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Harry P. Erba, MD, PhD

Professor of Medicine
Division of Hematologic Malignancies and Cellular Therapy
Director, Duke Leukemia Program
Chair, SWOG Leukemia Committee
Duke University
Durham, North Carolina

Dr Erba graduated from Yale University with a Bachelor of Science degree in Biology. He earned his medical degree and doctor of philosophy in Biophysics from Stanford University School of Medicine in California. He completed his internship, residency and fellowship training at the Brigham and Women's Hospital and Harvard Medical School. He is currently Professor of Medicine in the Division of Hematologic Malignancies and Cellular Therapy at Duke University. He serves as the Director of the Leukemia Program at Duke as well as the Chair of the Leukemia Committee of the Southwest Oncology Group.

Dr Erba is interested in the clinical development of novel therapies for acute myeloid leukemia, myelodysplastic syndromes, myeloproliferative neoplasms (such as chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, and myelofibrosis), and acute lymphoblastic leukemia. He has served as the principal investigator for studies on small-molecular inhibitors, antibody-drug conjugates, and cytotoxic chemotherapy. Dr Erba's research has appeared in numerous peer-reviewed publications, including Blood, Journal of Clinical Oncology, Leukemia & Lymphoma, Lancet Haematology, and Clinical Lymphoma, Myeloma & Leukemia.

Most Important Advances in Myeloid Cancers

Two available drugs in a single AML indication: How do you choose?

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Duke University

DukeHealth

VIALE-A Study Design

Eligibility

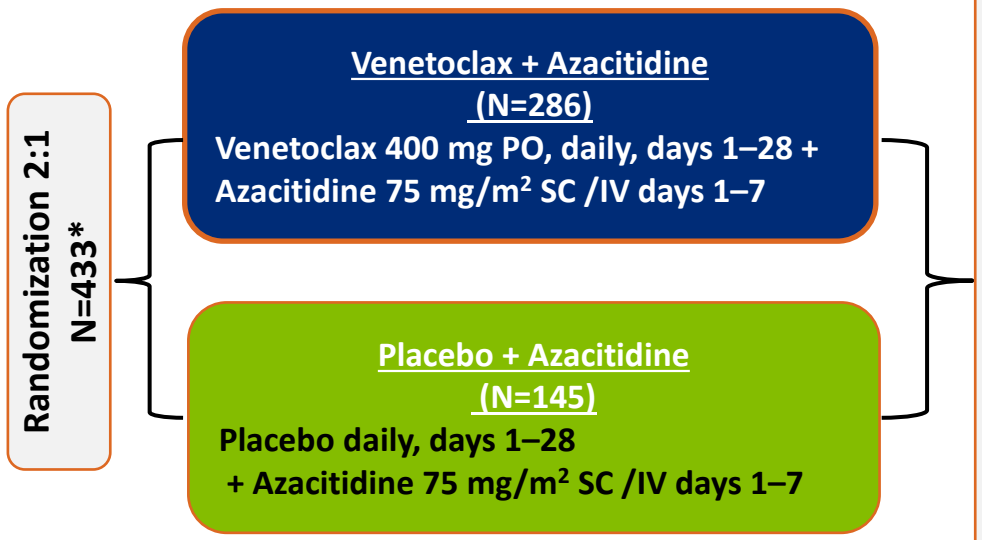
Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ≥75 years of age
  - 18 to 74 years of age with at least one of the co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤ 65% or FEV1 ≤ 65%
    - ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

Treatment



Endpoints

Primary

- Overall survival

Secondary

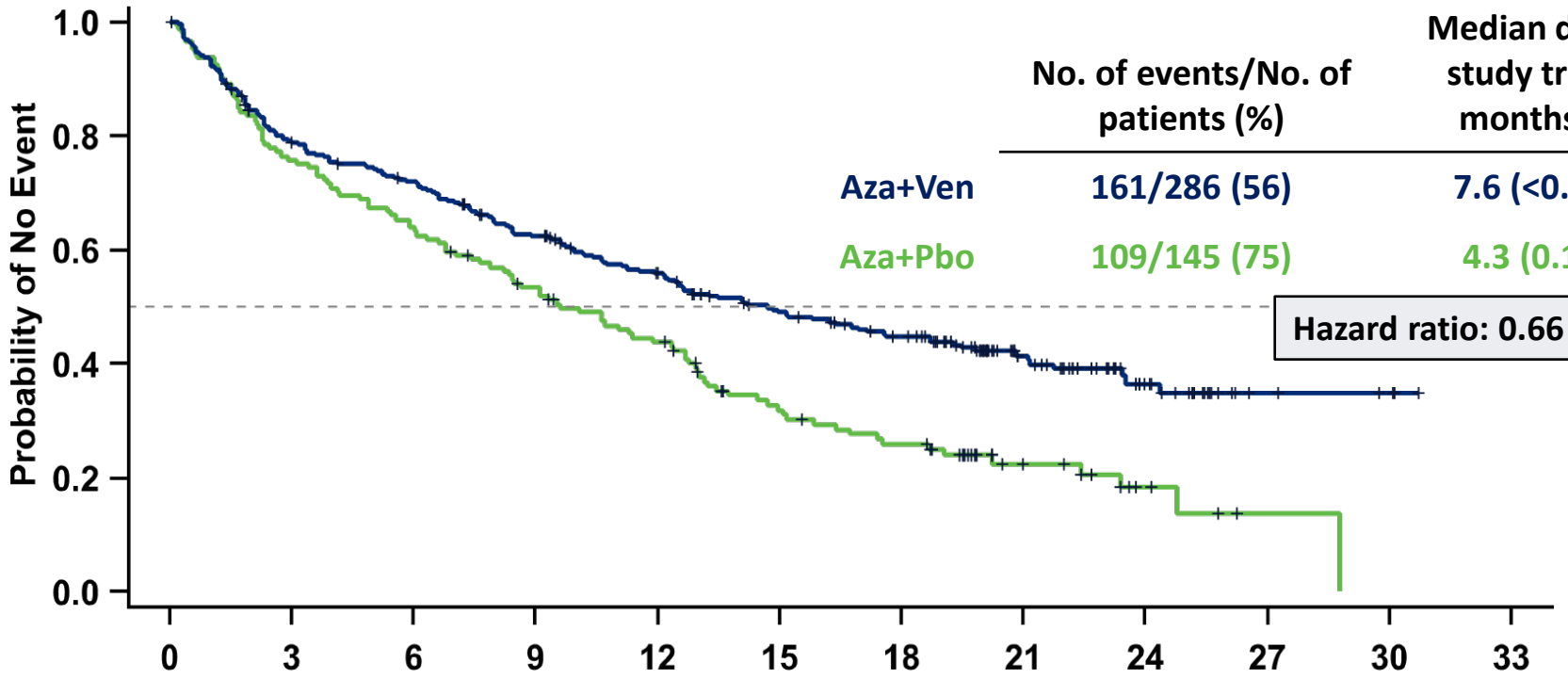
- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

Randomization Stratification Factors Age (<75 vs. ≥75 years); Cytogenetic Risk (intermediate, Poor); Region

Venetoclax dosing ramp-up **Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg
Cycle 2 → Day 1-28: 400 mg

DiNardo C, et al. *N Engl J Med* 2020; 383(7): 617-629.

