Quizartinib: An Effective Option for FLT3-mutated AML

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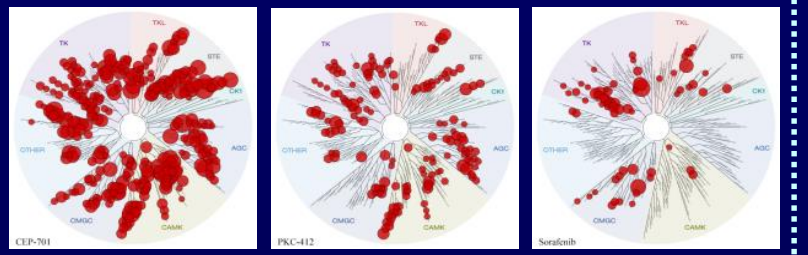
Disclosures

- Research support:
  - Novartis, Daiichi, Astellas, Arog
- Consultant:
  - Novartis, Daiichi, Astellas

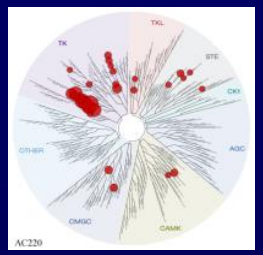
FLT3 Inhibitors Under Development

Preclinical	Phase I	Phase II	Phase III
VX-322	SKI-G-801	PLX3397	Midostaurin
VX-398	Ponatinib	MLN-518	Quizartinib
MC-2002	CHIR-258		Gilteritinib
MC-2006	KW-2449		Sorafenib
F-10101	IMC-EB10		Crenolanib
	FLX-925		Lestaurtinib

Quizartinib: a Highly Potent and Selective FLT3 Inhibitor

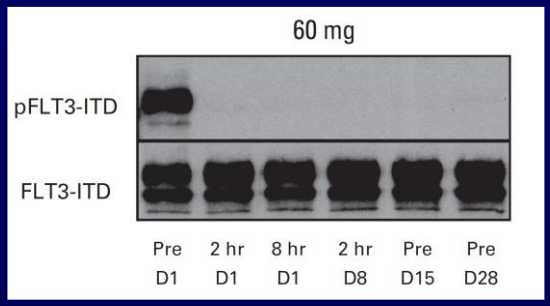


First-generation multikinase inhibitors[2]



Second-generation FLT3 inhibitor[3]

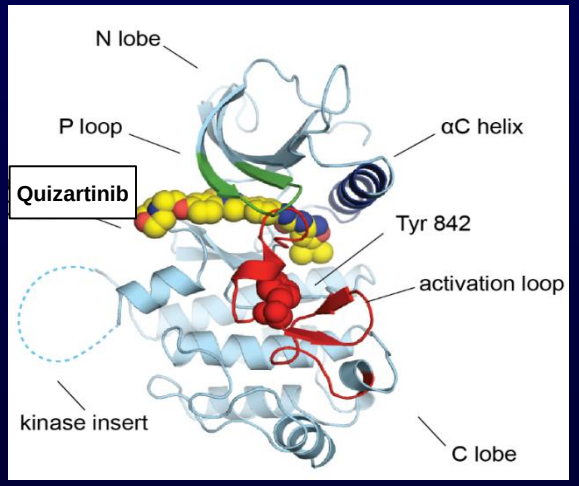
Davis MI, et al. *Nat Biotechnol*. 2011;29(11):1046-105.



Cortes JE, et al. *J Clin Oncol*. 2013;31(29):3681-3687.

Quizartinib properties

- Oral, highly potent, selective[3]
- Nanomolar affinity (1.6 ± 0.7 nM) against FLT3[3] and complete suppression of FLT3 phosphorylation in *ex vivo* PIA assays[4]
- Highly selective for FLT3 when screened against 402 human kinases (other kinases with K_d within 10-fold that of FLT3 were closely related RTKs, eg, KIT)[3]

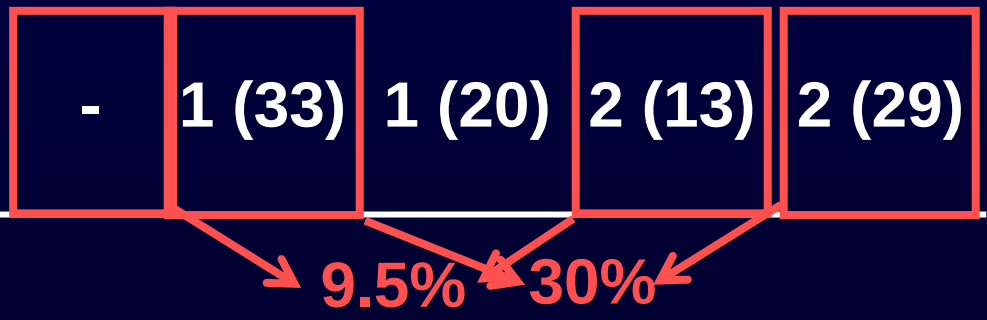


Zorn JA, et al. *PLoS One*. 2015;10(4):e0121177.

1. Davis MI, et al. *Nat Biotechnol.* 2011;29:1046-1051. 2. Stone R, et al. *N Engl J Med*. 2017;377:454-464.
3. Zarrinkar P, et al. *Blood*. 2009;114:2984-2992. 4. Cortes JE, et al. *J Clin Oncol*. 2013;31:3681-3687.

AC220 Phase 1 QTcF Changes

QTcF	No. (%) by dose (mg/day) and schedule						
	12-60 ID	90-135 ID	200 ID	300 ID	450 ID	200 CD	300 CD
No.	26	8	5	3	6	16	7
↑ >60 msec	1 (4)	1 (13)	-	1 (33)	2 (40)	4 (27)	5 (71)
>500 msec	1 (4)	-	-	1 (33)	1 (20)	2 (13)	2 (29)



