Assessment, Incidence and Clinical Significance of FLT3 Mutations in AML

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Disclosures – Richard M. Stone, MD

Consulting relationships past three years:

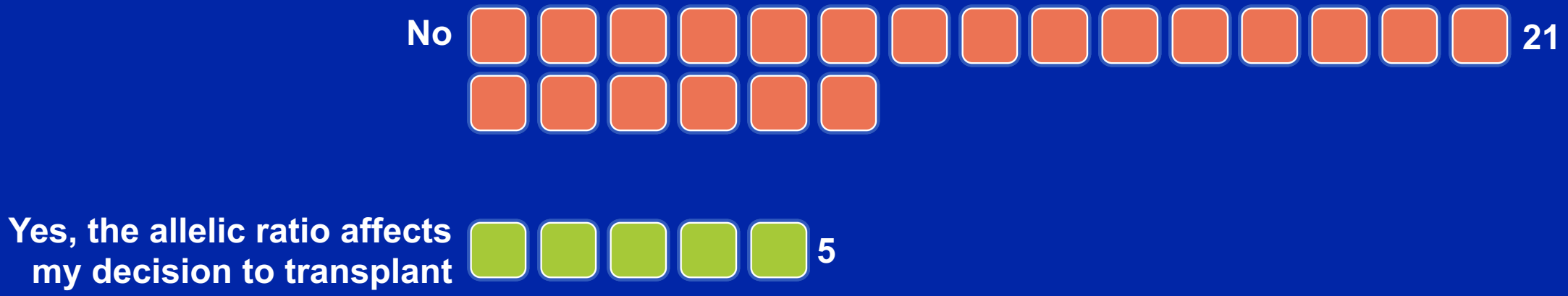
- AbbVie*; Actinium; Agios*; Amgen; argenx (DSMB); Arog*; Astellas; AstraZeneca; BioLineRx; Celgene (includes DSMB and steering committee); FUJIFILM; Janssen; Juno; MacroGenics; Novartis*; Ono; Orsenix; Pfizer; Roche; Stemline; Sumitomo; Takeda (DSMB), Trovagen

  * denotes support to my institution for clinical trials on which I was local PI

Securities, employment, promotional activities, intellectual property, gifts, grants

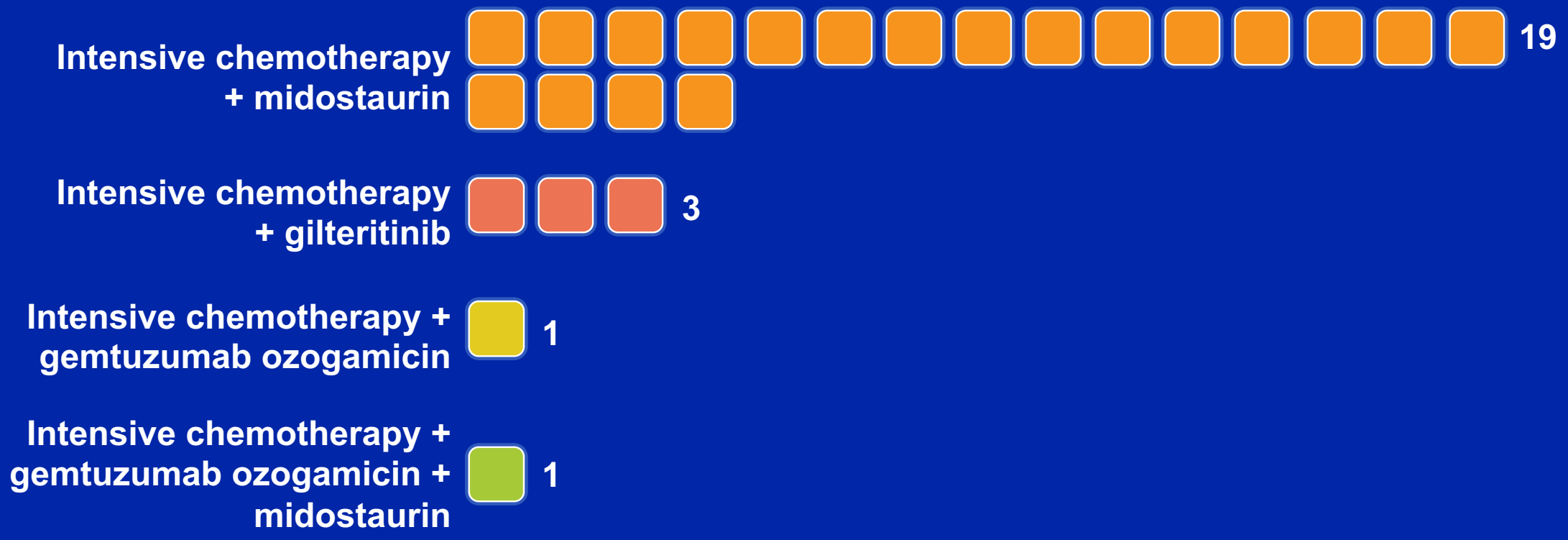
- None

A 32-year-old man is diagnosed with AML after evaluation at an urgent care for respiratory symptoms and petechiae. WBC is 55K with circulating blasts. Bone marrow demonstrates 80% CD33+ blasts with NPM1 and FLT3-ITD mutation. Does the FLT3-ITD allelic ratio affect your treatment decisions?



N = 26

A 32-year-old man is diagnosed with AML after evaluation at an urgent care for respiratory symptoms and petechiae. WBC is 55K with circulating blasts. Bone marrow demonstrates 80% CD33+ blasts with NPM1 and FLT3-ITD mutation with an allelic ratio of 0.2. What treatment would you recommend?

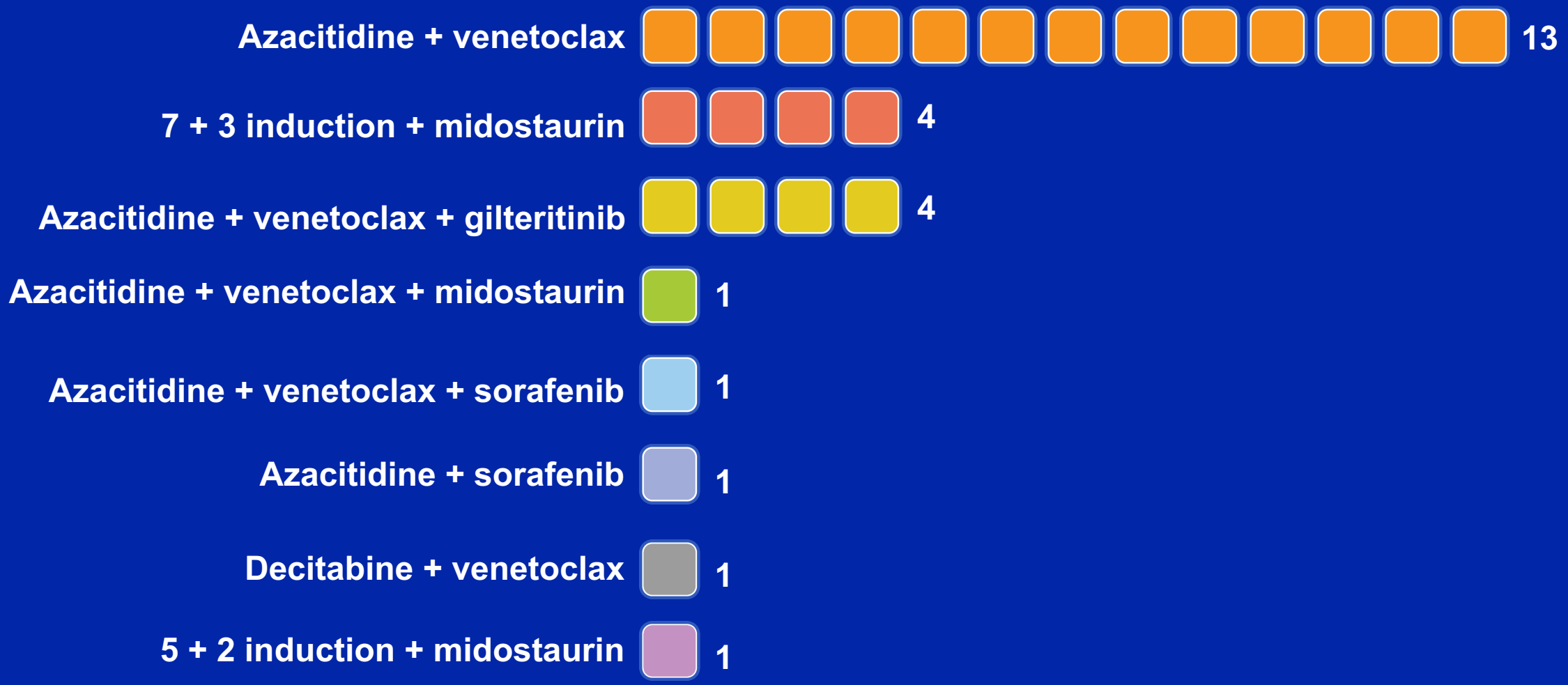


N = 24

A 76-year-old otherwise healthy woman presents with mildly symptomatic AML with normal karyotype, WBC = 20K with 50% blasts, HCT = 28 and PLT = 42. A FLT3-ITD mutation is detected by PCR with an allelic burden of 0.07. What initial therapy would you recommend?