VIALE A: Overall Survival



	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)

Hazard ratio: 0.66 (95% CI: 0.52 – 0.85), p<0.001

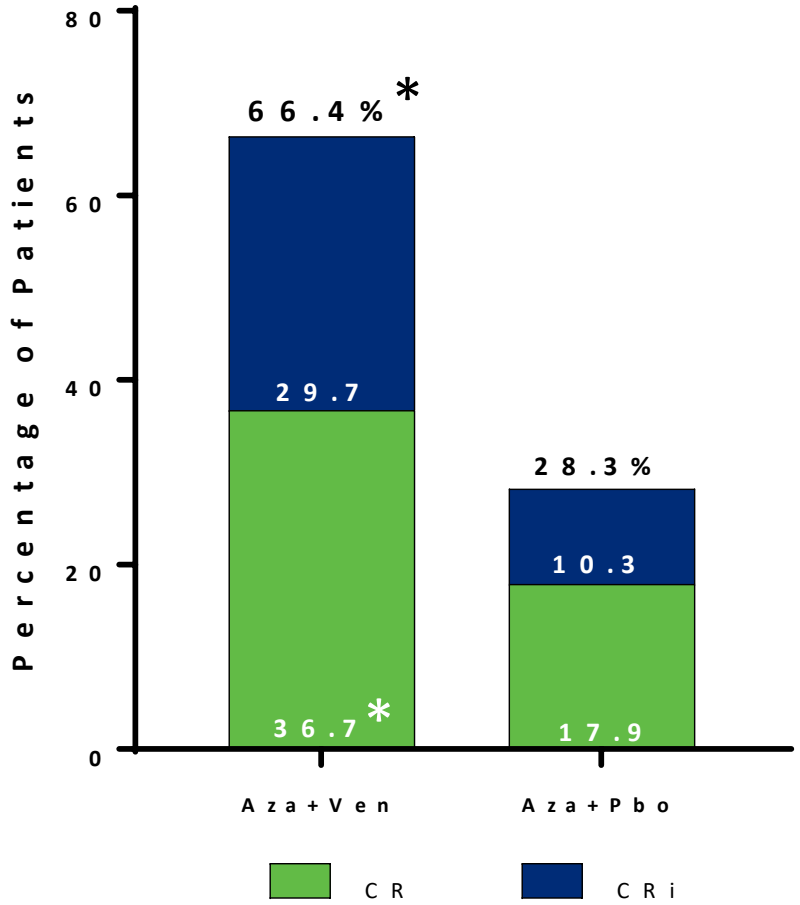
Patients at Risk

Aza+Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza+Pbo	145	109	92	74	59	38	30	14	5	1	0	0

Median follow-up time: 20.5 months (range: <0.1 – 30.7)

DiNardo C, et al. *N Engl J Med* 2020; 383(7): 617-629.

VIALE A: Composite Response Rate (CR+CRi)



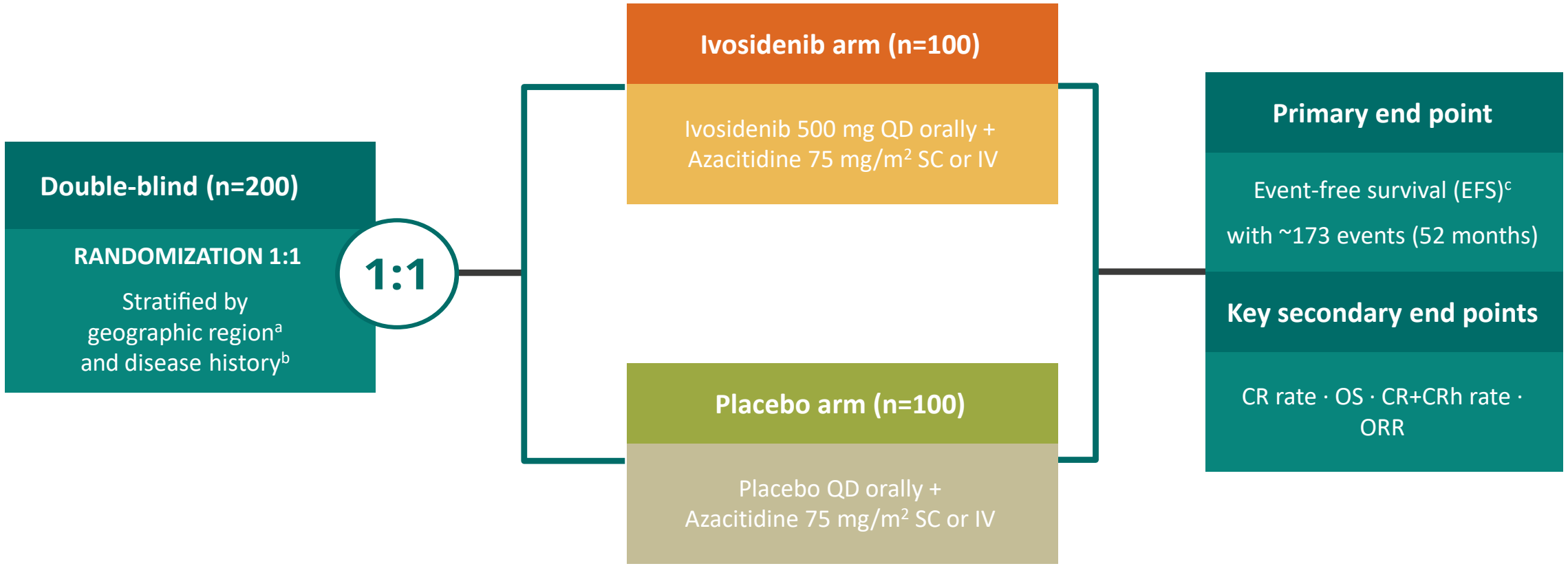
	No. of treatment cycles, median (range)	Median time to CR/CRi, Months (range)	*CR+CRi by initiation of Cycle 2, n (%)
Aza+Ven (n=286)	7.0 (1.0 – 30.0)	1.3 (0.6 – 9.9)	124 (43.4)
Aza+Pbo (n=145)	4.5 (1.0 –26.0)	2.8 (0.8 – 13.2)	11 (7.6)

*CR+CRi rate, CR rate, and CR+CRi by initiation of cycle 2 are statistically significant with p<0.001 by CMH test

Aza: Azacitidine; Pbo: Placebo; Ven: Venetoclax; CR: Complete remission; CRi: CR with incomplete-count recovery; CR was defined as absolute neutrophil count >10^3/µL, platelets >10^5/µL, red cell transfusion independence (TI), and bone marrow with <5% blasts; CRi was defined as all criteria for CR, except for neutropenia ≤10^3/µL or thrombocytopenia ≤10^5/µL.
CR + CRi rate was compared using Cochran-Mantel-Haenszel (CMH) test stratified by age (18 – < 75, ≥ 75) and cytogenetic risk (intermediate, poor).