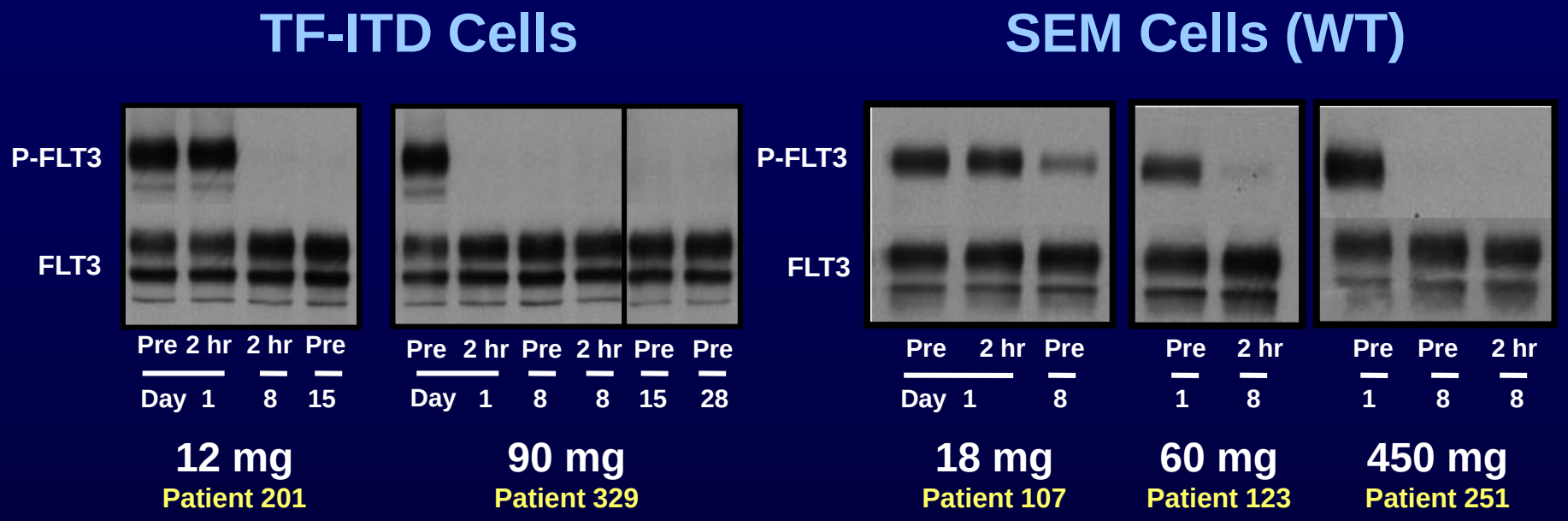
Cortes et al. JCO 2013; 31: 3681-7

AC220 Phase 1 Clinical Response Data

Dose (mg)	No. Treated	Responses	
		CR, CRp, CRi	PR
12	3		
18	8		1
27	6		2
40	5	1CRp	1
60	5	1CRi	1
90	3		1
135	5		1
200	6	1CRp	1
300	4	1CRi	1
450	6		2
200 CD	17	2CR, 3CRi	
300 CD	8	1CRi	1
Total	**76**	**10 (13%)**	**13 (17%)**

Cortes et al. JCO 2013; 31: 3681-7

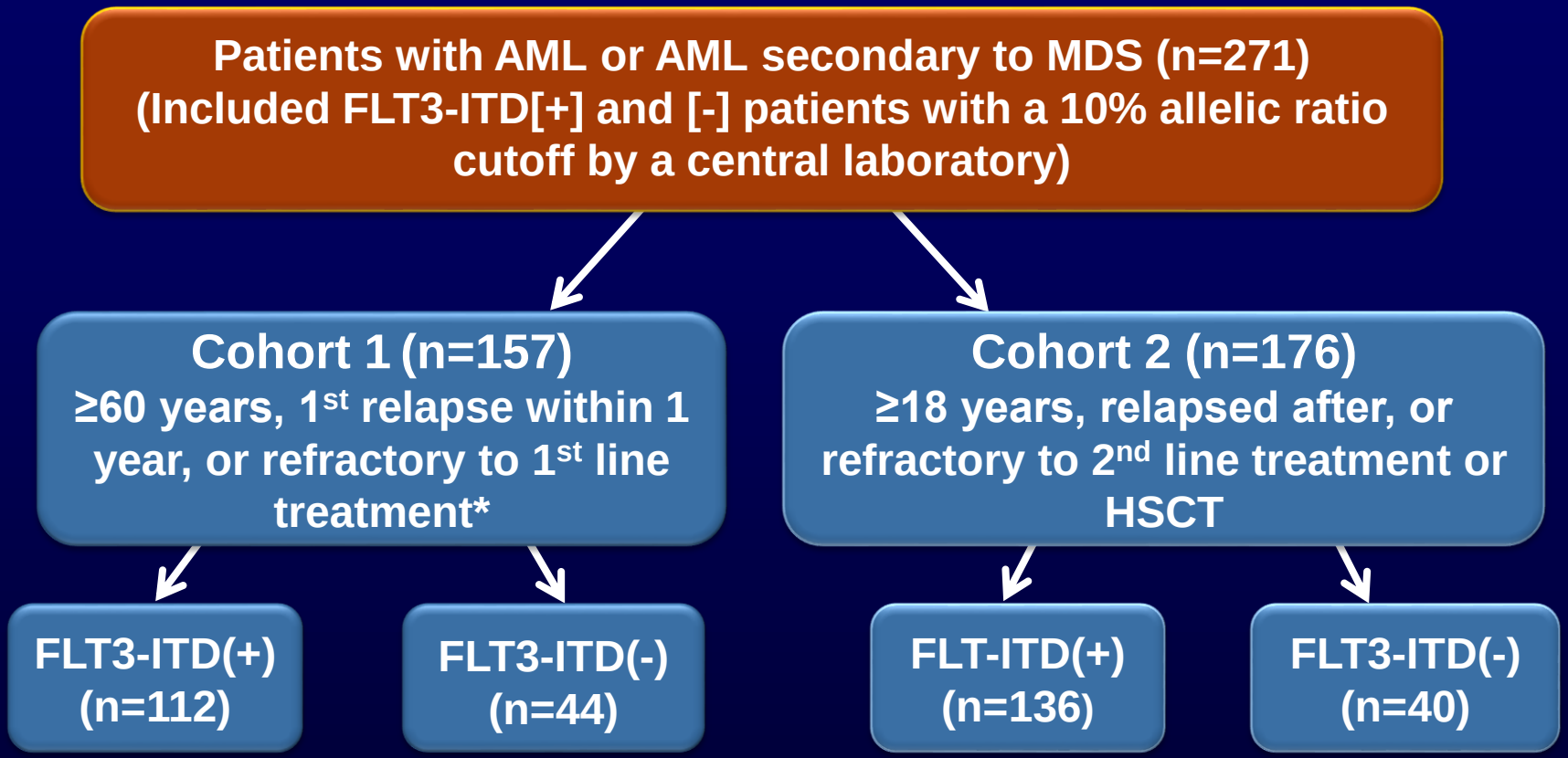
AC220 Phase 1
AC220 Inhibits p-FLT3 in an *ex vivo* Plasma Inhibitory Assay



- AC220 treated patient plasma potently inhibits p-FLT3 in:
  - FLT3 ITD + cells at ≥12 mg QD
  - FLT3 ITD - cells at higher doses

