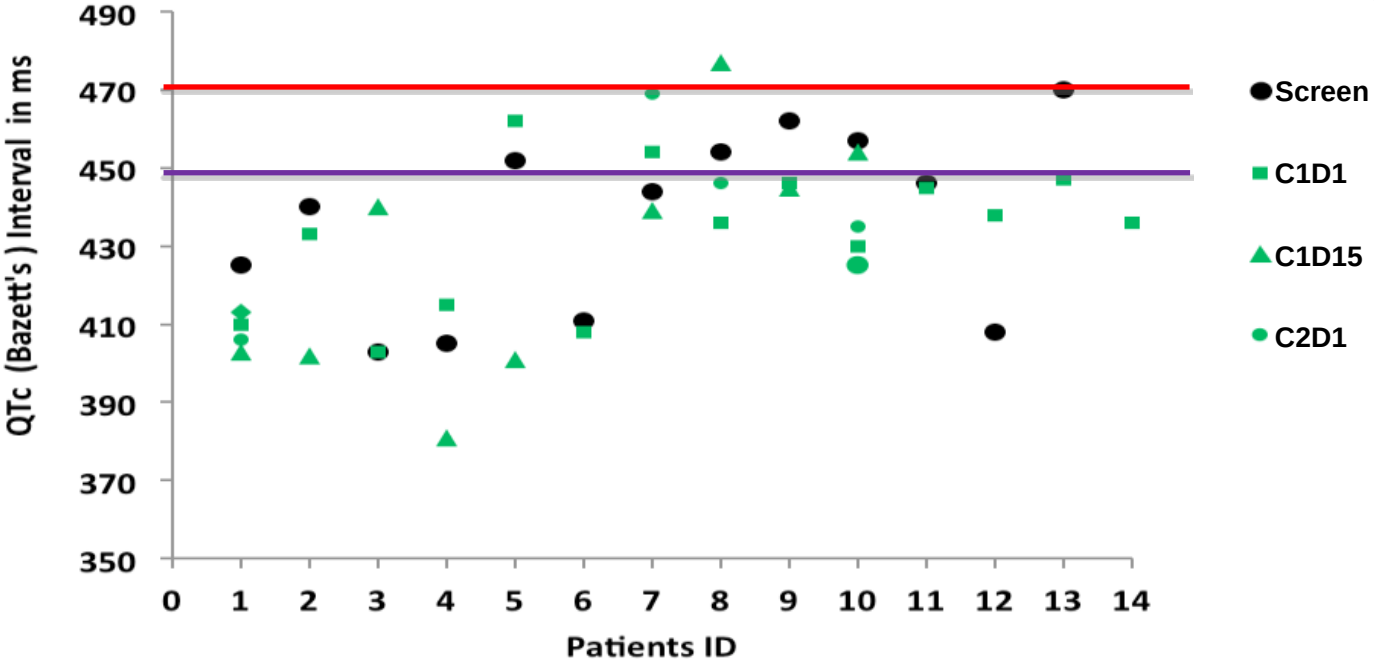
Selected TEAE Grade 3-4 (regardless of attribution)

Event Name	n (%)	
	Grade 3	Grade 4
Gastrointestinal hemorrhage	11 (16)	1 (1)
Sepsis	-	6 (9)
Respiratory failure	1 (1)	6 (9)
Pericardial effusion	2 (3)	-
AST elevation	4 (6)	1 (1)
ALT elevation	3 (4)	1 (1)
Bilirubin elevation	4 (6)	-
Rash maculo-papular	1 (1)	-

- 2/69 patients discontinued crenolanib due to adverse events
  - 1 Grade 3 fatigue, abdominal pain, and headache
  - 1 Grade 3 pneumonia
- Two neutropenic septic deaths (2 and 21 days after discontinuation of crenolanib, respectively)

Crenolanib Phase 2 in FLT3-Mutated R/R AML
EKG Analysis (n=14)

EKG done at screening, C1D1, C1D15 and C2D1



- QTc interval was less than <475ms in all patients at all times tested

Crenolanib Phase 2 in FLT3-Mutated R/R AML
Conclusions

- Clinical benefit with Crenolanib in R/R FLT3-mutated AML
- Better outcome in FLT3-TKI naïve population
  - Mostly CRi in patients exposed to FLT-3 TKI's
- Responses seen in FLT3-ITD, D835, ITD+D835 as well as in FLT3-A833, D839, N841
- Secondary FLT3 resistance mutations not seen at time of relapse
- Favorable toxicity profile
- No crenolanib accumulation over time

	Ongoing Trials	Identifier
ARO-006	Crenolanib + Chemotherapy, Newly Diagnosed AML	NCT02283177
ARO-009	Crenolanib Single Agent, Post-SCT Maintenance	NCT02400255
ARO-008	Crenolanib + Sorafenib, R/R Hematologic Malignancies, Pediatric/AYA	NCT02270788
ARO-010	Crenolanib + 5-Azacytidine or Cytarabine/Idarubicin, R/R AML	NCT02400281
ARO-007 AMLSG	Crenolanib + HAM, 1st R/R AML, Double-blind, randomized	NCT02298166

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