DiNardo C, et al. *N Engl J Med* 2020; 383(7): 617-629.

AGILE: study design and end points



- As of the data cutoff date (18March2021), 146 patients have been randomized (IVO+AZA, n=72; PBO+AZA, n=74).
- As of 12May2021, the IDMC recommended to halt enrollment based on a noted difference in clinical importance between the treatment groups, not related to safety.
- A total of 148 patients were enrolled at 155 active sites in 20 countries.

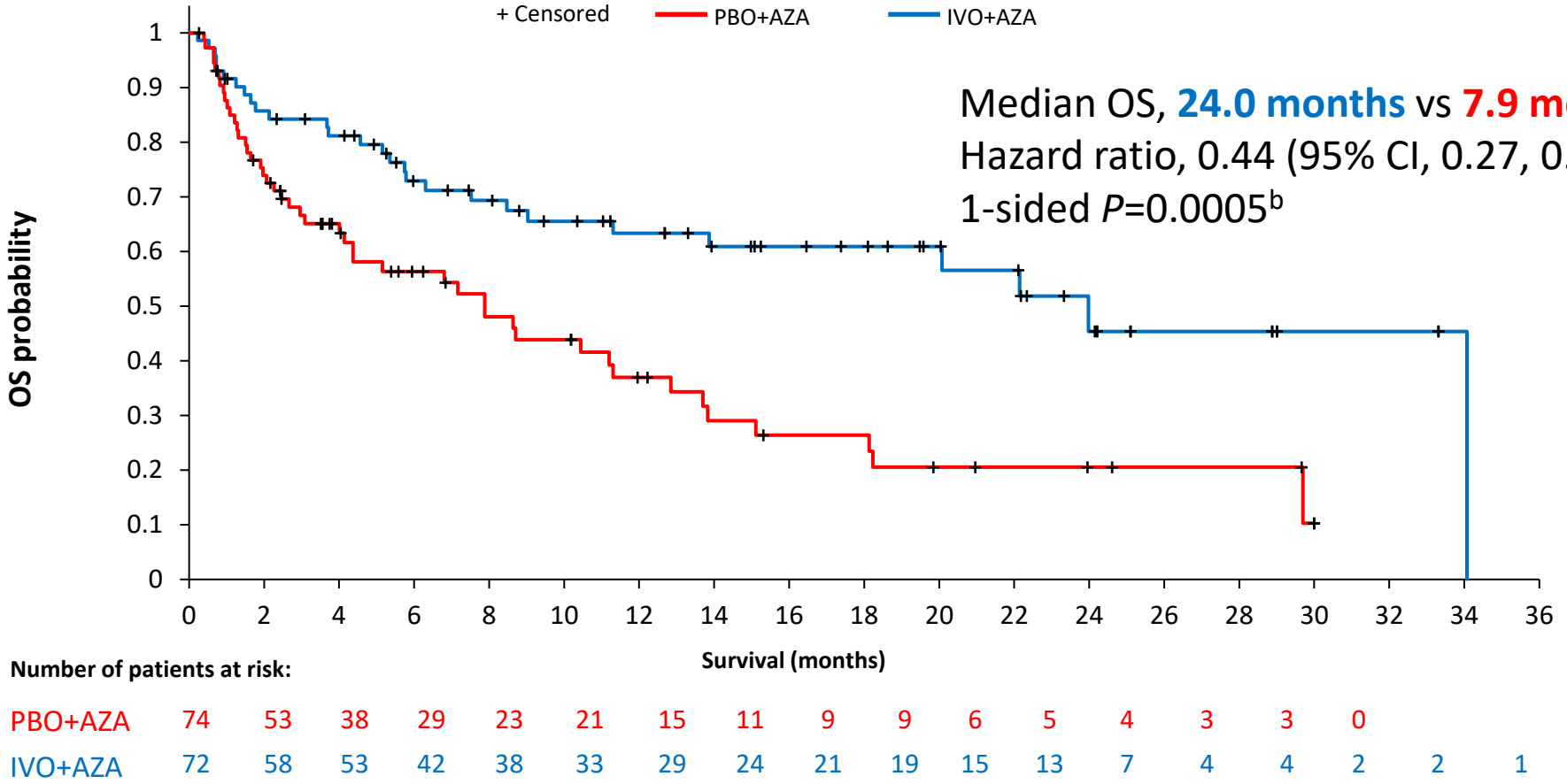
Montesinos P, et al. *N Engl J Med* 2022; 386: 1519-1531

AGILE: Baseline demographic and disease characteristics

Characteristic	IVO+AZA (n=72)	PBO+AZA (n=74)
Median (range) age, years	76 (58–84)	75.5 (45–94)
Sex, n (%)		
Male/Female	42 (58.3)/30 (41.7)	38 (51.4)/36 (48.6)
ECOG PS score, n (%)		
0/1/2	14 (19.4)/32 (44.4)/26 (36.1)	10 (13.5)/40 (54.1)/24 (32.4)
Disease history (per investigator), n (%)		
De novo AML	54 (75.0)	53 (71.6)
Secondary AML[a]	18 (25.0)	21 (28.4)
Median (range) m*IDH1* VAF in BMA, % (range)[b]	36.7 (3.1–50.5)	35.5 (3.0–48.6)
Cytogenetic risk, n (%)[c]		
Favorable/intermediate/poor	3 (4.2); 48 (66.7); 16 (22.2)	7 (9.5); 44 (59.5); 20 (27.0)
Median (range) bone marrow blasts, %	54 (20–95)	48.0 (17–100)