Cortes et al. JCO 2013; 31: 3681-7

Phase 2 Study of Quizartinib in AML Study Design

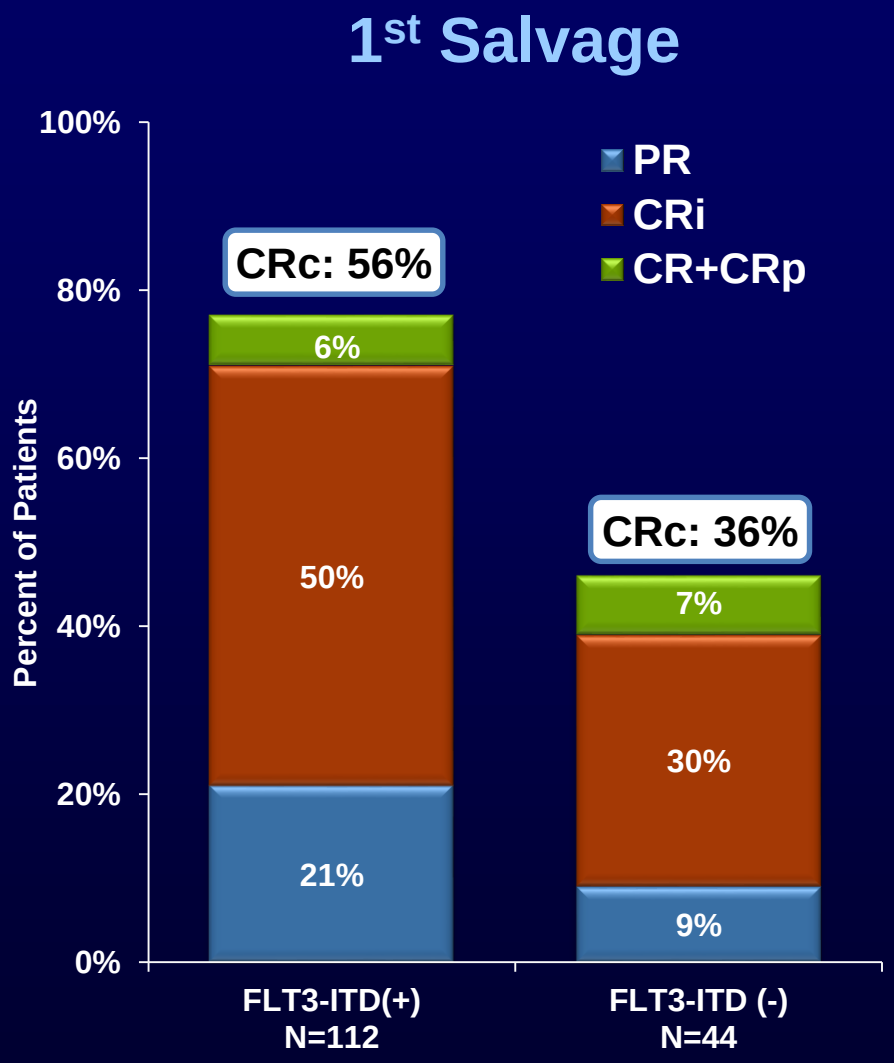


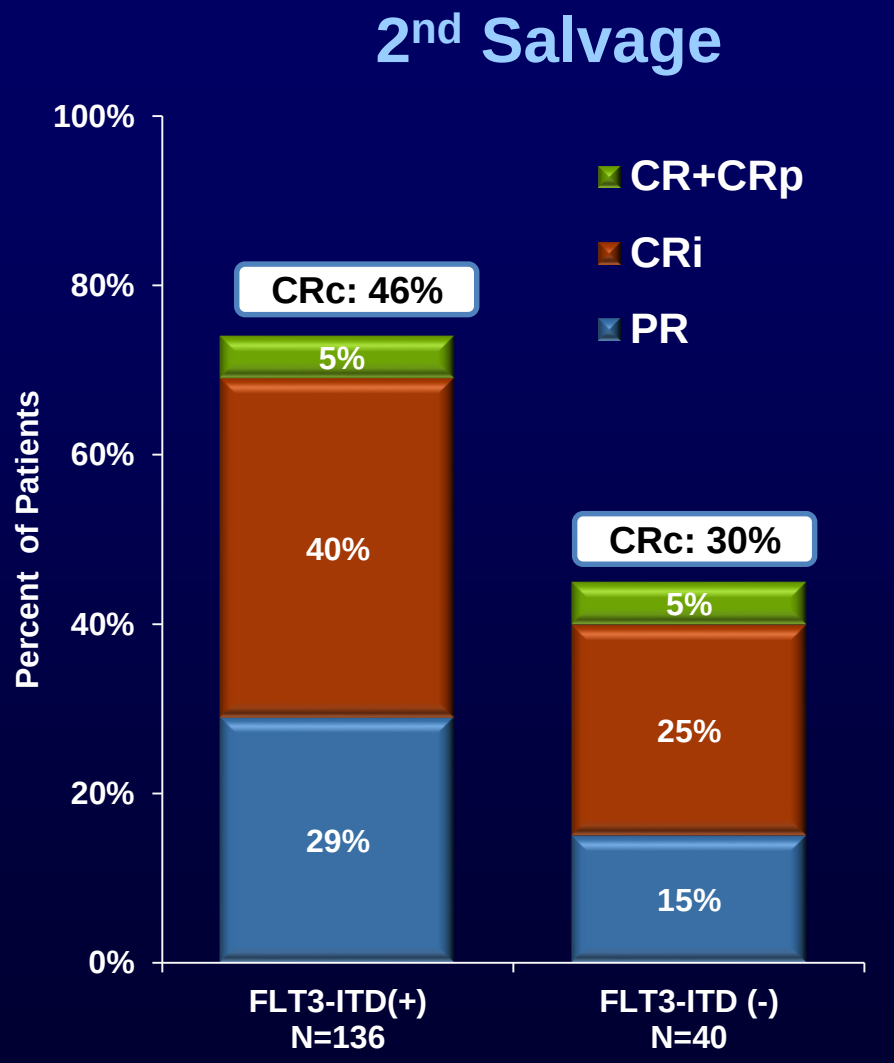
- 332 patients enrolled (first 62 in an exploratory phase)
- Primary endpoint: Composite CR (CRc = CR + CRp + CRi)
- Secondary endpoints: CR, duration of response, bridge to HSCT & OS