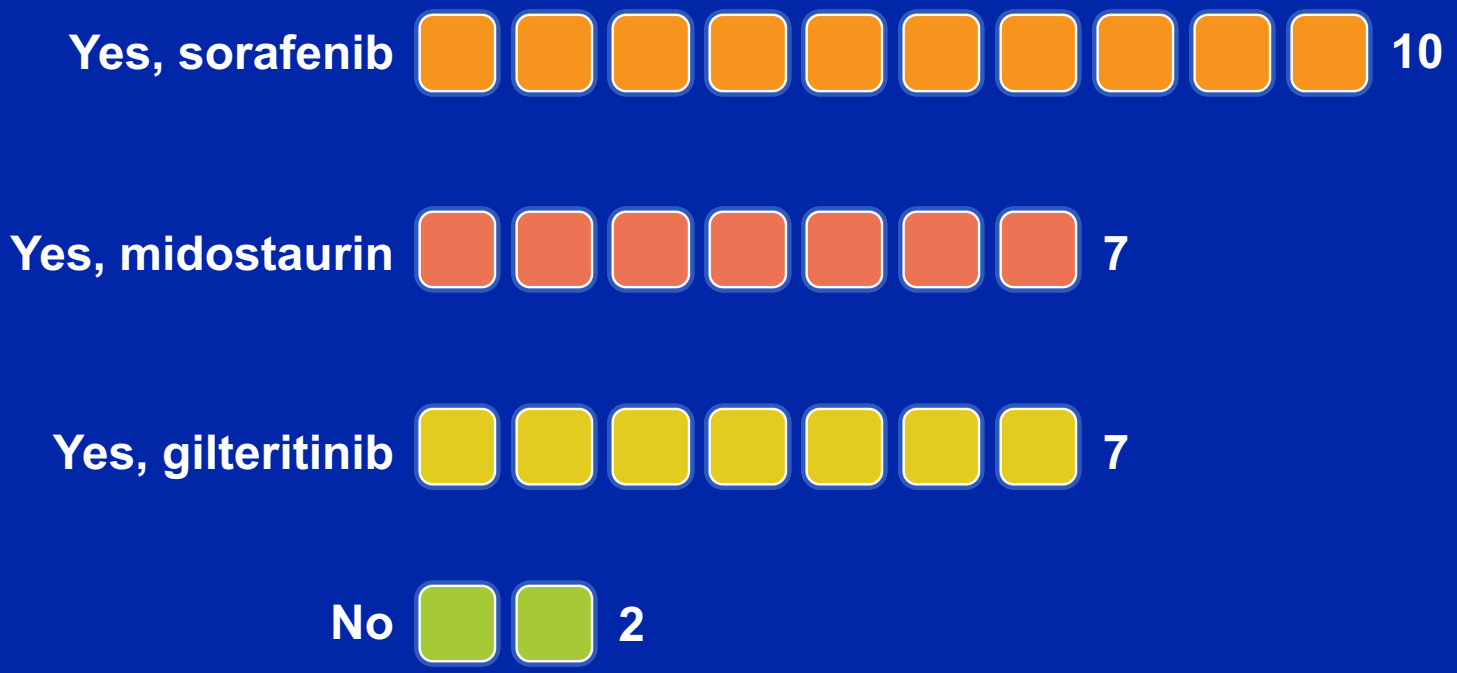
N = 25

A 76-year-old otherwise healthy woman presents with mildly symptomatic AML with normal karyotype, WBC = 20K with 50% blasts, HCT = 28 and PLT = 42. A FLT3-TKD mutation is detected by next-generation sequencing (VAF 15%). What initial therapy would you recommend?



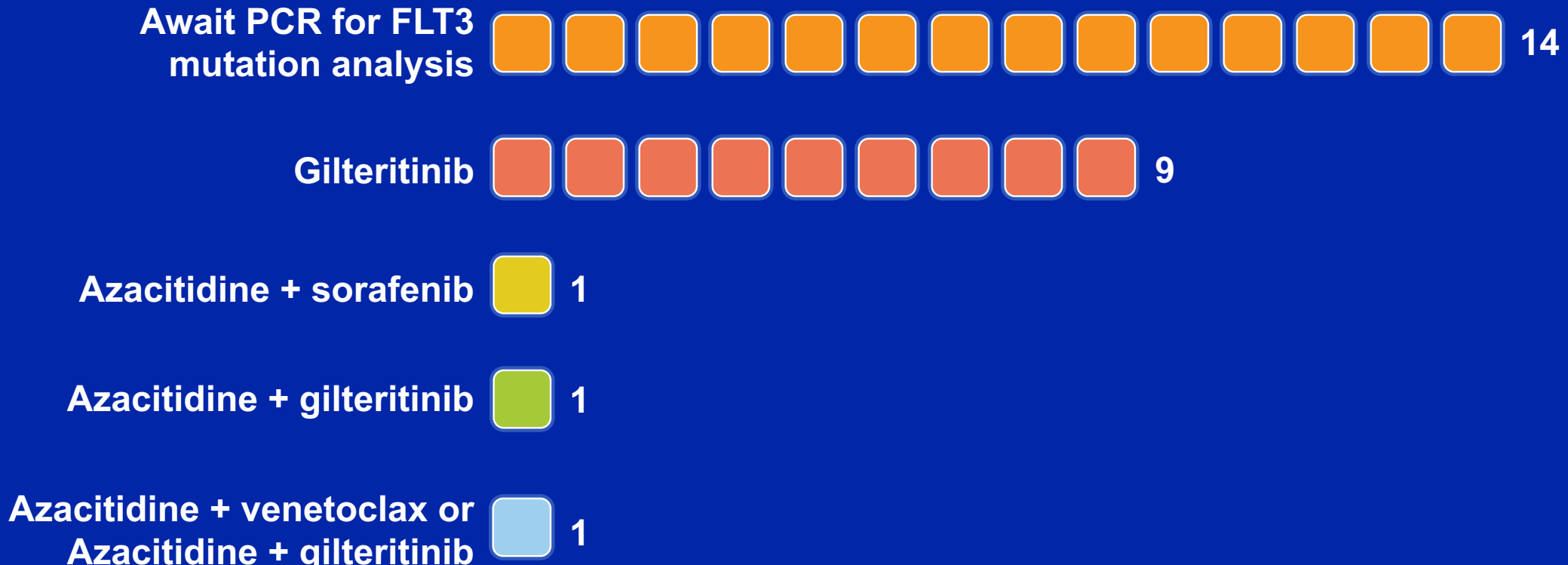
N = 26

In your patients with AML with a FLT3-ITD mutation who proceed to transplant, do you generally administer maintenance therapy with a FLT3 inhibitor?



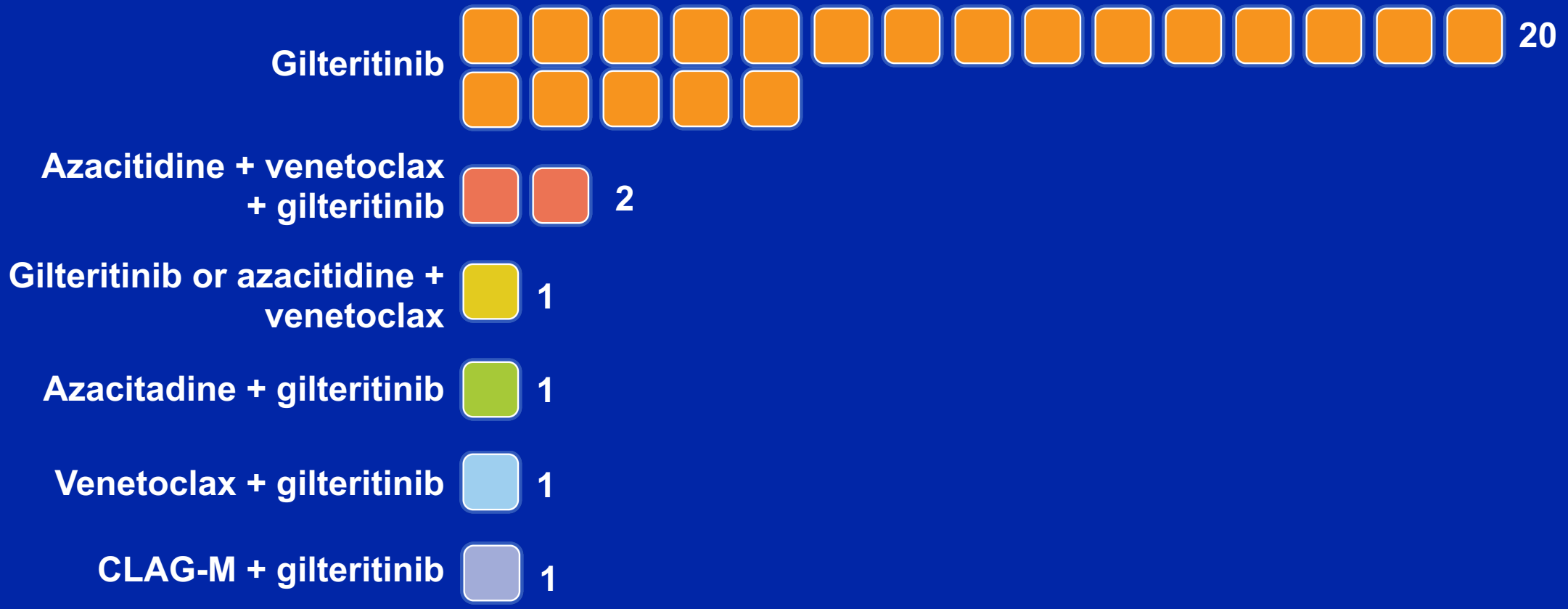
N = 26

A 62-year-old otherwise healthy man with AML with a FLT3 mutation receives 7 + 3 induction and midostaurin, attains remission and receives consolidation with 3 cycles of modified high-dose cytarabine and midostaurin. Four months after completion of therapy, he experiences disease progression. What would you recommend?