Montesinos P, et al. *N Engl J Med* 2022; 386: 1519-1531

AGILE: IVO+AZA significantly improves OS compared with PBO/AZA

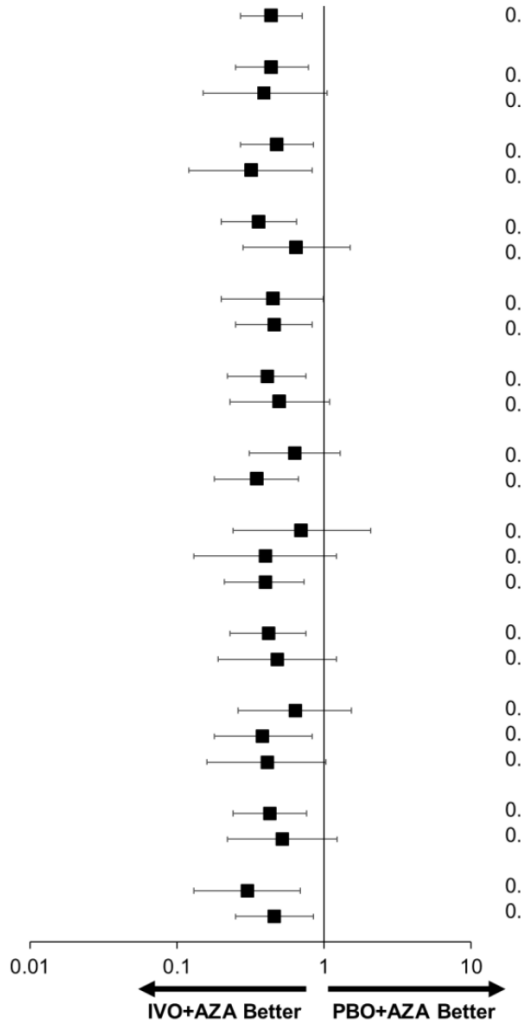


OS benefit was consistent across subgroups: de novo status, region, age, baseline ECOG PS score, sex, race, baseline cytogenetic risk status, WHO classification of AML, baseline white blood cell count, baseline BM blast percentage.

Montesinos P, et al. *N Engl J Med* 2022; 386: 1519-1531

AGILE: Overall Survival in ITT Population in Patient Subsets

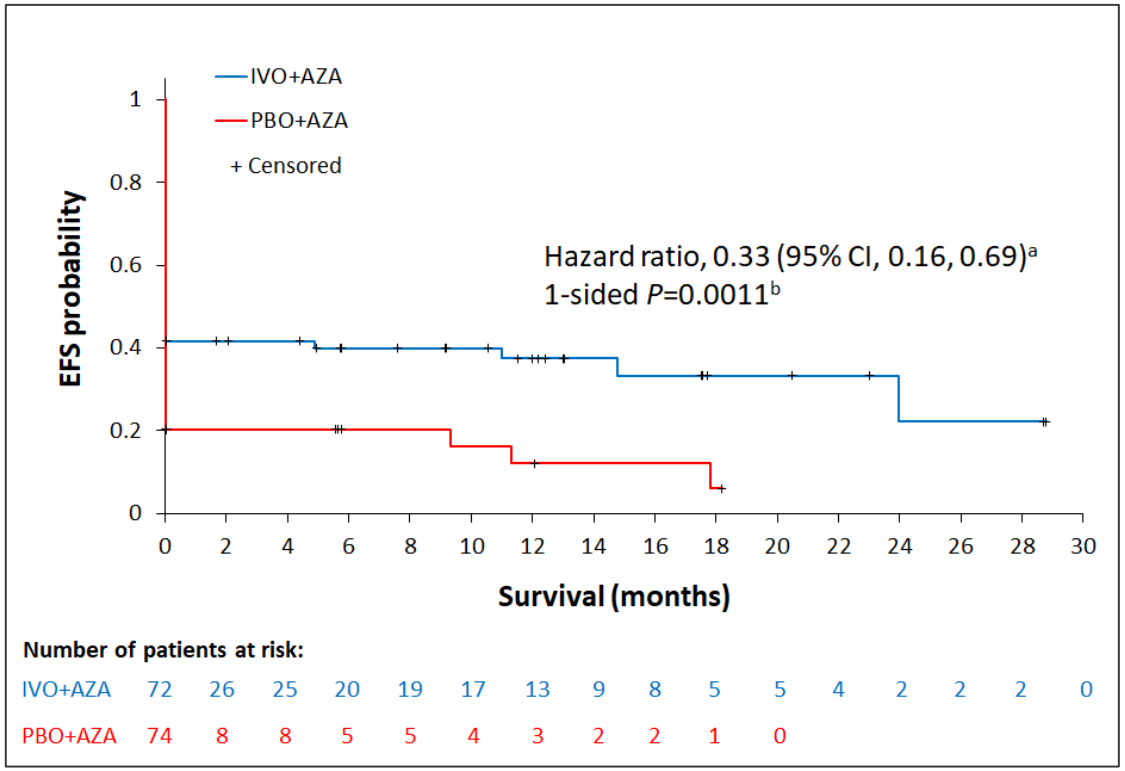
	IVO+AZA Events/N*	PBO+AZA Events/N*	HR	Lower 95% CI	Upper 95% CI
Overall	28/72	46/74	0.44	0.27	0.71
Primary AML on basis of IRT					
Yes	21/56	33/55	0.44	0.25	0.78
No	7/16	13/19	0.39	0.15	1.05
Primary AML on basis of investigator from eCRF					
Yes	21/54	31/53	0.48	0.27	0.85
No	7/18	15/21	0.32	0.12	0.83
Region					
United States, Canada, Western Europe, Israel, or Australia	17/48	34/50	0.36	0.20	0.65
Japan or ROW	11/24	12/24	0.65	0.28	1.51
Age					
<75 years	11/33	16/31	0.45	0.20	0.99
≥75 years	17/39	30/43	0.46	0.25	0.83
Baseline ECOG PS score					
0 or 1	17/46	30/50	0.41	0.22	0.75
≥2	11/26	16/24	0.50	0.23	1.09
Sex					
Female	12/30	22/36	0.63	0.31	1.29
Male	16/42	24/38	0.35	0.18	0.67
Race or ethnic group					
White	6/12	8/12	0.70	0.24	2.07
Asian	5/15	9/19	0.40	0.13	1.22
Other†	17/45	29/43	0.40	0.21	0.73
Baseline cytogenetic risk status					
Favorable or intermediate risk	18/51	31/51	0.42	0.23	0.75
Poor risk	7/16	13/20	0.48	0.19	1.22
WHO classification of AML					
AML with recurrent genetic abnormalities	8/16	15/24	0.64	0.26	1.53
AML with myelodysplasia-related changes	12/28	18/26	0.38	0.18	0.83
Therapy-related myeloid neoplasms or AML not otherwise specified‡	8/28	13/24	0.41	0.16	1.03
Baseline WBC count					
≤5×10⁹/liter	20/51	30/49	0.43	0.24	0.76
>5×10⁹/liter	8/21	16/25	0.52	0.22	1.23
Baseline bone marrow blast level§					
≤50%	9/30	22/40	0.30	0.13	0.69
>50%	18/41	24/34	0.46	0.25	0.85