* One pt unknown FLT3 status

Cortes et al. Lancet Oncol 2018; 19(7): 889-903

Phase 2 of Quizartinib in 1st Salvage AML – Response

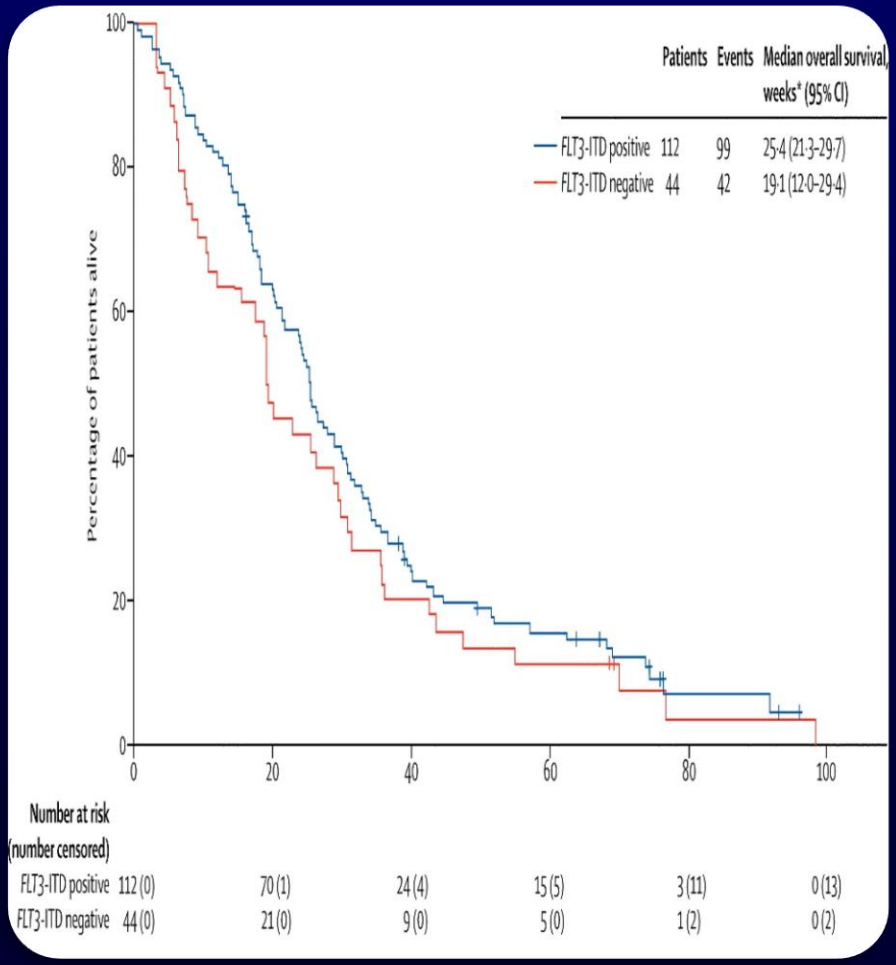




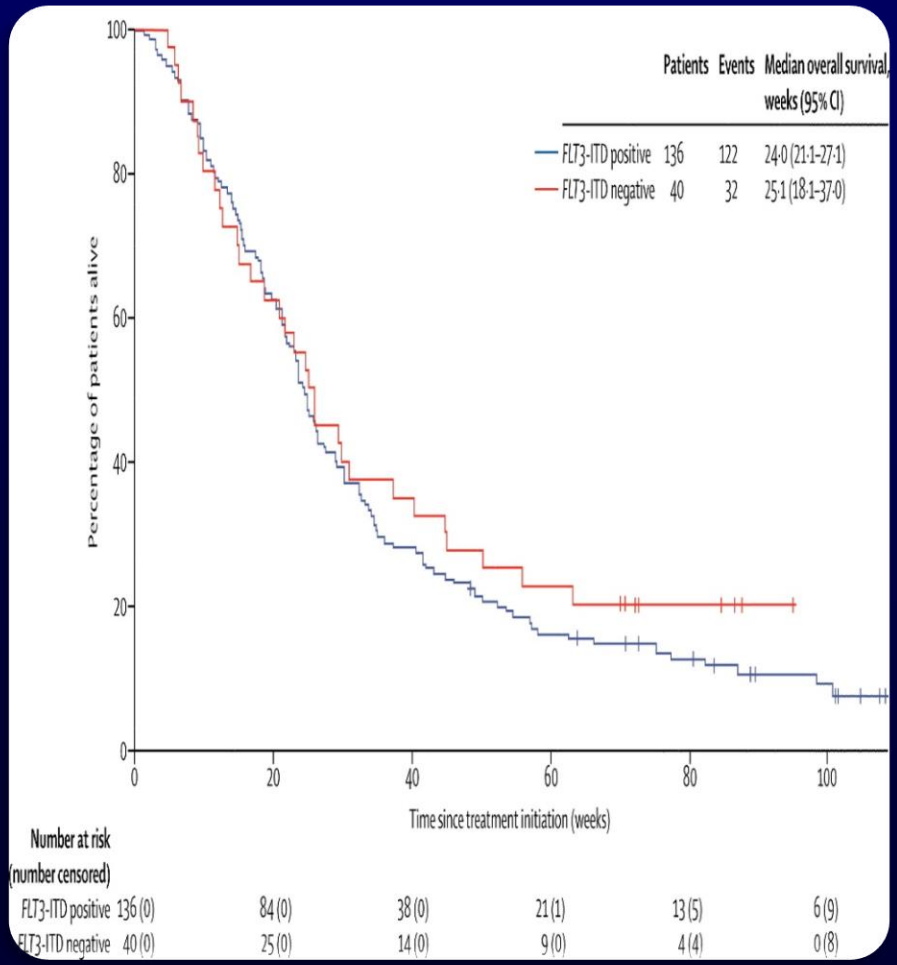
Cortes et al. Lancet Oncol 2018; 19(7): 889-903

Phase 2 of Quizartinib in AML – Overall Survival by FLT3-ITD Status

1st Salvage



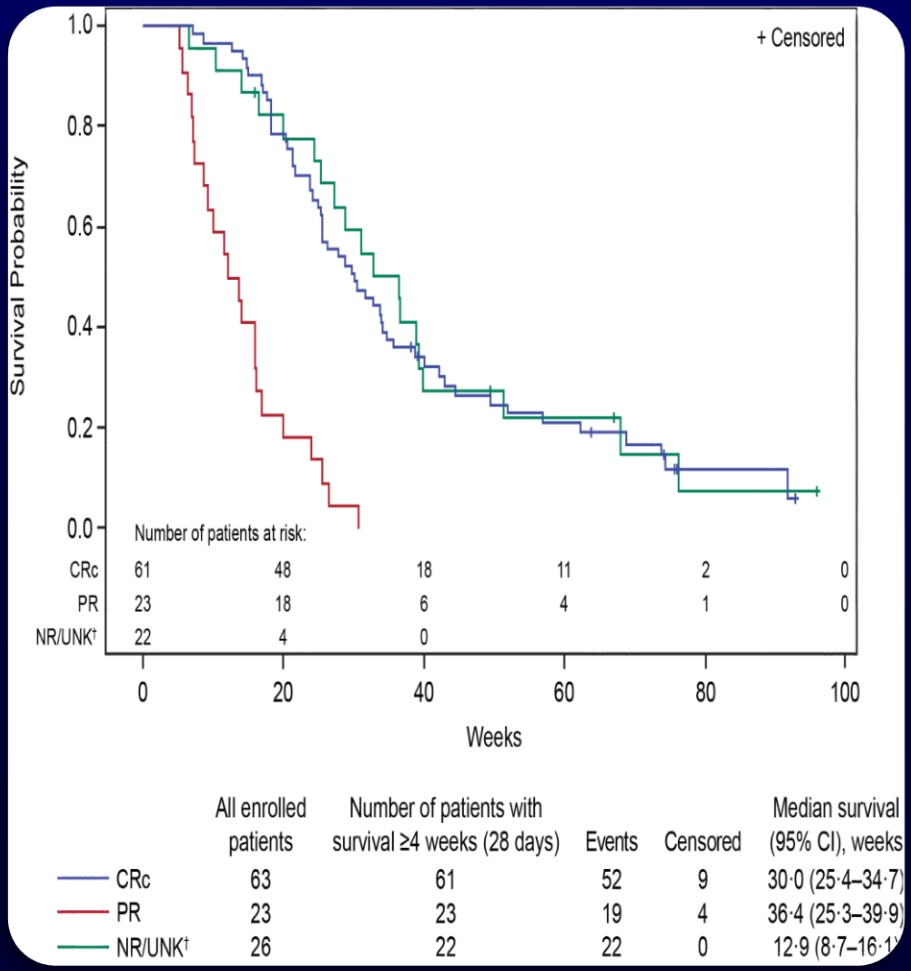
2nd Salvage



Cortes et al. Lancet Oncol 2018; 19(7): 889-903

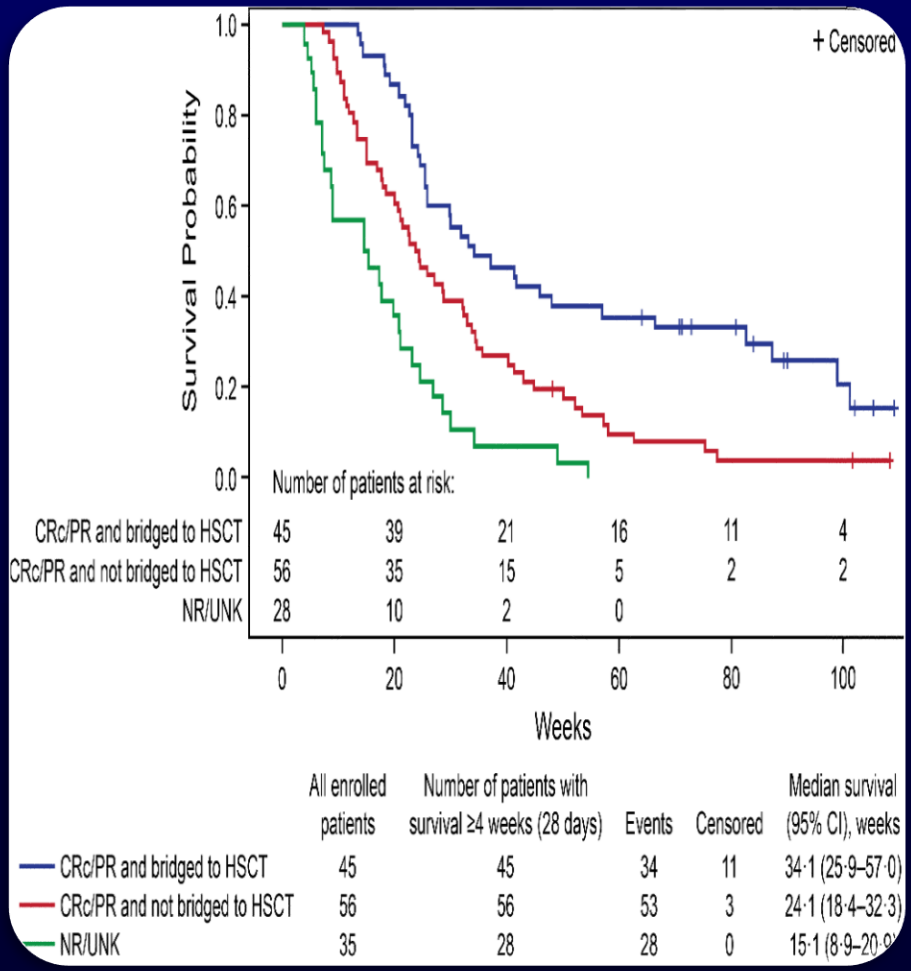
Phase 2 of Quizartinib in AML – OS in FLT3-ITD(+) by Response