N = 26

A 66-year-old otherwise healthy man with AML with a FLT3 mutation receives 7 + 3 induction and midostaurin, attains remission and receives consolidation with 3 cycles of modified high-dose cytarabine and midostaurin. Four months after completion of therapy, he experiences disease progression and a FLT3-ITD mutation (allelic burden of 0.4) is found. What would you recommend?



N = 26

A 56-year-old patient with AML who received 7 + 3 induction is found to have both a FLT3-ITD mutation and an IDH1 mutation at the time of relapse after a 9-month remission. What would you recommend?

N = 25

45 YO MAN WITH LEUKOCYTOSIS

PRESENTING WITH FATIGUE AND GUM BLEEDING

WBC=35,500/ul, Hgb=9 mg/dl; PLT=23K/ul

PEX: Negative, except petechiae on ankles

MARROW EXAM

60% blasts, cytochemistry and immunophenotype c/w myelomonoblasts

Normal Karyotype

PCR; FLT3 ITD, 0.4 allelic ratio

NGS: DNMT3A (45% VAF), NPMI (42% VAF)

TREATMENT

Daunorubicin 60 mg/m2 d 1-3, cytarabine 200 mg/m2/d day 1-7 IVIC, midostaurin 50 mg bid day 8-21

RESULT

Achieved remission, underwent sib match allogeneic SCT, received sorafenib after GVHD ppx meds stopped.

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62 YO MAN WITH LEUKOCYTOSIS

PRESENTING WITH LETHARGY AND FATIGUE

WBC=12,500/ul, Hgb=9 mg/dl; PLT=23K/ul

PEX: Negative, except petechiae on ankles

HISTORY

Rec'd alloSCT 1.5 y ago for high risk MDS (EZH2, TET2 mutant, trisomy 8, 15% blasts; blast reduction achieved with 4 azacitidine cycles pre-transplant) off all GVHD ppx meds

MARROW EXAM

30% blasts, cytochemistry and immunophenotype c/w myeloblasts

Trisomy 8

PCR; FLT3 ITD, 0.4 allelic ratio

NGS: EZH2 (45% VAF), TET2 (42% VAF)

TREATMENT

Gilteritinib 120 mg orally daily

RESULT

Achieved remission, discussion underway re second transplant v DLI.

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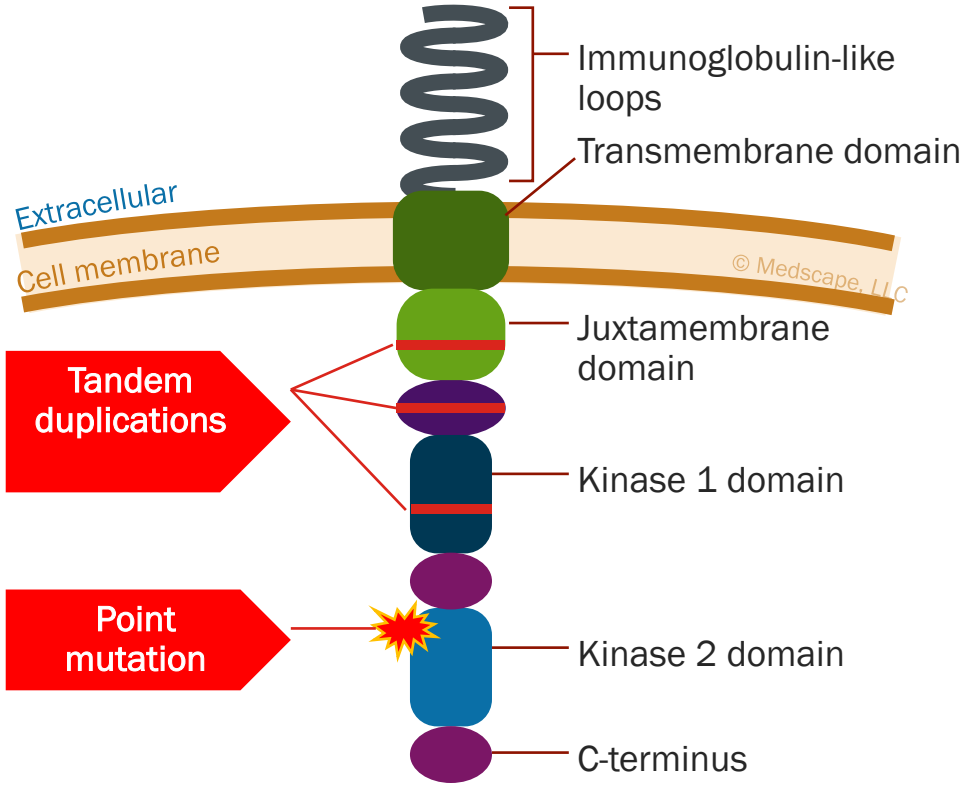
Overview

- Genomic Abnormalities in AML
- Prognostic Relevance of FLT3 mutations
- Midostaurin for upfront use
- Use of Gilteritinib in relapsed disease
- QuANTUM-R study, lack of FDA approval for quizartinib
- Ongoing Clinical Trials in mutant FLT3 AML

FLT3 Mutations in AML

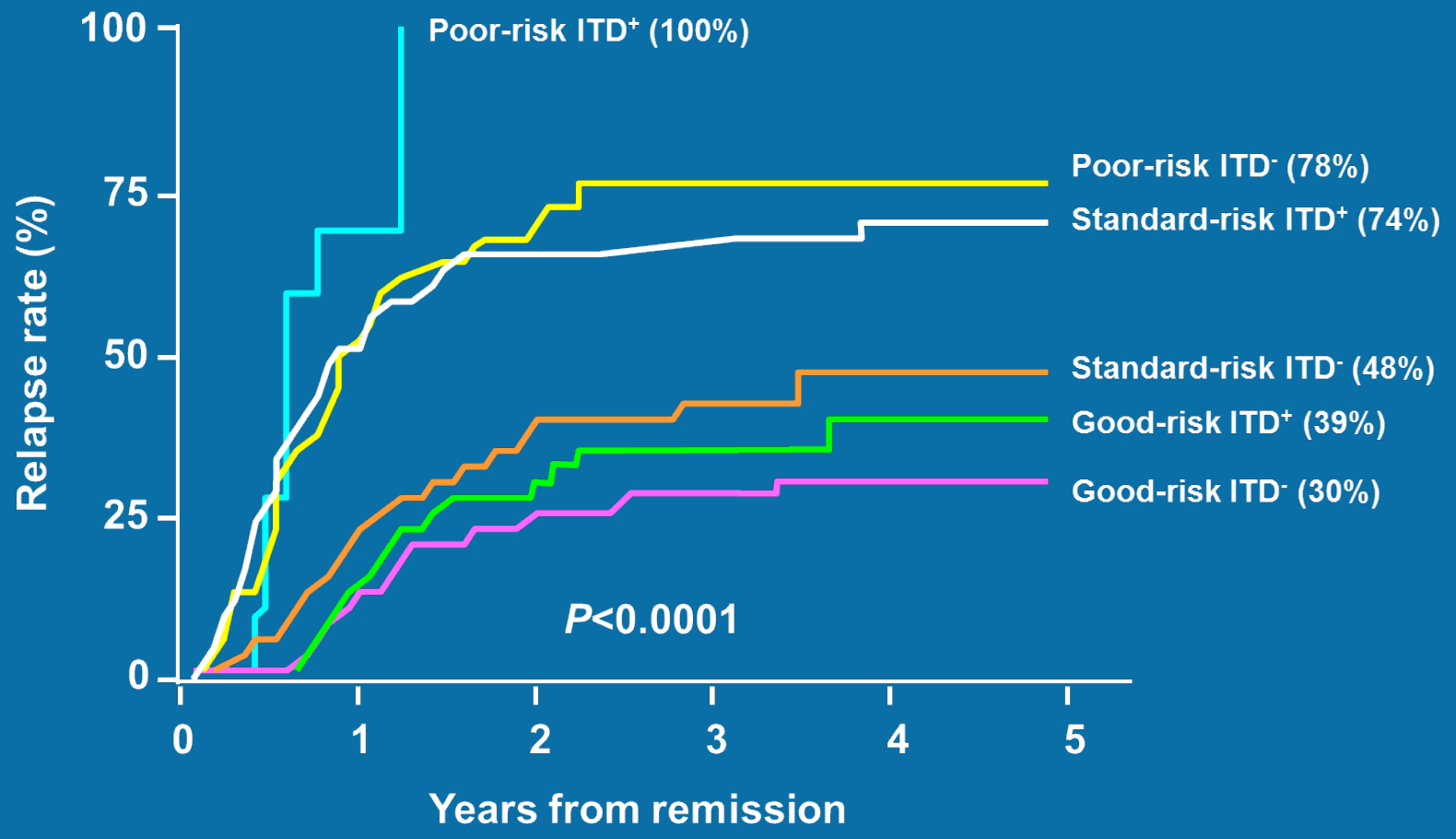
Structure of *FLT3* and AML Mutations[a,b]



- ~25% of patients with AML[c,d]
- High incidence in AML with:[c]
  - NPM1 mutations (40%)[e]
  - t(15;17)(q21;q21)/PML-RARA (40%-45%)
  - t(6;9)(p23;q34)/DEK-NUP214 (75%)[f]
- Associated with inferior prognosis:
  - Allelic ratio (mut/wt)[d]
  - ITD insertion site[g]

a. Nakao M, et al. *Leukemia.* 1996;10:1911-1918; b. Breitenbuecher F, et al. *Blood.* 2009;113:4074-4077; c. Thiede C, et al. *Blood.* 2002;99:4326-4335; d. Gale RE, et al. *Blood.* 2008;111:2776-2784; e. Boddu P, et al. *Blood Adv.* 2017;1:1546-1550; f. Slovak ML, et al. *Leukemia.* 2006;20:1295-1297; g. Whitman SP, et al. *Cancer Res.* 2001;61:7233-7239.