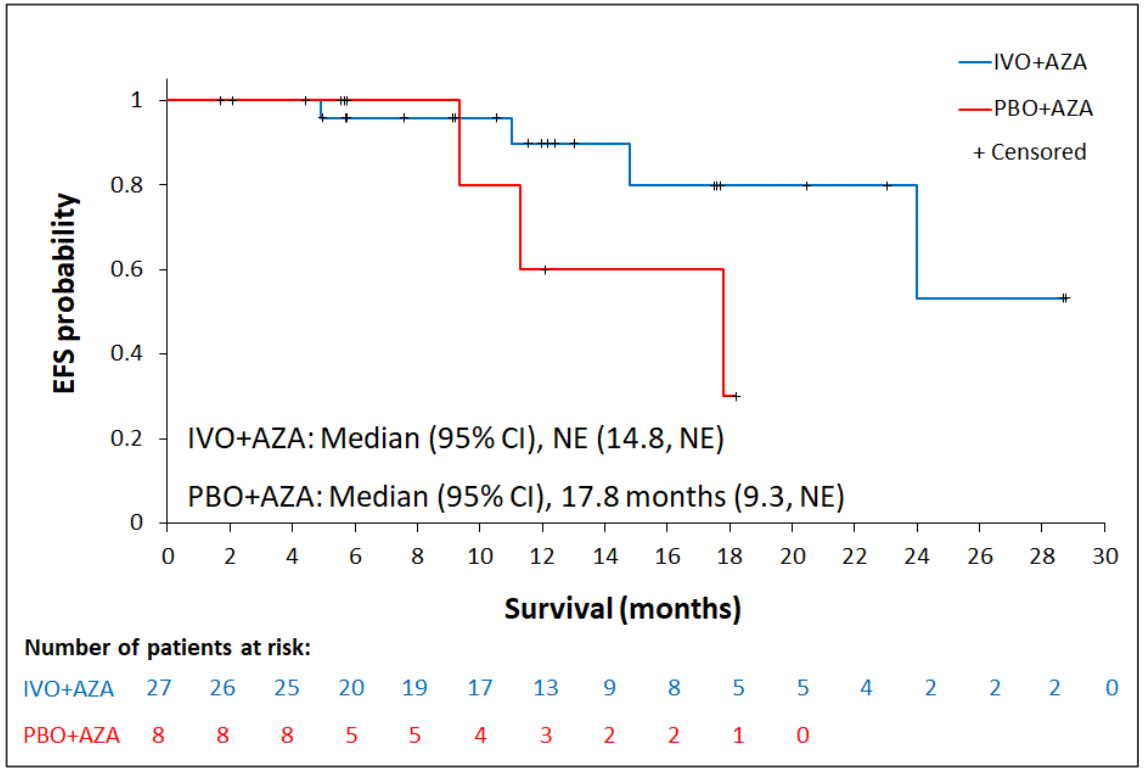
Montesinos P, et al. *N Engl J Med* 2022; 386: 1519-1531

AGILE: EFS in the intent-to-treat population

IVO+AZA significantly improves EFS



EFS among patients who achieved CR by 24 weeks



- Patients who did not achieve CR by week 24 were considered to have had an event at day 1 of randomization.
- EFS benefit was consistent across subgroups: de novo status, region, age, baseline ECOG PS score, sex, race, baseline cytogenetic risk status, WHO classification of AML, baseline white blood cell count, baseline percentage of bone marrow blasts.

Montesinos P, et al. *N Engl J Med* 2022; 386: 1519-1531

AGILE: Response Rate, Response Duration, and Time to Response

Response Category	Ivosidenib + Azacitidine (N = 72)	Placebo + Azacitidine (N = 74)
Complete remission		
Percentage of patients (95% CI)	47 (35–59)	15 (8–25)
Odds ratio vs. placebo (95% CI); P value	4.8 (2.2–10.5); two-sided P<0.001	
Median duration of complete remission (95% CI) — mo	NE (13.0–NE)	11.2 (3.2–NE)
Median time to complete remission (range) — mo	4.3 (1.7–9.2)	3.8 (1.9–8.5)
Complete remission or complete remission with partial hematologic recovery		
No. of patients	38	13
Percentage of patients (95% CI)	53 (41–65)	18 (10–28)
Odds ratio vs. placebo (95% CI); P value	5.0 (2.3–10.8); two-sided P<0.001	
Median duration of complete remission or complete remission with partial hematologic recovery (95% CI) — mo	NE (13.0–NE)	9.2 (5.8–NE)
Median time to complete remission or complete remission with partial hematologic recovery (range) — mo	4.0 (1.7–8.6)	3.9 (1.9–7.2)

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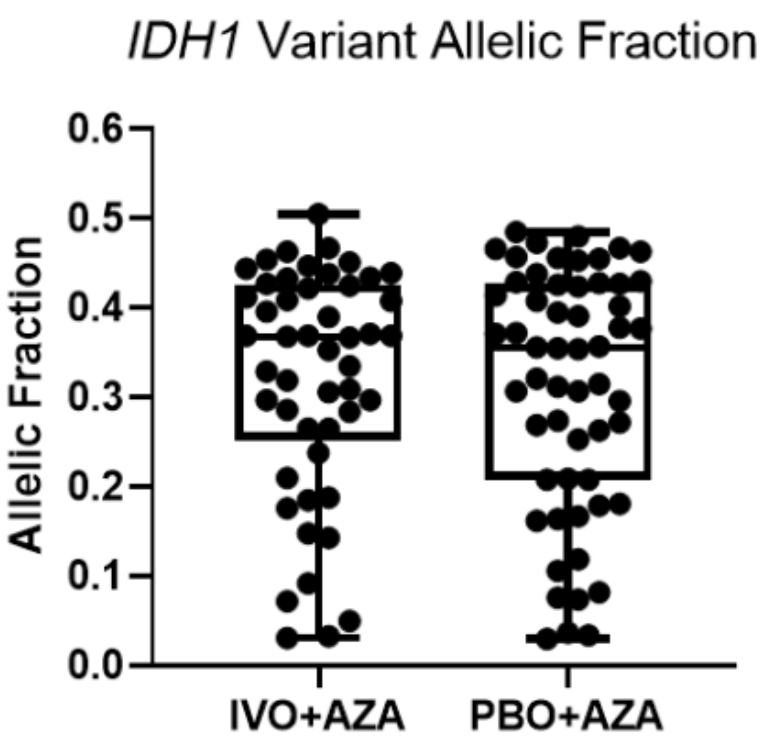
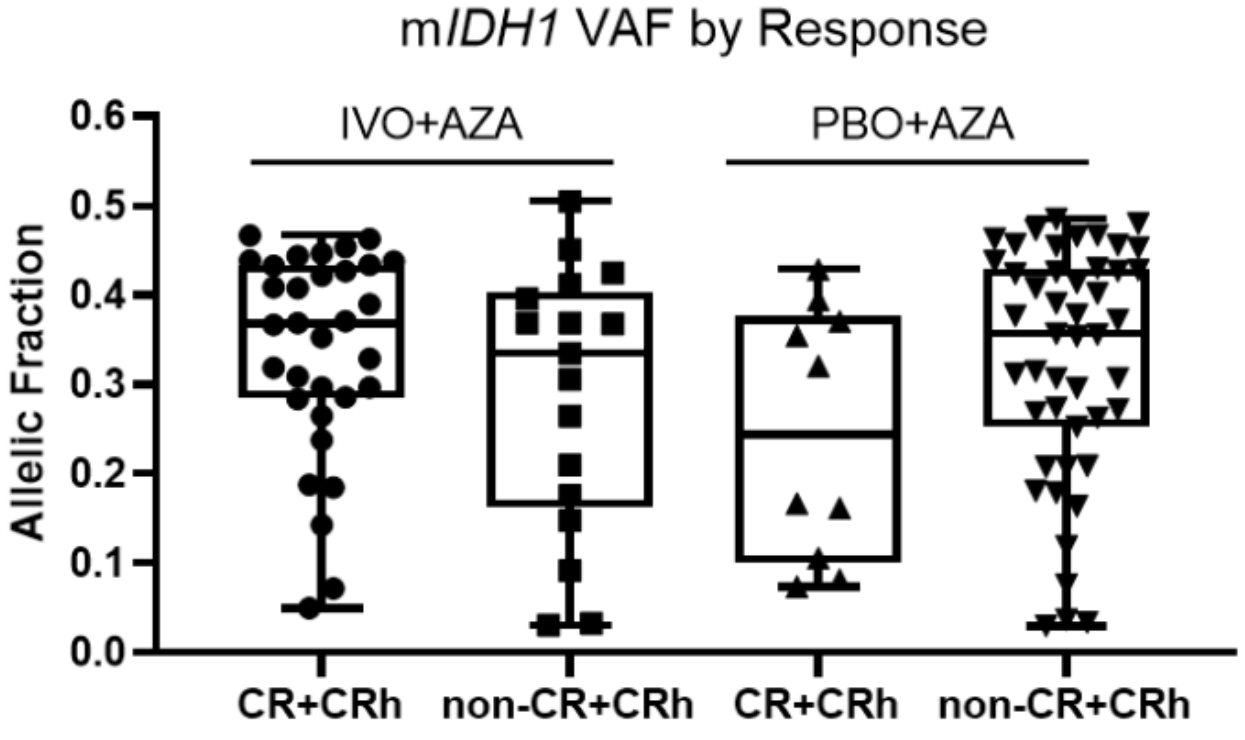
AGILE: m*IDH1* VAF and Response