1st Salvage



	All enrolled patients	Number of patients with survival ≥4 weeks (28 days)	Events	Censored	Median survival (95% CI), weeks
CRc	63	61	52	9	30·0 (25·4–34·7)
PR	23	23	19	4	36·4 (25·3–39·9)
NR/UNK†	26	22	22	0	12·9 (8·7–16·1)

2nd Salvage



	All enrolled patients	Number of patients with survival ≥4 weeks (28 days)	Events	Censored	Median survival (95% CI), weeks
CRc/PR and bridged to HSCT	45	45	34	11	34·1 (25·9–57·0)
CRc/PR and not bridged to HSCT	56	56	53	3	24·1 (18·4–32·3)
NR/UNK	35	28	28	0	15·1 (8·9–20·9)

Cortes et al. Lancet Oncol 2018; 19(7): 889-903

Lower Dose Quizartinib Study Design

- Eligibility
  - ≥ 18 yrs
  - Primary AML or secondary to MDS
  - FLT3-ITD(+) by central laboratory
  - Relapsed after, or refractory to 1 line of salvage therapy or relapsed after HSCT
- Randomized to 30 mg or 60 mg continuous daily dosing
- Dose reduction
  - Grade 2 or higher QTcF prolongation
  - Grade 3 or higher related non-hematologic toxicity
  - Myelosuppression for subjects in CRc
- Dose increase for lack of CRc after 1 cycle or loss of response
- 76 pts enrolled from May 21, 2012 to March 27, 2013

Cortes et al. Blood 2018; 132: 598-607

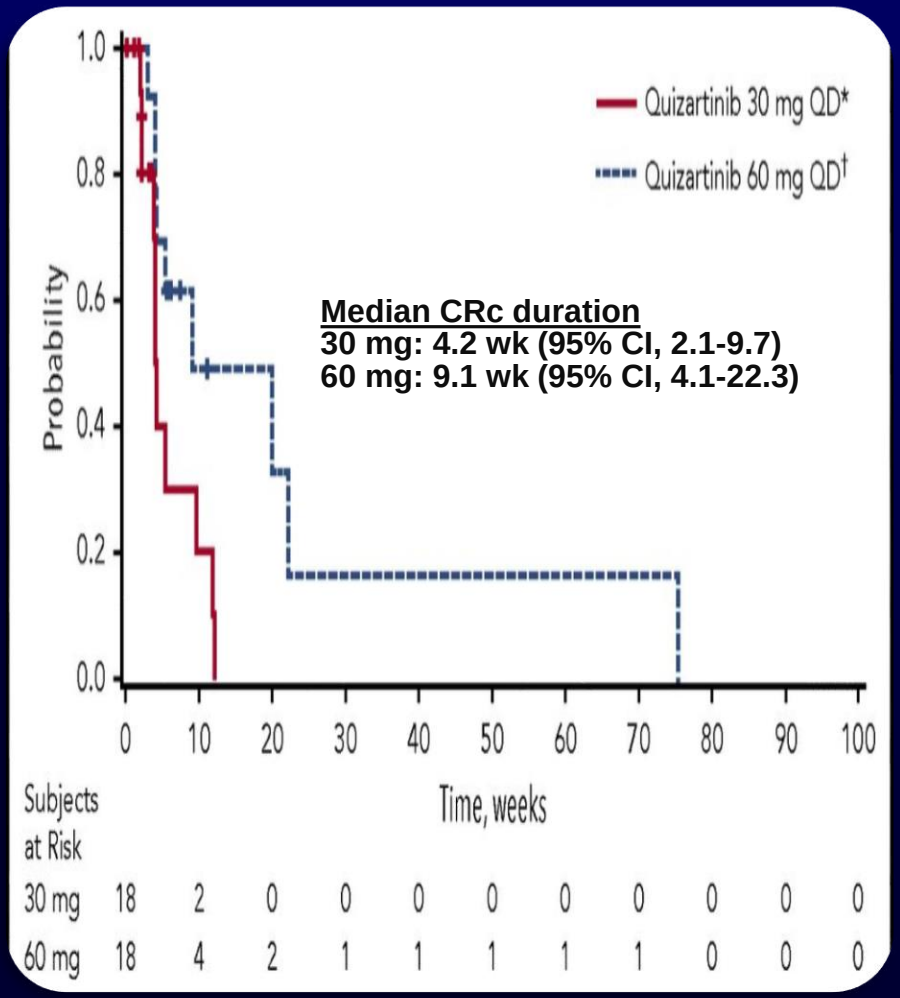
Lower Dose Quizartinib Overall Response

Best Response	No. (%) 30 mg/day* (N = 38)	60 mg/day* (N = 38)	Total (N = 76)
CRc (CR+CRp+CRi)	18 (47)	18 (47)	36 (47)
CR	2 (5)	1 (3)	3 (4)
CRp	0	2 (5)	2 (3)
CRi	16 (42)	15 (40)	31 (41)
CRc+PR	23 (61)	27 (71)	50 (66)
PR	5 (13)	9 (24)	14 (18)

Cortes et al. Blood 2018; 132: 598-607

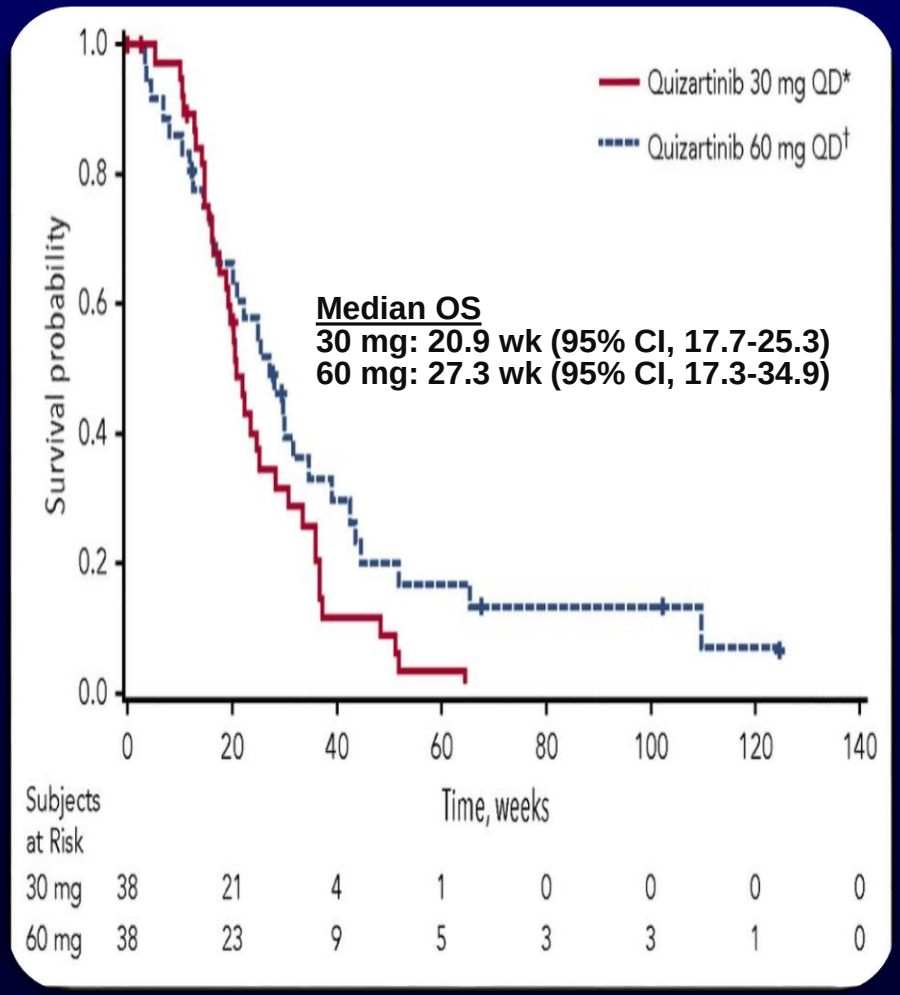
Lower Dose Quizartinib CRc Duration and OS by Dose