FLT3 ITD and relapse



Kottaridis PD, et al. Blood. 2001;98:1752-1759.

Effects of Allelic Ratio on Outcomes

Increasing Allelic Ratio

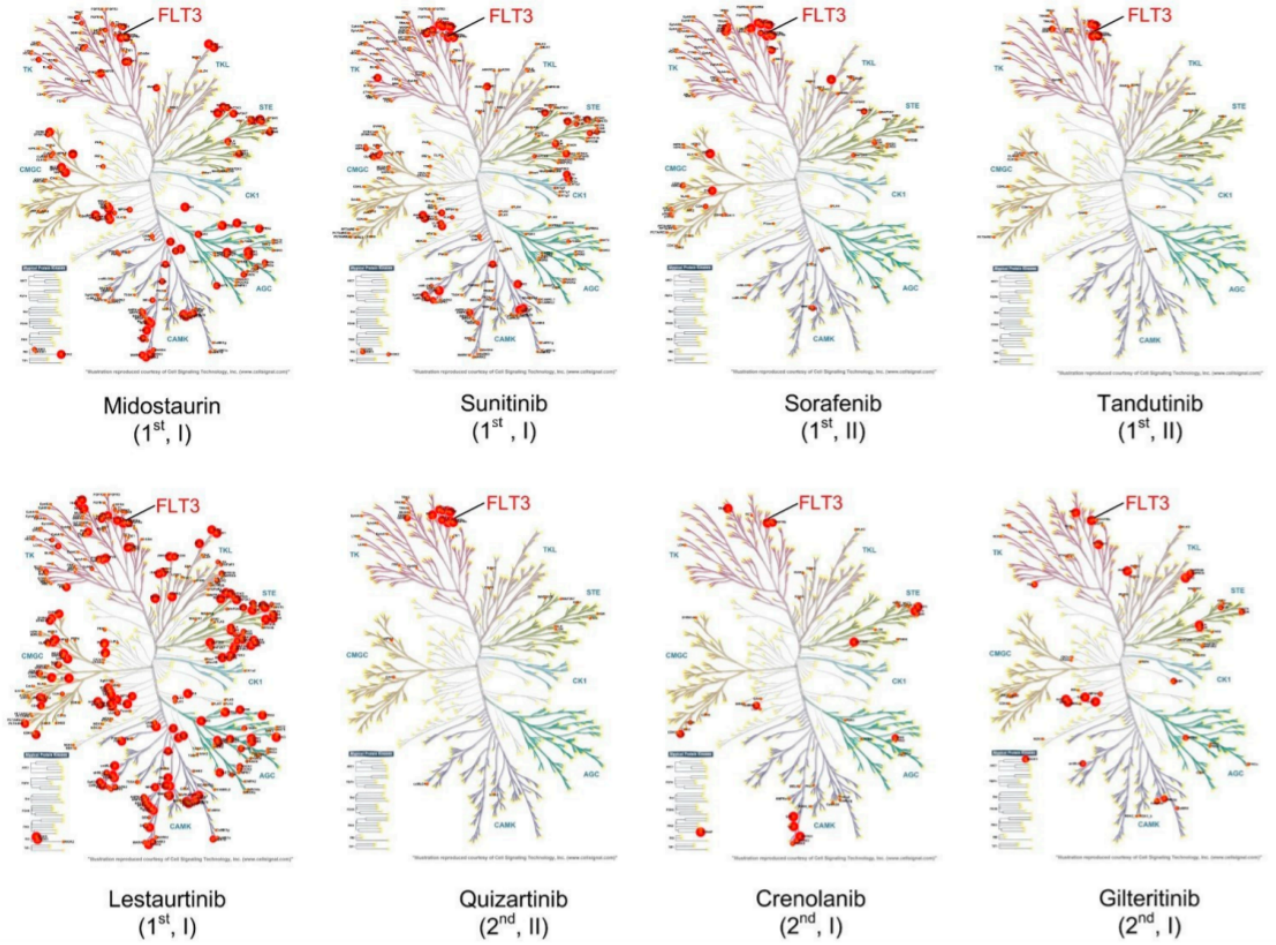
	Quartile 1 (0.01-0.20)	Quartile 2 (0.20-0.53)	Quartile 3 (0.53-0.80)	Quartile 4 (0.80-10.19)	*P* Value
CR, %	81.5	79.8	69.1	57.5	.003
Median OS, years	2.19	2.15	1.2	0.9	.0006
Median EFS, years	0.75	0.81	0.49	0.25	.001
Prognosis (CR, OS, EFS)					

Worsening Prognosis

- Higher allelic ratio is associated with poorer outcome than lower allelic ratio

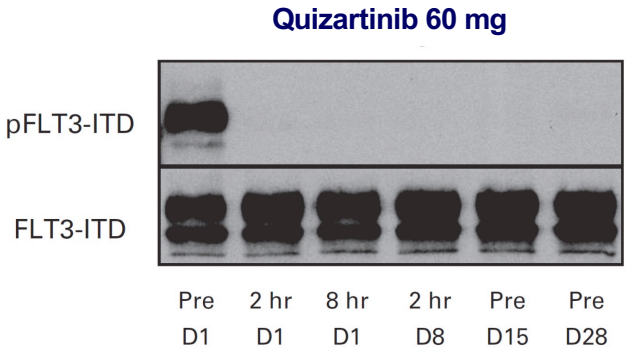
Schlenk RF, Kayser S, et al. *Blood.* 2014;124(23):3441-3449.

Tyrosine Kinase Inhibitors Selectivity and Potency

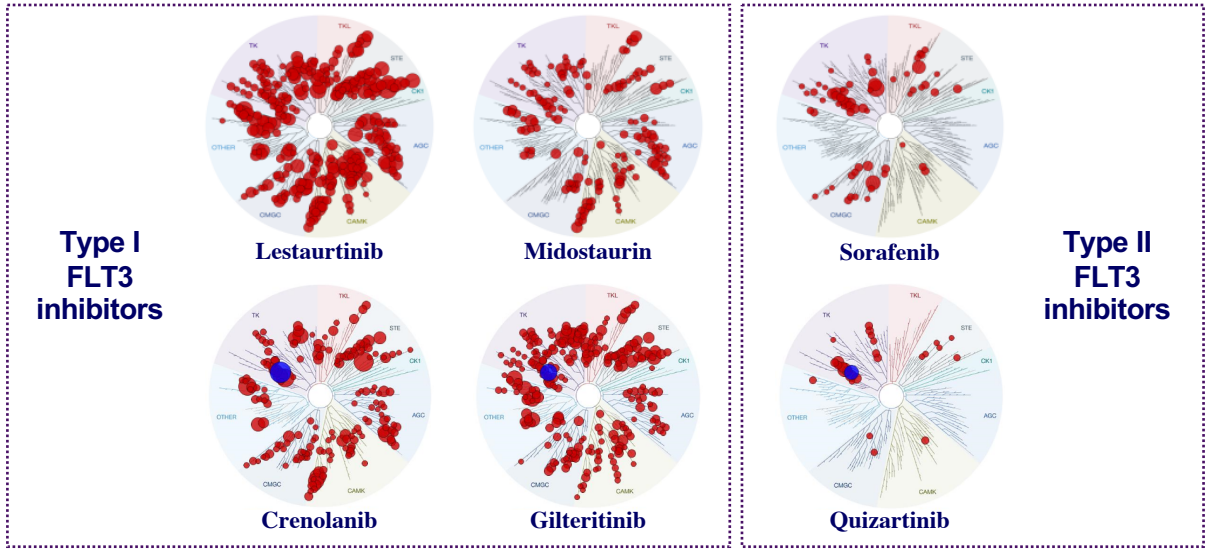


Staudt D, et al. *Int J Molec Sci.* 2018;19. pii:E3198.

Quizartinib and Gilteritinib: Second-Generation FLT3 Inhibitors



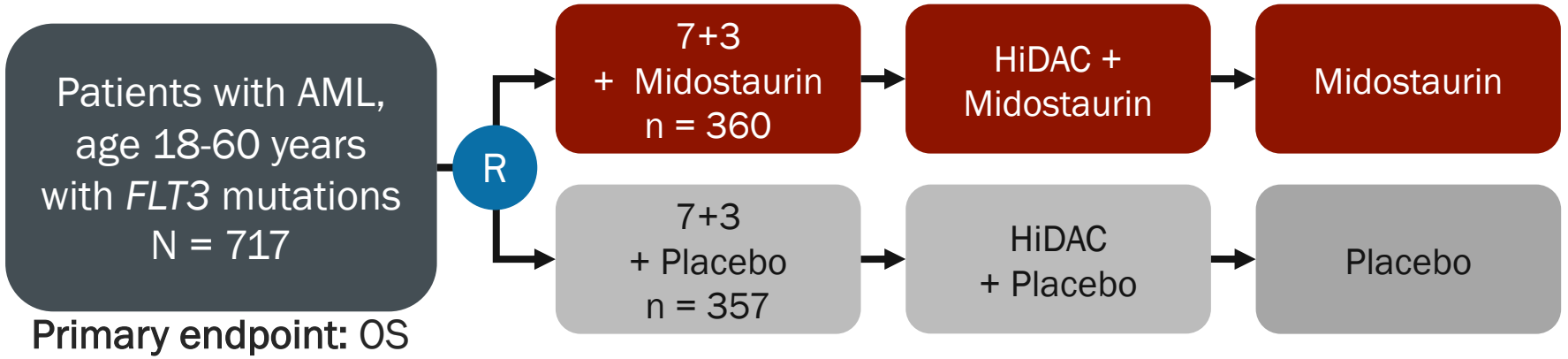
Cortes JE, et al. *J Clin Oncol*. 2013;31(29):3681-3687. Reprinted with permission. © 2013 American Society of Clinical Oncology. All rights reserved.