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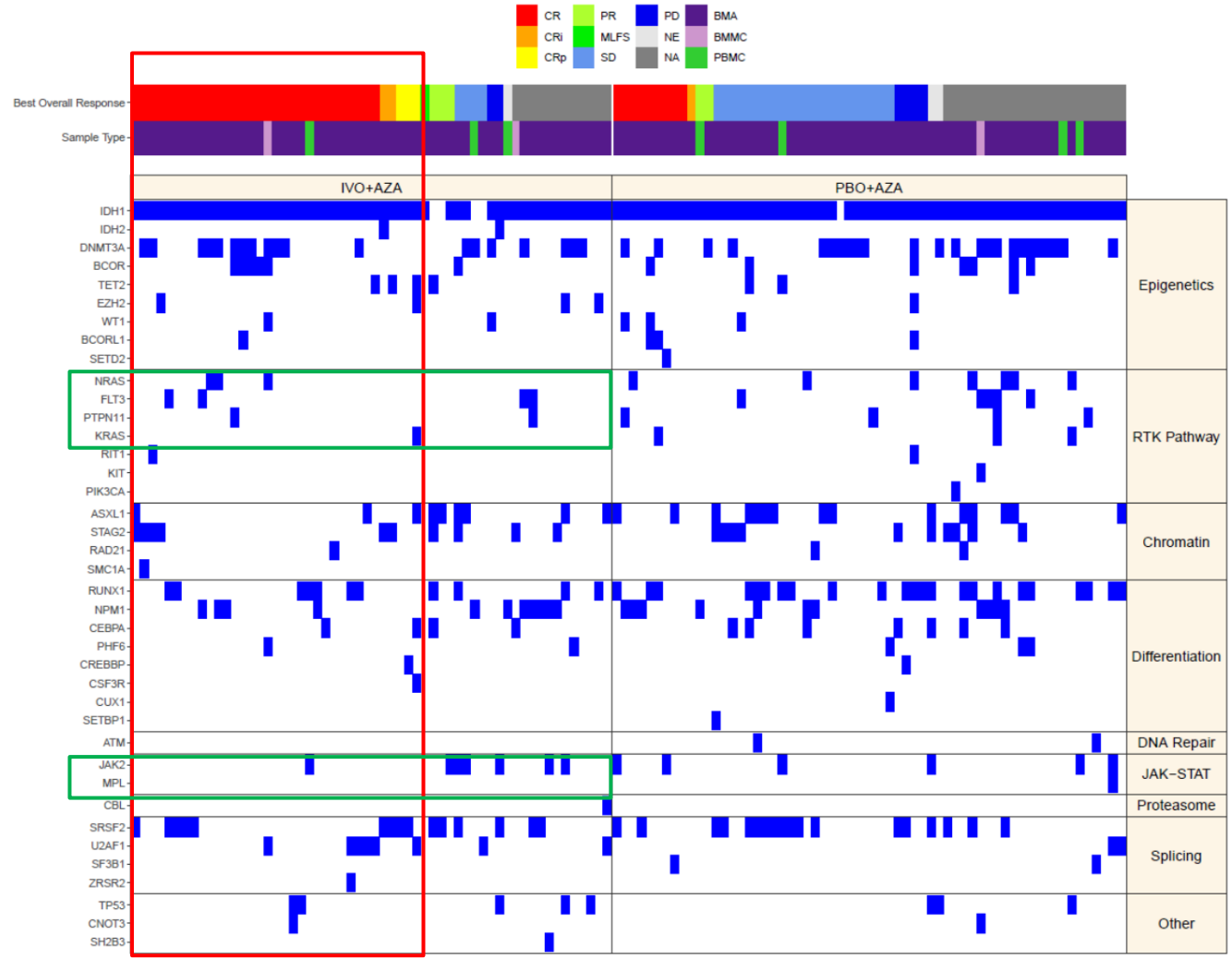
AGILE: Response based on co-mutations