CRc Duration



Median CRc duration
30 mg: 4.2 wk (95% CI, 2.1-9.7)
60 mg: 9.1 wk (95% CI, 4.1-22.3)

Overall Survival



Median OS
30 mg: 20.9 wk (95% CI, 17.7-25.3)
60 mg: 27.3 wk (95% CI, 17.3-34.9)

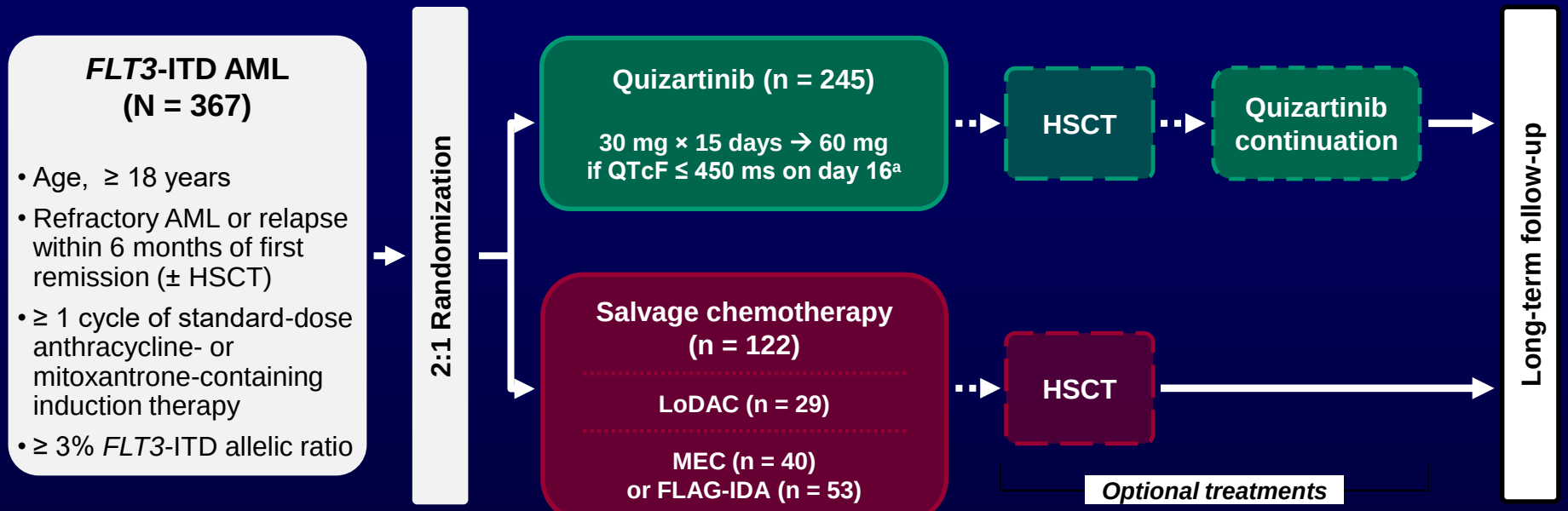
Cortes et al. Blood 2018; 132: 598-607

Response and QTc Effect by Quizartinib Dose in Phase 2 Studies

	2689-CL-2004		AC220-002 (Cohort 2)		
	30 mg/day (N = 38)	60 mg/day (N = 38)	90 mg/day (N=57)	135 mg/day (N=67)	200 mg/day (N=12)
Best Response					
CRc Rate	47%	47%	47%	45%	42%
PR Rate	13%	24%	25%	28%	50%
Maximum change in QTcF from baseline (msec)					
≤ 30	50%	44%	9%	9%	0%
> 30 to ≤ 60	47%	36%	46%	51%	8%
> 60	3%	19%	46%	39%	92%

Cortes et al. Lancet Oncol 2018; 19(7): 889-903; Cortes et al. Blood 2018; 132: 598-607

QuANTUM-R Study Design



- **Primary endpoint:** overall survival (ITT population)
- **Secondary endpoint:** event-free survival (ITT population)
- **Select exploratory endpoints:** CRc rate, duration of CRc, and transplant rate
- Enrollment dates: May 2014 (first patient) to September 2017 (last patient)
- Data cutoff: February 2018

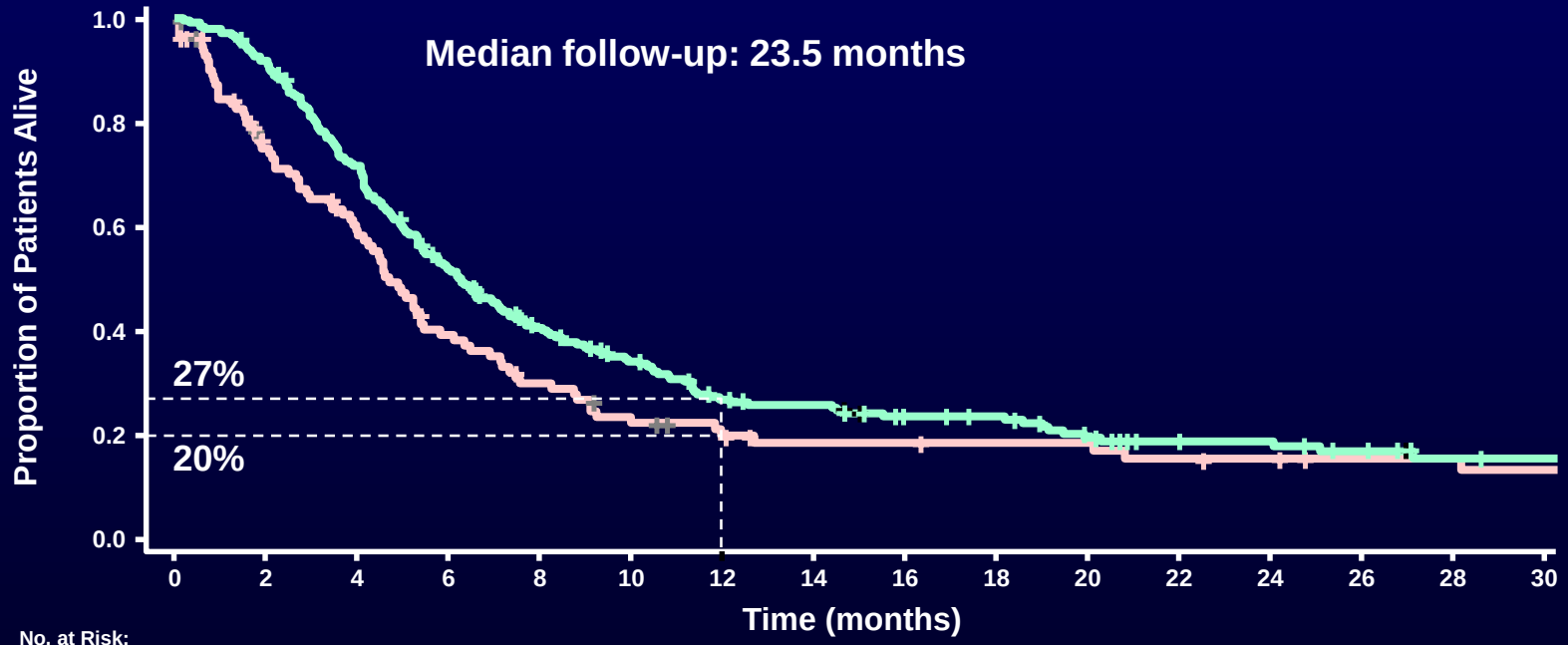
[a]20 mg × 15 days → 30 mg if concomitantly taking CYP3A4 inhibitors.