- Quizartinib is more potent in vivo than any other FLT3 inhibitor to date
- FLT3-TKD mutations are an established mechanism of resistance in quizartinib-treated patients
- Possible QT prolongation at higher doses

- Gilteritinib 'hits' both ITD and TKD subtypes
- Well tolerated
- Within 10-fold that of FLT3 were closely related RTKs, eg, KIT

CALGB10603 (RATIFY): Prospective Phase 3, Double-Blinded, Randomized Study of Induction and Consolidation +/- Midostaurin in Newly Diagnosed Patients < Age 60 With *FLT3*-Mutated AML



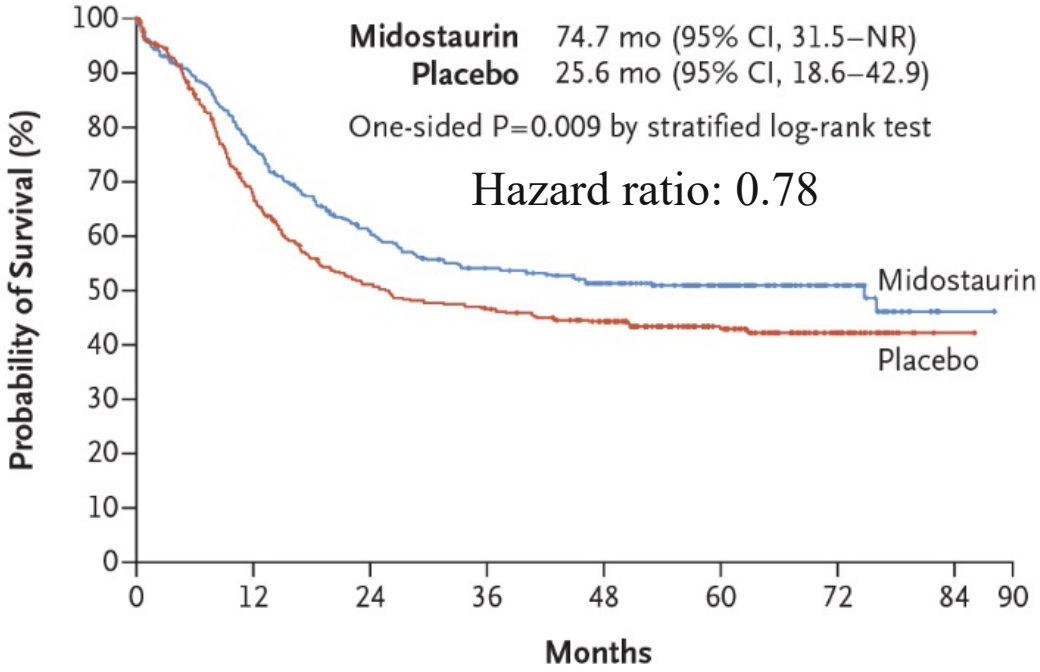
Primary endpoint: OS

Induction (Second cycle given based on day 21 marrow)	Daunorubicin	60 mg/m^2 IVP days 1-3
	Cytarabine	200 mg/m^2/day on days 1-7 via IVCI
	Midostaurin or placebo	50 mg orally twice daily on days 8-21
Consolidation (up to 4 cycles)	Cytarabine	3 gm/m^2 over 3 hours every 12 hours on days 1, 3, 5
	Midostaurin or placebo	50 mg orally twice daily on days 8-21
Maintenance	Midostaurin or placebo	50 mg orally twice daily days 1-28 x 12 cycles

Stone RM, et al. *N Engl J Med*. 2017;377:454-464.

CALGB 10603 (RATIFY): Overall Survival (Primary Endpoint)

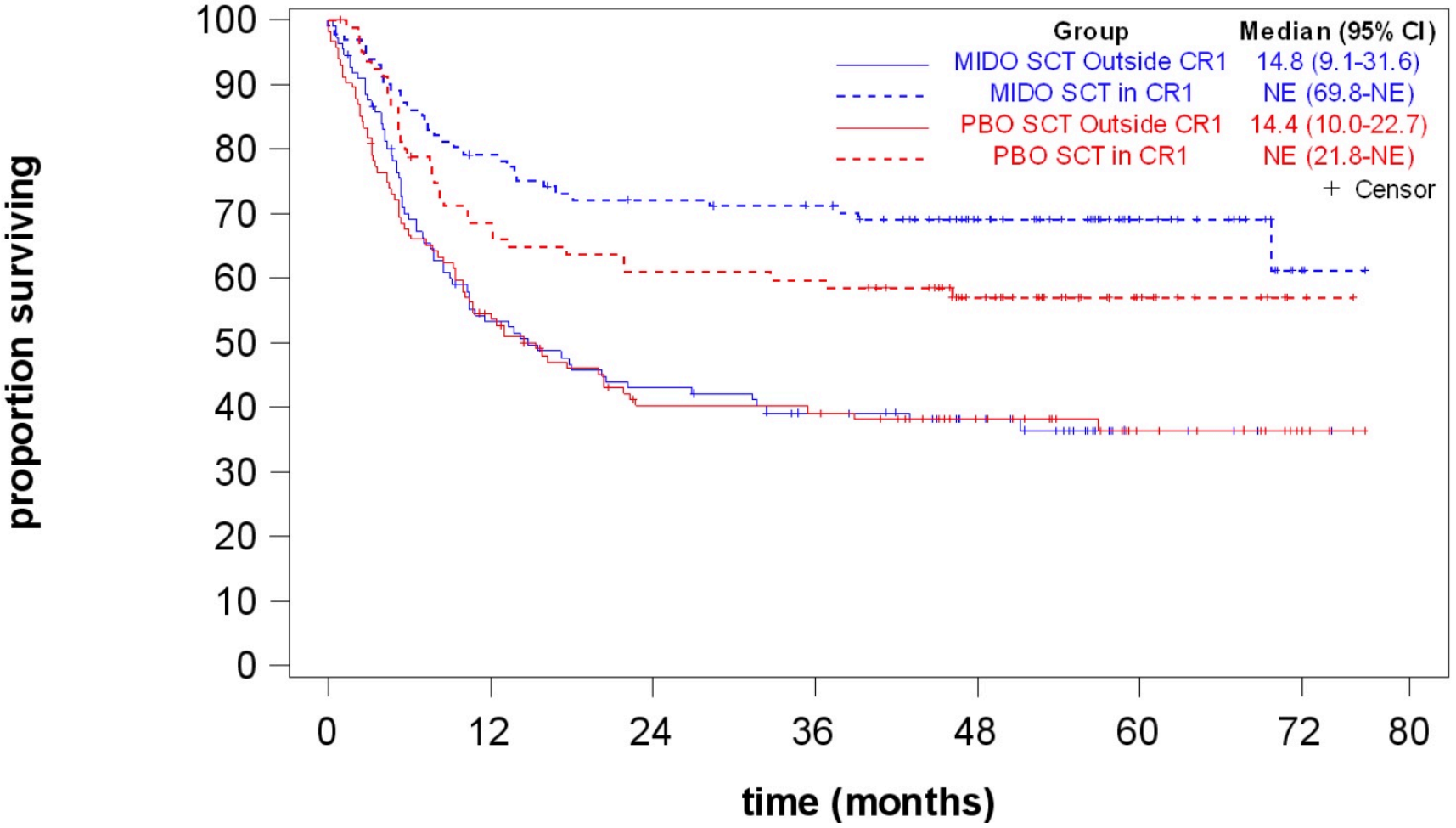
22% Reduced Risk of Death in Midostaurin Arm



Subgroup analysis demonstrates the benefit of midostaurin is maintained in *FLT3* mutation subtypes (TKD mutation; ITD mutations with a high [> 0.7] or low ratio [0.05-0.7] of mutant to wild-type alleles)

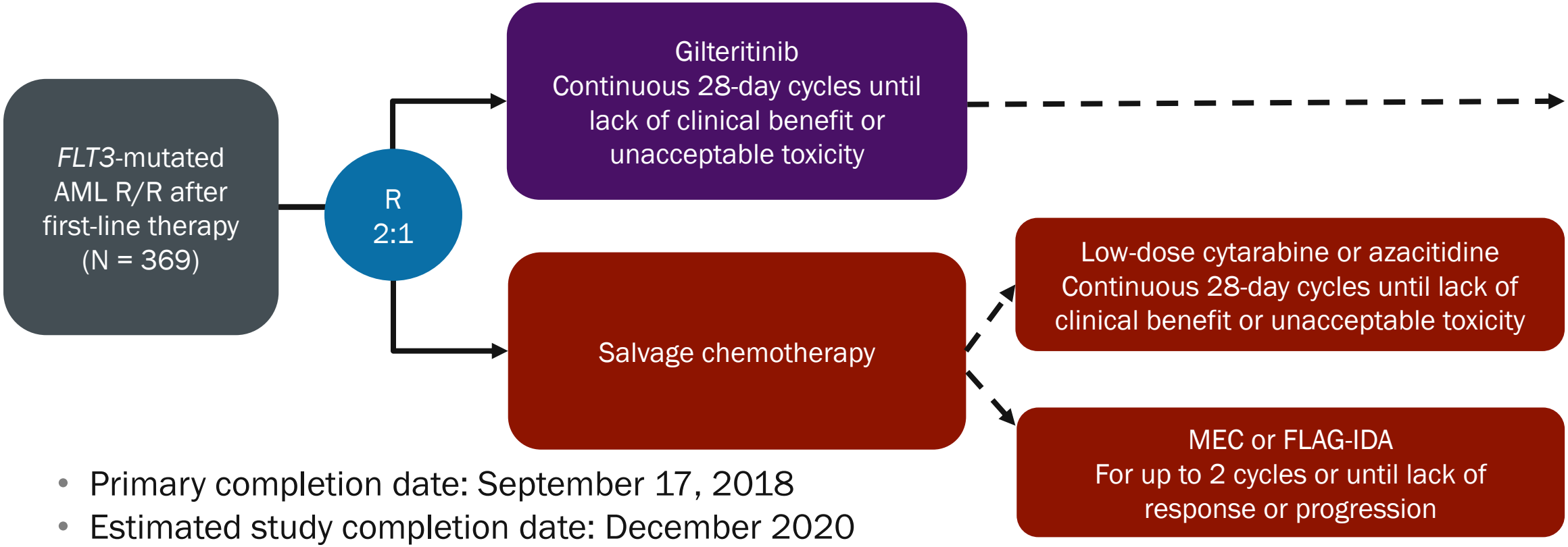
Stone RM, et al. *N Engl J Med*. 2017;377:454-464.