Responses seen among subjects with RTK and RAS/MAP pathway mutations

Montesinos P, et al. *N Engl J Med* 2022; 386: 1519-1531

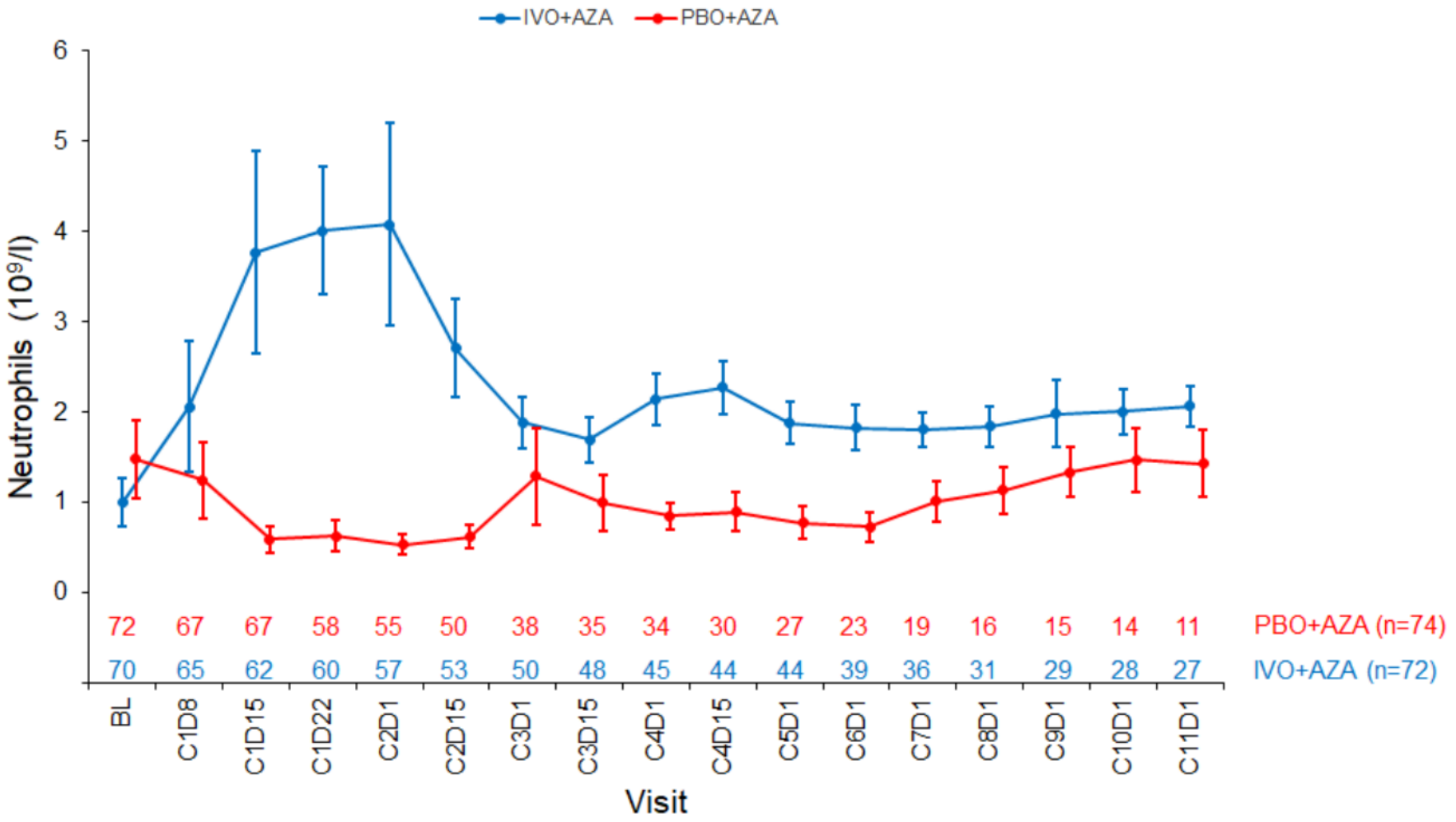
AGILE: Treatment-emergent adverse events (TEAEs)

	IVO+AZA (n=71)		PBO+AZA (n=73)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE, n (%)	70 (98.6)	66 (93.0)	73 (100)	69 (94.5)
Any hematologic TEAEs, n (%)	55 (77.5)	50 (70.4)	48 (65.8)	47 (64.4)
Most common hematologic TEAEs (>20%[a]), n (%)				
Anemia	22 (31.0)	18 (25.4)	21 (28.8)	19 (26.0)
Febrile neutropenia	20 (28.2)	20 (28.2)	25 (34.2)	25 (34.2)
Neutropenia	20 (28.2)	19 (26.8)	12 (16.4)	12 (16.4)
Thrombocytopenia	20 (28.2)	17 (23.9)	15 (20.5)	15 (20.5)
Most common TEAEs (>20%[a]), n (%)				
Nausea	30 (42.3)	2 (2.8)	28 (38.4)	3 (4.1)
Vomiting	29 (40.8)	0	19 (26.0)	1 (1.4)
Diarrhea	25 (35.2)	1 (1.4)	26 (35.6)	5 (6.8)
Pyrexia	24 (33.8)	1 (1.4)	29 (39.7)	2 (2.7)
Constipation	19 (26.8)	0	38 (52.1)	1 (1.4)
Pneumonia	17 (23.9)	16 (22.5)	23 (31.5)	21 (28.8)
Bleeding, n (%)	29 (40.8)	4 (5.6)	21 (28.8)	5 (6.8)
Infections, n (%)	20 (28.2)	15 (21.1)	36 (49.3)	22 (30.1)

- TEAEs of special interest with IVO+AZA vs PBO+AZA included grade ≥2 differentiation syndrome (14.1% vs 8.2%) and grade ≥3 QT prolongation (9.9% vs 4.1%).
- Infections were less common with IVO+AZA (28.2%) compared with PBO+AZA (49.3%).
- There were no deaths deemed related to treatment.

Montesinos P, et al. *N Engl J Med* 2022; 386: 1519-1531

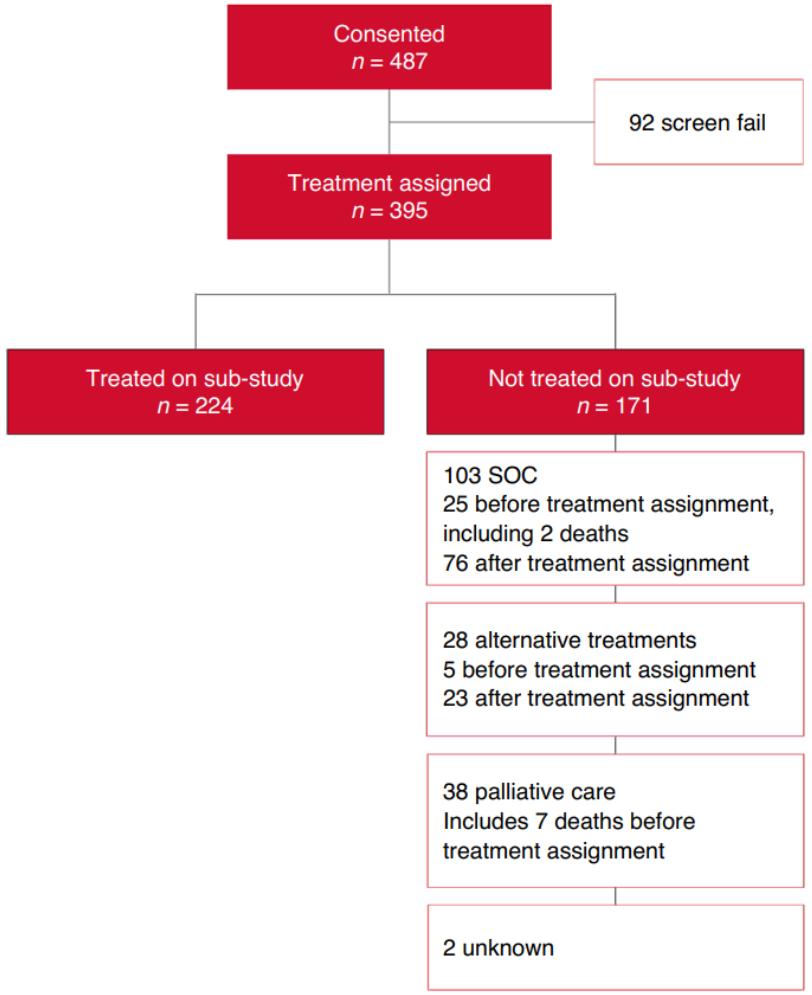
AGILE: Neutrophil Recovery from Baseline