QUANTUM-R: Primary Endpoint: Overall Survival

HR, 0.76 (95% CI, 0.58-0.98)
***P* = 0.0177** **(1-sided, stratified log-rank)**

Median overall survival:
Quizartinib (n = 245): 6.2 months (95% CI, 5.3-7.2 months)
Salvage chemotherapy (n = 122): 4.7 months (95% CI, 4.0-5.5 months)

Median follow-up: 23.5 months



No. at Risk:																
Quizartinib	245	224	173	122	89	71	53	48	38	36	27	20	20	16	11	10
Salvage chemotherapy	122	77	59	38	28	21	15	13	13	12	12	10	9	7	7	6

QUANTUM-R: Best Response

Characteristic	Percentage (95% CI)	
	Quizartinib n = 245	Salvage Chemotherapy n = 122
Best response		
CRc[a]	48 (42-55)	27 (19-36)
CR	4 (2-7)	1 (0-5)
CRp	4 (2-7)	0 (0-3)
CRi	40 (34-47)	26 (19-35)
PR	21 (16-27)	3 (1-8)
ORR (CRc + PR)	69 (63-75)	30 (22-39)
No response	25 (20-31)	37 (28-46)
Nonevaluable	5 (3-9)	33 (25-42)

[a]Nominal *P* = 0.0001 for between-group comparison of CRc.

QUANTUM-R: Duration of CRc and Transplant Rate

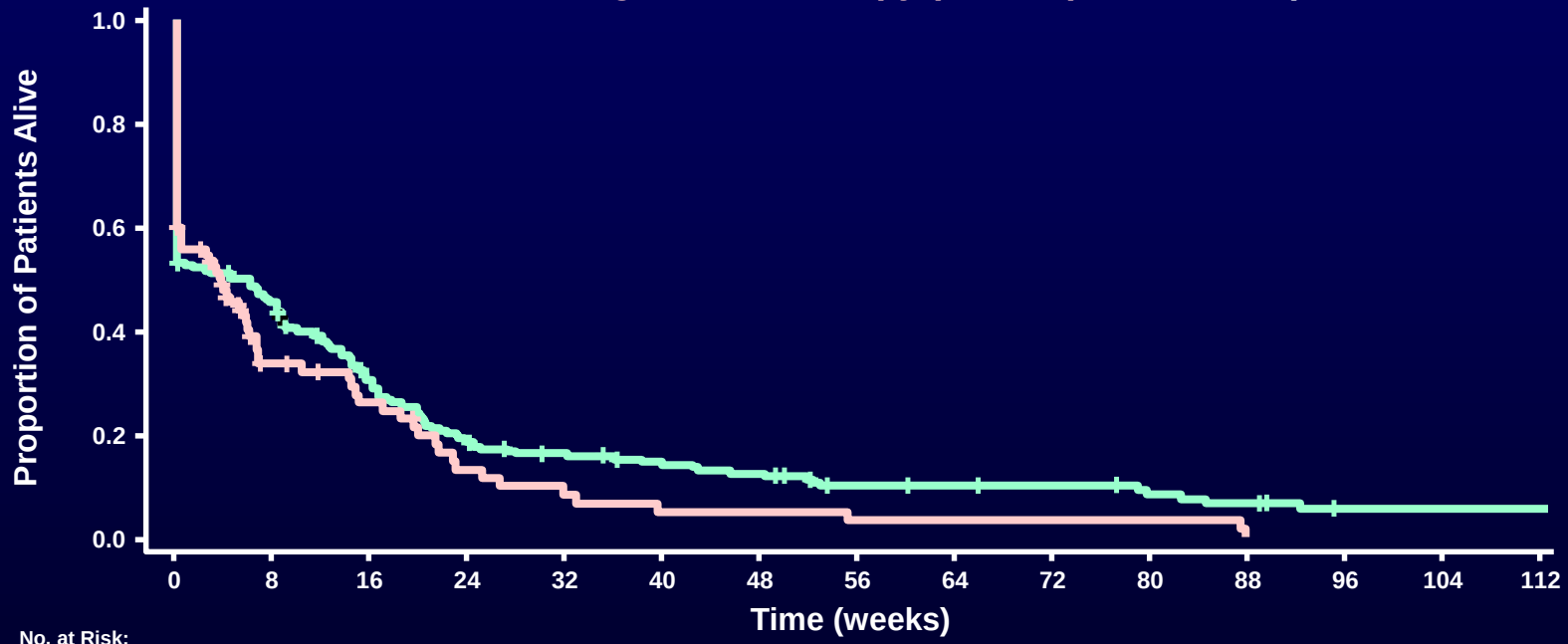
Characteristic	Quizartinib n = 245	Salvage Chemotherapy n = 122
Duration of CRc (95% CI), weeks		
Median	12.1 (10.4-27.1)	5.0 (3.3-12.6)
Transplant, %		
Transplant rate[a]	32	12

[a]Nominal *P* < 0.0001 for between-group comparison of transplant rate.

Quantum-R: Secondary Endpoint: Event-free Survival

HR, 0.90 (95% CI, 0.70-1.16)
***P* = 0.1071** **(1-sided, stratified log-rank)**

Median event-free survival:
Quizartinib (n = 245): 6.0 weeks (95% CI, 0.1-8.3 weeks)
Salvage chemotherapy (n = 122): 3.7 weeks (95% CI, 0.4-5.9 weeks)



No. at Risk:															
Quizartinib	245	110	67	41	32	27	23	15	14	13	10	8	4	4	4
Salvage chemotherapy	122	24	17	8	5	3	3	2	2	2	2	0	0	0	0

QUANTUM-R: Non-Hematologic TEAEs - All Grades in ≥ 20% or Grade ≥ 3 in ≥ 5%

TEAEs	Percentage			
	Quizartinib (n = 241)		Salvage Chemotherapy (n = 94)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Sepsis or septic shock	22	16	27	18
Abdominal pain	22	2	17	1
Headache	22	< 1	17	0
Peripheral edema	21	1	23	0
Dyspnea	20	5	9	5
Constipation	20	0	23	0
Decreased appetite	20	3	11	1
Pneumonia	16	12	11	9
Hypophosphatemia	10	5	11	5

TEAEs included in this analysis were those that fulfilled the criteria for grade ≥ 3 in ≥ 5% of patients or all grades in ≥ 20% of patients in the quizartinib arm (as reported by the investigator).

QUANTUM-R: QTcF Prolongation (by central reading)

QTcF Parameter	Percentage	
	Quizartinib (n = 241)	Salvage Chemotherapy (n = 94)
Maximum QTcF interval[a]		
> 450 ms to ≤ 480 ms (grade 1)	35	6
> 480 ms to ≤ 500 ms (grade 2)	12	0
> 500 ms (grade 3)	3	0
Maximum QTcF change[a]		
> 60 ms	12	1

[a] Based on central readings of triplicate electrocardiograms.