CALGB 10603 (RATIFY): OS After Allogeneic HSCT in CR1



Stone RM, et al. *N Engl J Med*. 2017;377:454-464.

Phase 3 ADMIRAL Trial: Gilteritinib in R/R *FLT3*-Mutated AML



- Primary completion date: September 17, 2018
- Estimated study completion date: December 2020
- Primary endpoints: OS, CR/CRh rate
- Secondary endpoints: EFS, remission, LFS, duration of remission, transplantation rate, fatigue, transfusions

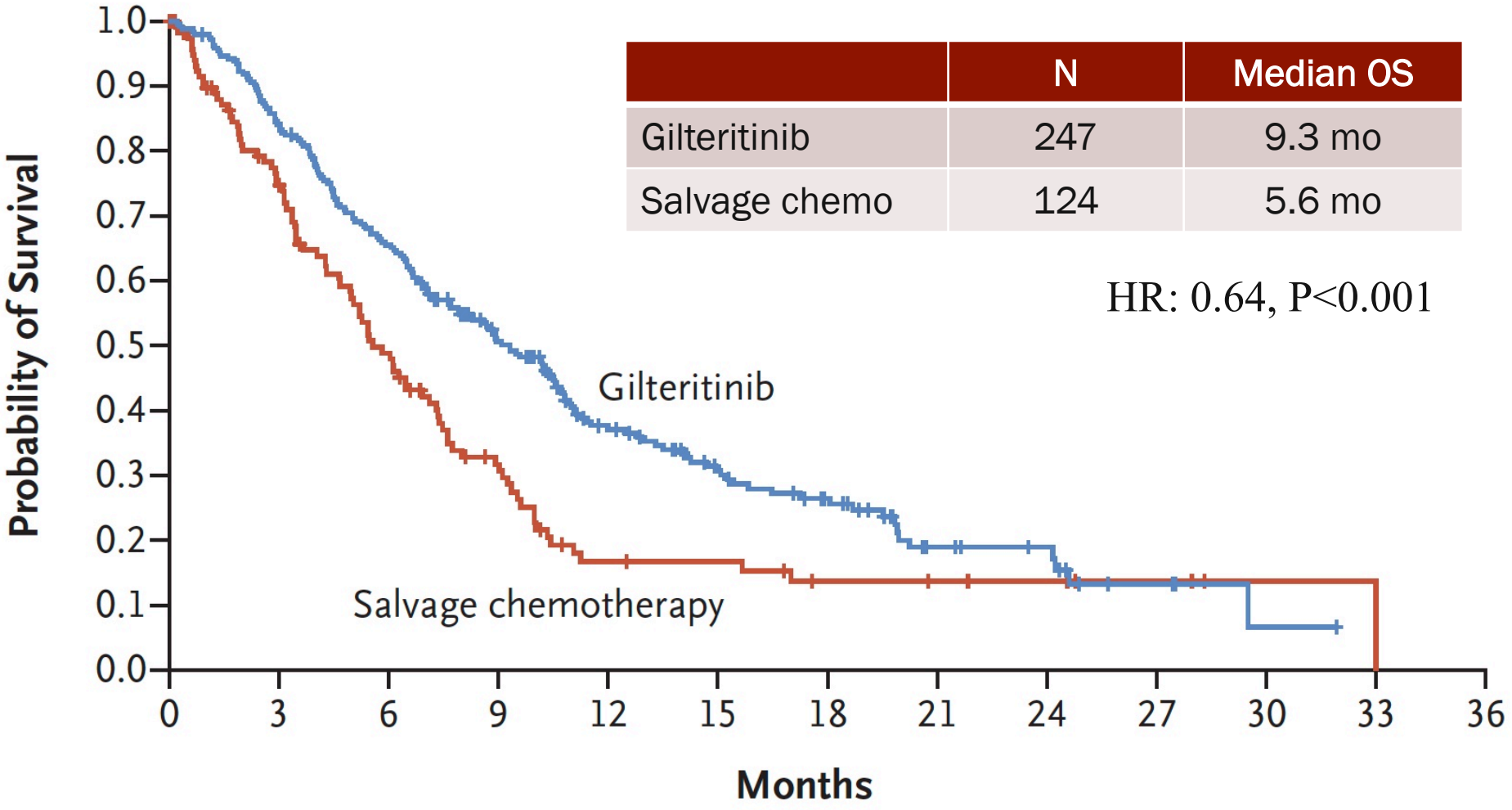
ClinicalTrials.gov. NCT02421939.

ADMIRAL: Antileukemic Responses (Intention-to-Treat Population)

Variable	Gilteritinib (N = 247)	Salvage Chemotherapy (N = 124)	Hazard Ratio or Risk Difference (95% CI)†
Median overall survival (95% CI) — mo	9.3 (7.7–10.7)	5.6 (4.7–7.3)	0.64 (0.49–0.83)
Median event-free survival (95% CI) — mo	2.8 (1.4–3.7)	0.7 (0.2–NE)	0.79 (0.58–1.09)
Response — no. (%)			
Complete remission	52 (21.1)	13 (10.5)	10.6 (2.8–18.4)
Complete remission or complete remission with partial hematologic recovery	84 (34.0)	19 (15.3)	18.6 (9.8–27.4)
Complete remission with partial hematologic recovery	32 (13.0)	6 (4.8)	ND
Complete remission with incomplete hematologic recovery	63 (25.5)	14 (11.3)	ND
Complete remission with incomplete platelet recovery	19 (7.7)	0	ND
Partial remission	33 (13.4)	5 (4.0)	ND
No response	66 (26.7)	43 (34.7)	ND
Composite complete remission‡	134 (54.3)	27 (21.8)	32.5 (22.3–42.6)
Overall response	167 (67.6)	32 (25.8)	
Median duration of remission (95% CI) — mo§	11.0 (4.6–NE)	NE (NE–NE)	NE
Time to composite complete remission — mo	2.3±1.9	1.3±0.5	NA
Median leukemia-free survival (95% CI) — mo	4.4 (3.6–5.2)	6.7 (2.1–8.5)	NE

Perl A et al. NEJM 2019;381:1728-40.

ADMIRAL: Overall Survival (Intention-to-Treat Population)



	N	Median OS
Gilteritinib	247	9.3 mo
Salvage chemo	124	5.6 mo

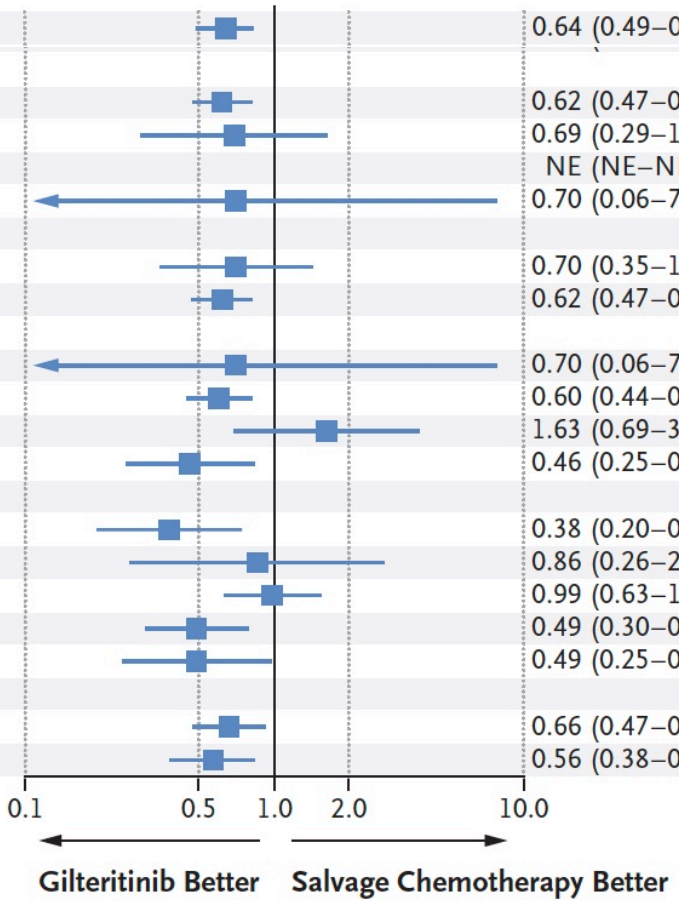
HR: 0.64, P<0.001

Gilteritinib approved in R/R AML

Perl A et al. NEJM 2019;381:1728-40.