- There were no occurrences of grade 4 QTcF prolongation
- 2 patients discontinued quizartinib treatment due to QTcF prolongation

Overall Experience in Quizartinib Trials

Characteristic	Phase 2[1] (*FLT3*-ITD population only)		Phase 2b[2]		Phase 3
	Cohort 1 (n = 112)	Cohort 2 (n = 136)	n = 38	n = 38	n = 245
Patient population					
AML treatment setting	1st salvage	2nd salvage[a]	2nd salvage[a]		1st salvage[a]
Relapsed/refractory, %	61/38	36/64	32/68	28/72	67/33
Median age (range), y	69 (66-73)	50 (39-59)	57 (19-77)	53 (20-74)	55 (19-81)
Dose, mg/day					
Starting daily dose	90, 135, and 200		30	60	30 → 60
Best response, %					
CRc (CRc+CRp+CRi)	56	46	47	47	48
ORR (CRc + PR)	77	74	61	71	69
Survival, weeks					
Median OS	25.4 (21.3-29.7)	24.0 (21.1-27.1)	20.9 (17.7-25.3)	27.3 (17.3-34.9)	27.0 (23.1-31.3)
Transplant, %					
Transplant rate	Not reported	35	32	42	32

[a]Also included patients who had been refractory to or relapsed after hematopoietic stem cell transplant.

1. Cortes JE, et al. *Lancet Oncol*. 2018 May 30. [Epub ahead of print]. 2. Cortes JE, et al. *Blood*. 2018 Jun 6. [Epub ahead of print].

Quizartinib + AZA or LDAC
Study Design

MDS, CMML or AML

FLT3-ITD and one of the following:

- Age ≥60 yrs with previously untreated disease
- Age ≥18 yrs with refractory or relapse disease with ≤1 prior treatment regimen (i.e., 1st salvage)
- Any age who received HMA and progressed to AML

N=61

Physician's Choice

Quizartinib + AZA

N=37

Phase I: n = 6
Phase II: n = 31

Quizartinib + LDAC

N=24

Phase I: n = 6
Phase II: n = 18

- **Primary endpoint**: Overall response (CR+CRi+PR+HI)
- **Secondary endpoints**: CRc (CR+CRp+CRi); overall survival and relapse free survival

Stop arm if the combination has:
- 98% probability for RR <50%, or
- 90% probability for toxicity rate >30%

Swaminathan et al. ASH 2017

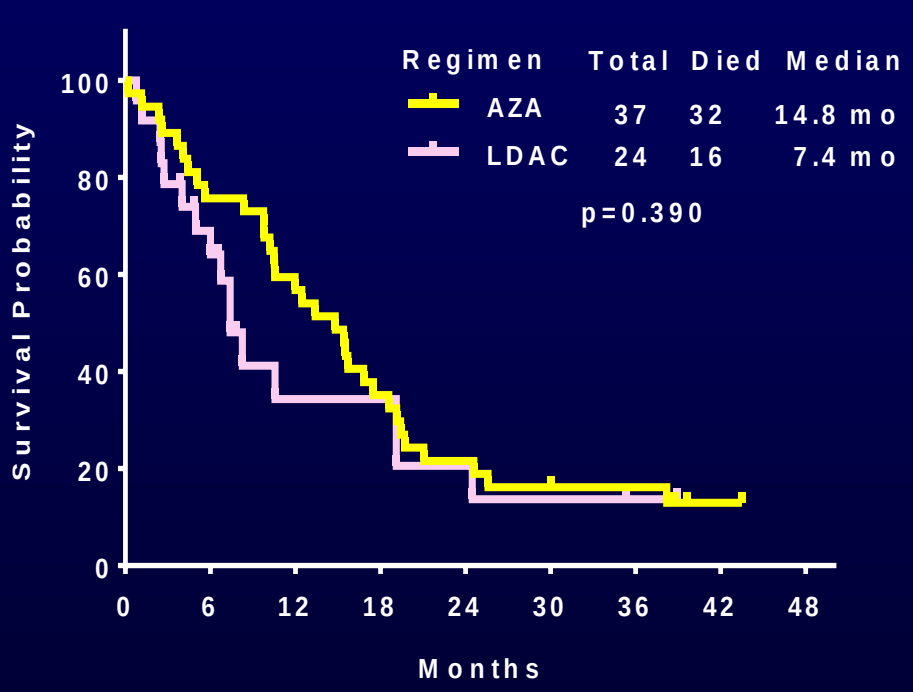
Quizartinib + AZA or LDAC
Response to Therapy

Best Response	N (%)		
	Q+AZA	Q+LDAC	Total
CR	8 (22)	2 (8)	10 (16)
CRp	2 (5)	5 (21)	7 (12)
CRi	15 (41)	7 (29)	22 (36)
CRc (CR+CRp+CRi)	25 (68)	14 (58)	39 (64)
OR (CRc+HI+PR)	26 (70)	16 (67)	42 (69)
NR	9 (24)	8 (33)	17 (28)
60-day mortality	2 (5)	0 (0)	2 (3)

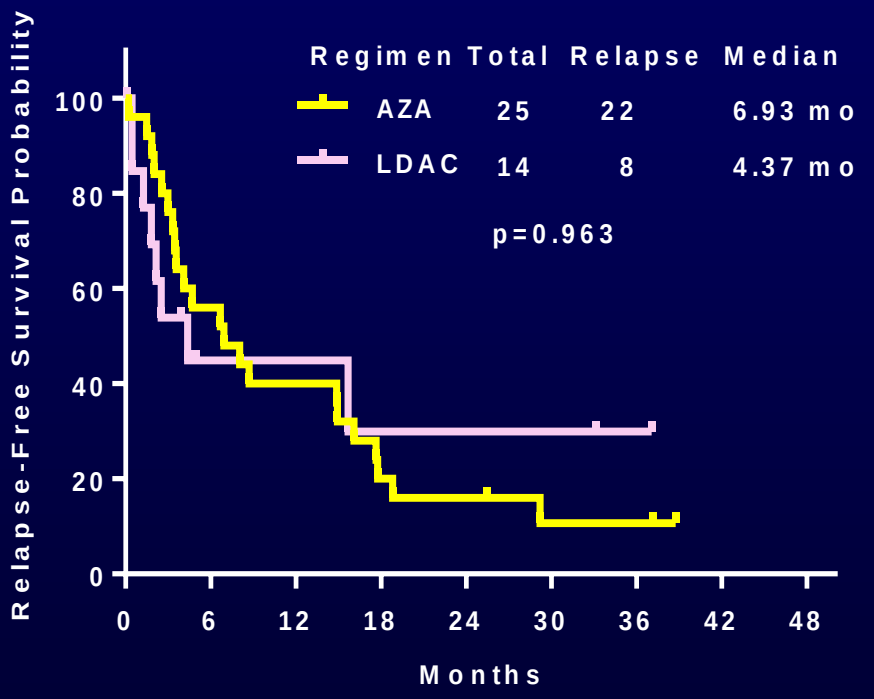
Swaminathan et al. ASH 2017

Quizartinib + AZA or LDAC
Results

Overall Survival



Relapse-Free Survival



Swaminathan et al. ASH 2017

Quizartinib in AML - Summary

- High efficacy in both FLT3 mutated and FLT3 non-mutated AML
- First FLT3 inhibitor to demonstrate OS benefit compared to standard therapy
- Favorable safety profile (>600 pts treated)
  - QTc 3-5% at currently used doses
  - Minimal non-hematologic toxicity
- Safe and effective combinations
  - More and more durable remissions
- QuANTUM-First: ongoing phase 3 study of standard chemotherapy ± quizartinib in newly diagnosed *FLT3*-ITD–mutated AML

Questions?

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