ADMIRAL: Subgroup Analysis of Overall Survival

Subgroup	Gilteritinib (*no. of events/total no. of patients*)	Salvage Chemotherapy (*no. of events/total no. of patients*)	Hazard Ratio for Death (95% CI)
All patients	171/247	90/124	0.64 (0.49–0.83)
FLT3 mutation type			
FLT3 ITD alone	145/215	81/113	0.62 (0.47–0.82)
FLT3 TKD alone	16/21	8/10	0.69 (0.29–1.64)
FLT3 ITD and *FLT3* TKD	6/7	0	NE (NE–NE)
Other	4/4	1/1	0.70 (0.06–7.92)
Previous use of *FLT3* inhibitor			
Yes	26/32	11/14	0.70 (0.35–1.44)
No	145/215	79/110	0.62 (0.47–0.82)
Cytogenetic risk status			
Favorable	3/4	1/1	0.70 (0.06–7.92)
Intermediate	119/182	63/89	0.60 (0.44–0.82)
Unfavorable	22/26	7/11	1.63 (0.69–3.85)
Unknown	27/35	19/23	0.46 (0.25–0.84)
Response to first-line therapy per IRT			
Relapse ≤6 mo after allogeneic HSCT	24/31	16/17	0.38 (0.20–0.75)
Relapse >6 mo after allogeneic HSCT	10/17	4/8	0.86 (0.26–2.80)
Primary refractory disease without HSCT	70/98	28/48	0.99 (0.63–1.55)
Relapse ≤6 mo after composite complete remission and no HSCT	47/67	28/34	0.49 (0.30–0.80)
Relapse >6 mo after composite complete remission and no HSCT	20/34	14/17	0.49 (0.25–0.98)
Preselected chemotherapy per IRT			
High intensity	96/149	52/75	0.66 (0.47–0.93)
Low intensity	75/98	38/49	0.56 (0.38–0.84)



Perl A et al. NEJM 2019;381:1728-40.

ADMIRAL: Select Adverse Events

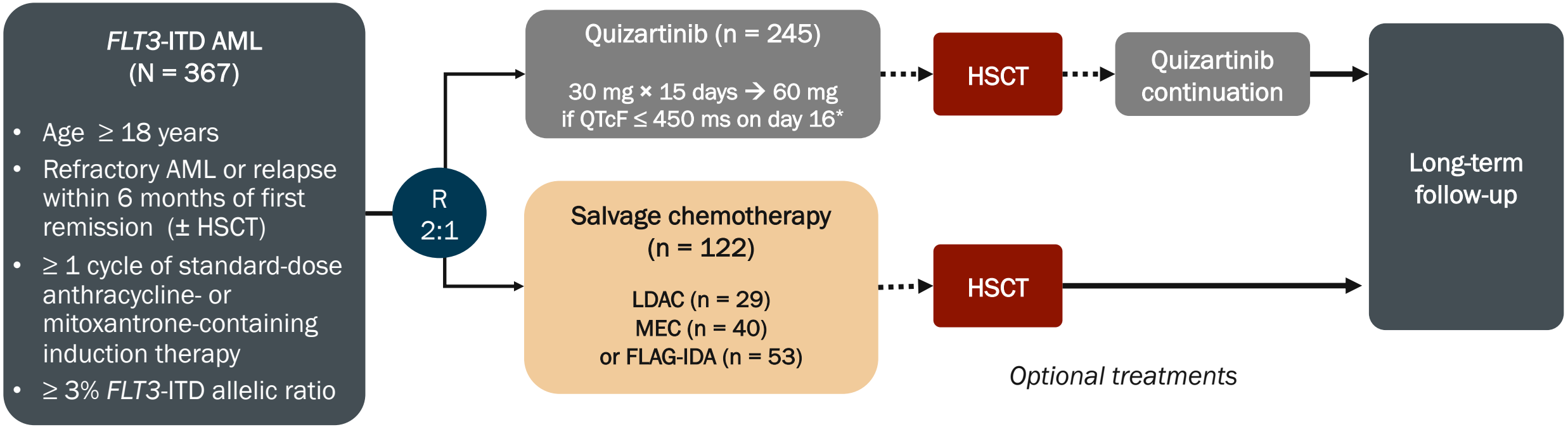
	Gilteritinib (N = 246)			Salvage Chemotherapy (N = 109)		
	Any Grade	Grade ≥3	Serious AE	Any Grade	Grade ≥3	Serious AE
Febrile neutropenia	47%	46%	31%	37%	37%	8%
Anemia	47%	41%	3%	35%	30%	0
Thrombocytopenia	26%	23%	2%	17%	17%	1%

Drug-related AEs leading to discontinuation of gilteritinib

- Elevated aspartate aminotransferase level: 4 pts (1.6%)
- Elevated alanine aminotransferase level: 3 pts (1.2%)
- Pneumonia: 3 pts (1.2%)

Perl A et al. NEJM 2019;381:1728-40.

QuANTUM-R Study Design



Primary endpoint: OS (ITT population)
Secondary endpoint: event-free survival (ITT population)
Select exploratory endpoints: CRc rate, duration of CRc, and transplant rate

*20 mg × 15 days → 30 mg if concomitantly taking CYP3A4 inhibitors.

Cortes J, et al. EHA 2018. Abstract LB2600; Cortes JE, et al. *Blood.* 2018;132:563.

QuANTUM-R: Best Response

Parameter	Quizartinib n = 245	Salvage Chemotherapy n = 122
Best response, %		
CRc*	48	27
CR	4	1
CRp	4	0
CRi	40	26
PR	21	3
ORR (CRc + PR)	69	30
No response	25	37
Nonevaluable	5	33
Median time to first CRc, weeks (range)	4.9 (3.7-19.7)	4.0 (2.0, 14.9)
Median duration of CRc, weeks (95% CI)	12.1 (10.4, 27.1)	5.0 (3.3, 12.6)

*Nominal *P* =.0001 for between-group comparison of CRc.

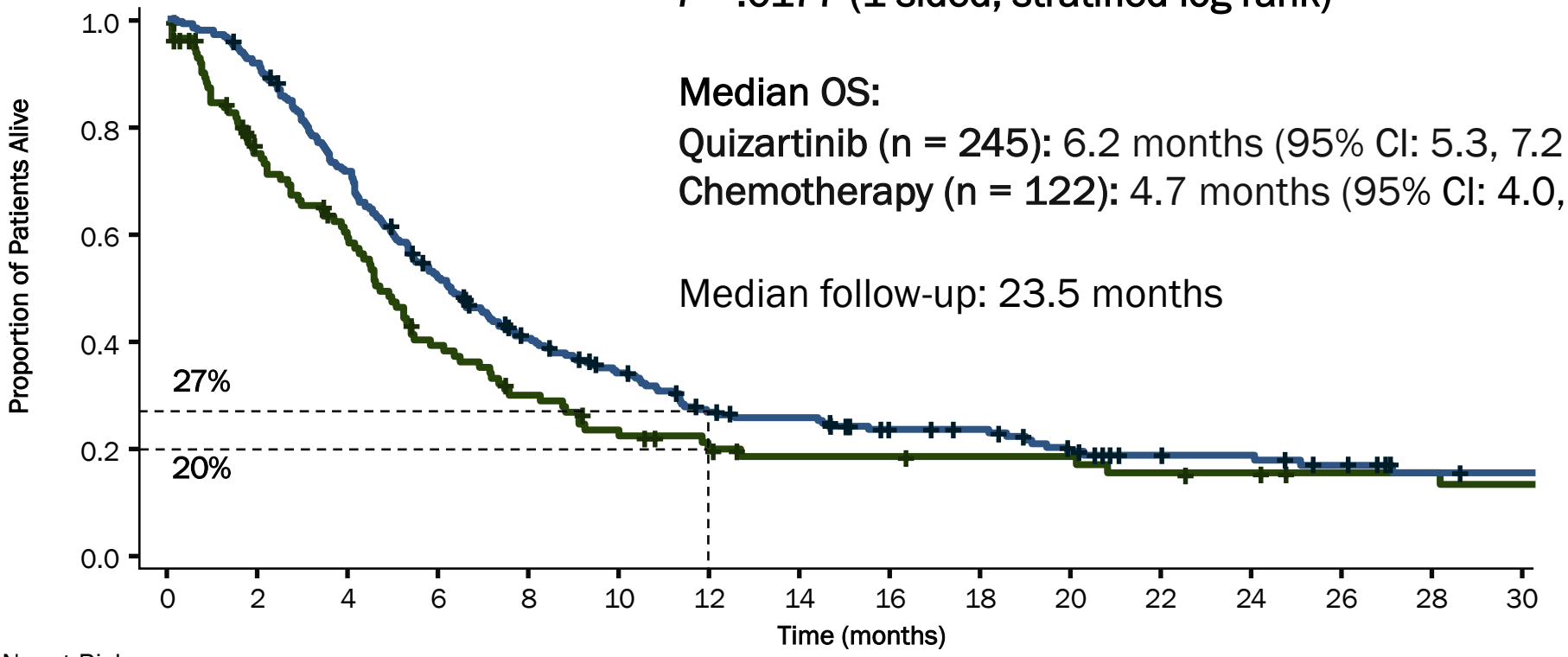
Cortes JE, et al. *Blood.* 2018;132:563.

QuANTUM-R Primary Endpoint
Overall Survival: ITT Population

HR = 0.76 (95% CI: 0.58, 0.98)
***P* =.0177 (1-sided, stratified log-rank)**

Median OS:
Quizartinib (n = 245): 6.2 months (95% CI: 5.3, 7.2 months)
Chemotherapy (n = 122): 4.7 months (95% CI: 4.0, 5.5 months)

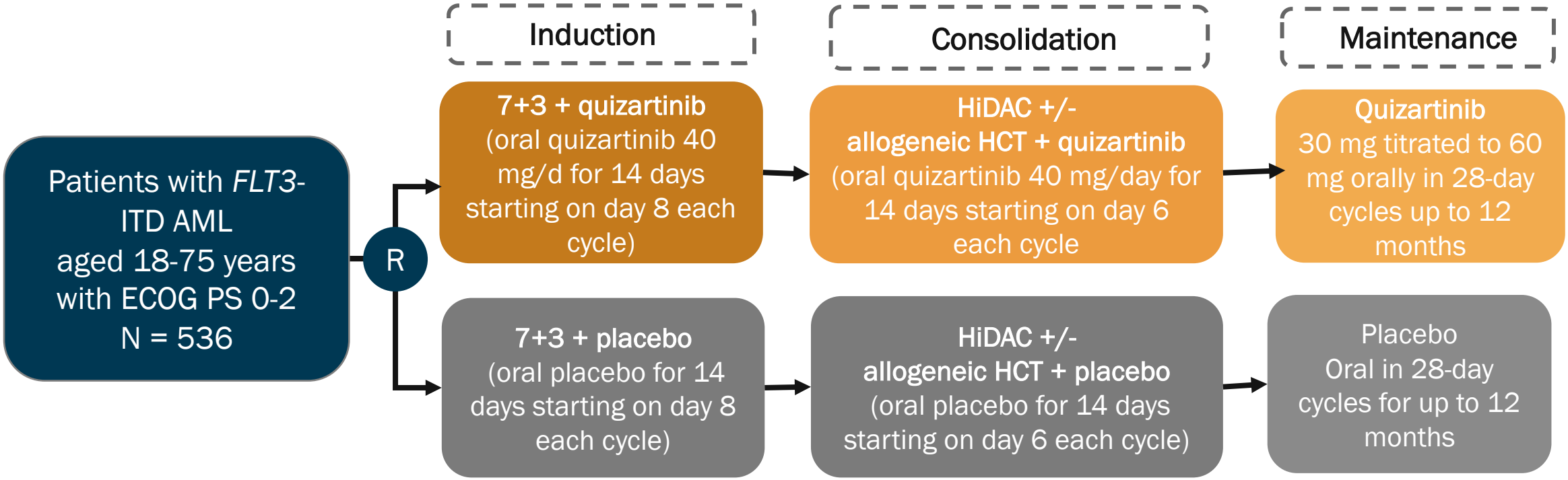
Median follow-up: 23.5 months



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

Cortes J, et al. EHA 2018. Abstract LB2600; Cortes JE, et al. *Blood.* 2018;132:563.

QuANTUM-First: Quizartinib in Induction, Consolidation, and as Maintenance in *FLT3*-ITD+ AML

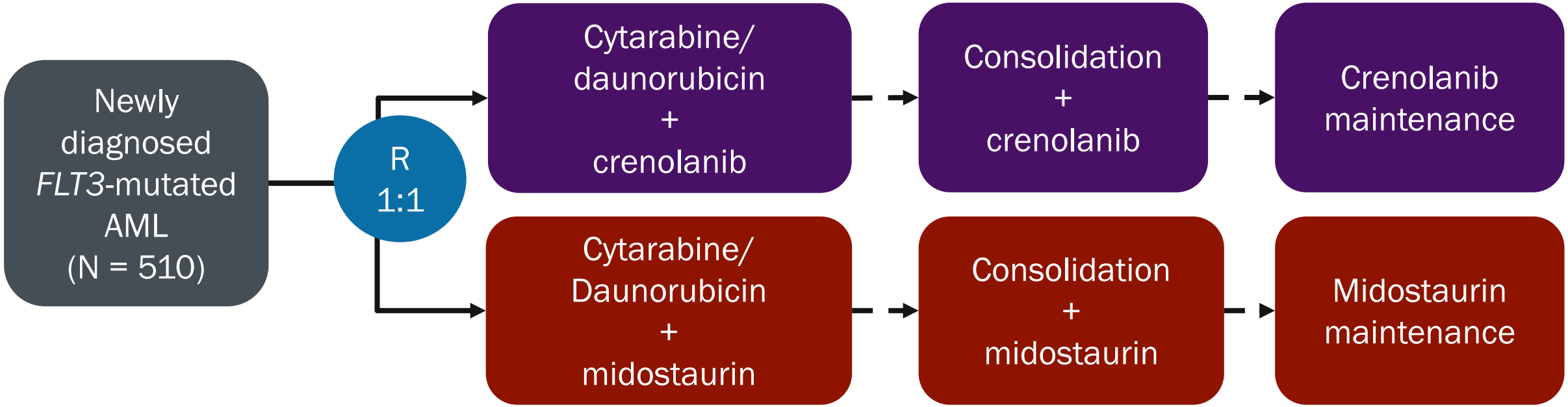


Primary endpoint: EFS

Secondary endpoints: OS, CR, CRc (CR + CRi per latest IWG definitions)

ClinicalTrials.gov. NCT02668653.

ARO-021: Phase 3 Comparison of Crenolanib With Midostaurin in Combination With Chemotherapy



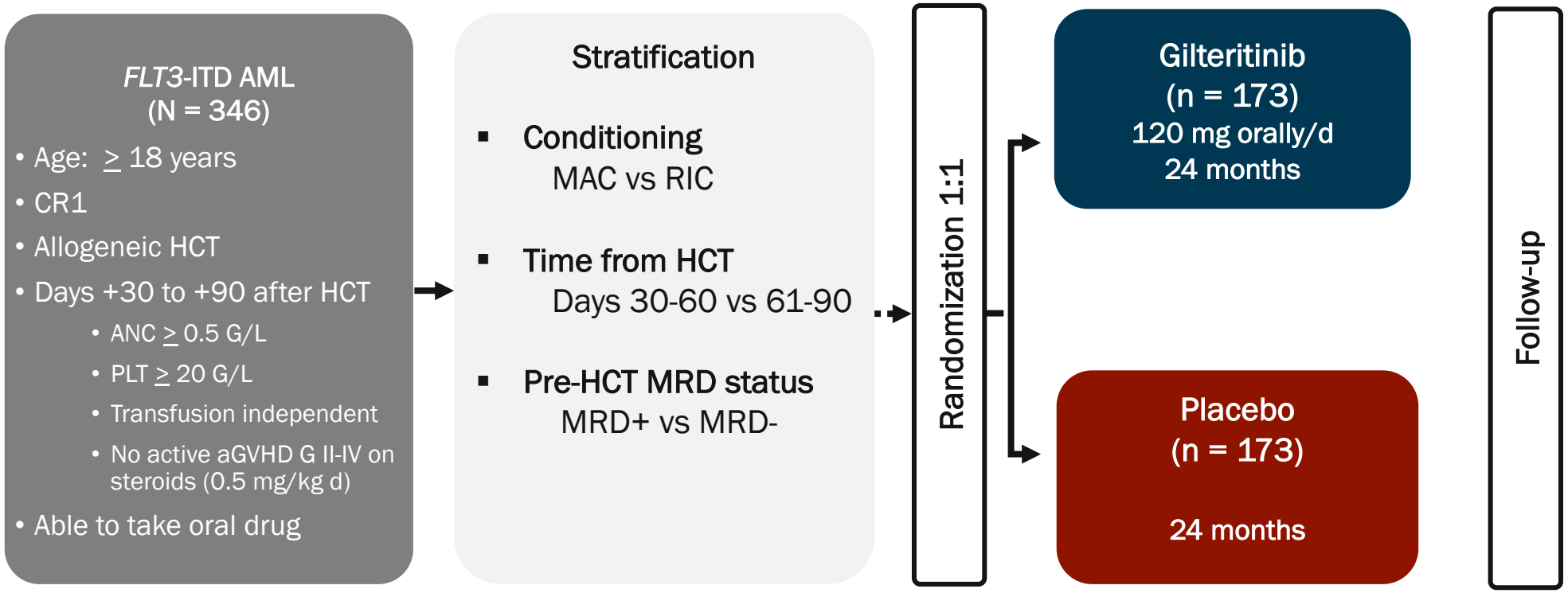
Primary endpoint: EFS

Secondary endpoints: OS, RFS, composite CR rate, DOR

Also:

- Quantum-F trial: chemo + quizartinib vs chemo alone (completed or nearly so)
- Chemo + midostaurin vs chemo + gilteritinib

Randomized, Phase 3 Trial of Gilteritinib as Maintenance After Allogeneic HCT in Patients With *FLT3*-ITD AML



Primary endpoint: RFS

Secondary endpoints: Safety, tolerability, OS, NRM, EFS at 12 and 24 months, cumulative incidence of aGVHD at 6 and 12 months, cumulative incidence of cGVHD at 24 months; cumulative incidence of detection of *FLT3*/ITD MRD at 24 months

ClinicalTrials.gov. NCT02997202.

Ongoing Clinical Trials of FLT3 Inhibitors in Combination With Venetoclax

- A Phase Ib/II Study of Venetoclax in Combination With Quizartinib in FLT3-Mutated Acute Myelogenous Leukemia (AML) (NCT03735875)

- A Multicenter, Open-Label Phase 1b Study to Assess Safety and Efficacy of Venetoclax in Combination With Gilteritinib in Subjects With Relapsed/Refractory AML (NCT03625505)

FLT3 Inhibitors: Conclusions

We have come a long way, but more mountains to climb

In 2019: FLT3 inhibitors include midostaurin, gilteritinib, sorafenib

Lots of work to do

- ?Best FLT3i w chemo upfront (midostaurin now)
- ?Role in post-transplant 'prophylactic setting'
  - (positive sorafenib trial, ongoing gilteritinib trial)
- ?Single or combo in chemo unfit or relapse
  - (single agent gilteritinib now or aza/sorafenib)