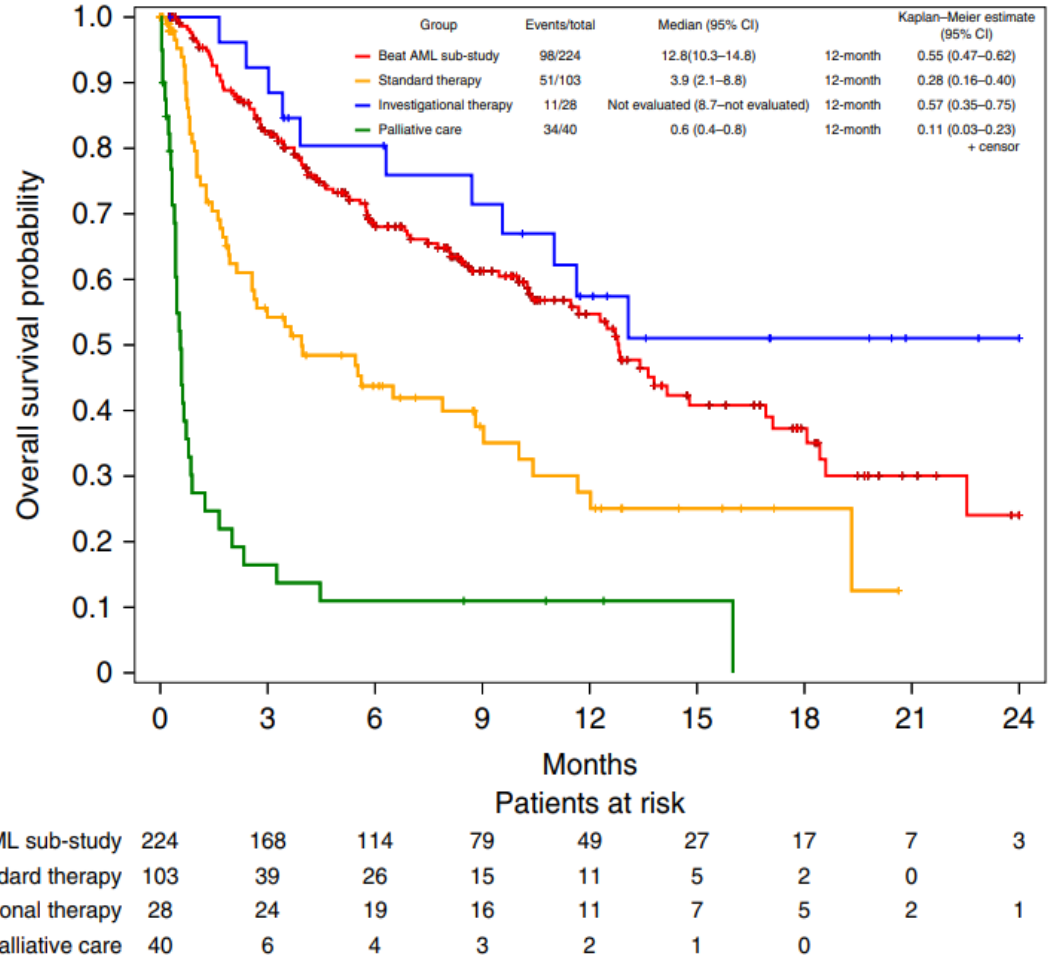


Montesinos P, et al. *N Engl J Med* 2022; 386: 1519-1531

Prospective Genomic Profiling in AML: BEAT AML

- Core binding factor
- *NPM1*$^{+}$ *FLT3*-ITD WT
- MLL-rearranged
- *IDH2*$^{+}$
- *IDH1*$^{+}$
- *TP53*$^{+}$
- *TP53* complex karyotype (>3 abn)
- *FLT3*-ITD^{+} or *FLT3*-TKD^{+}
- Hypermethylation*
- Marker-negative

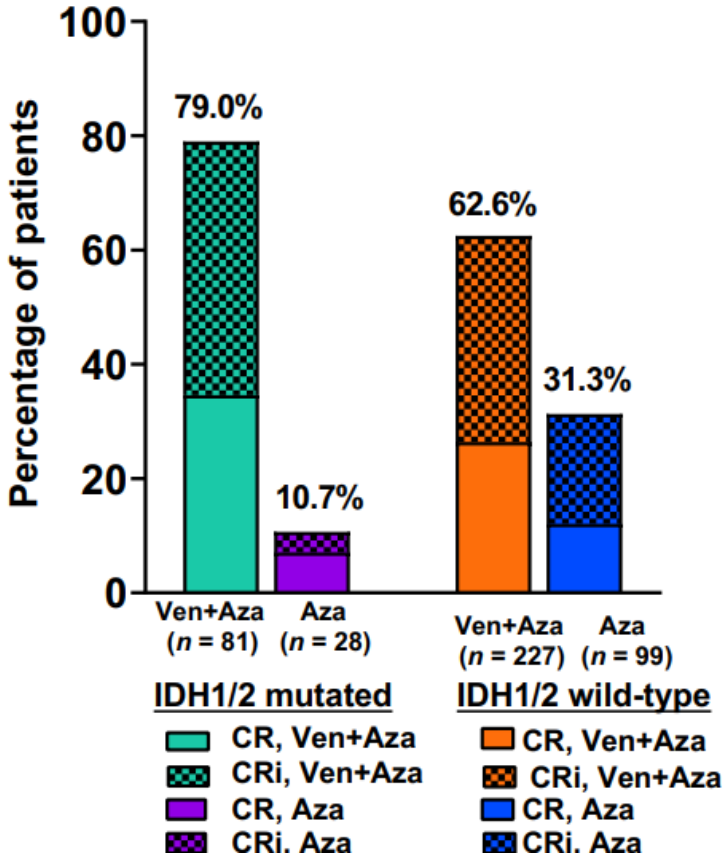




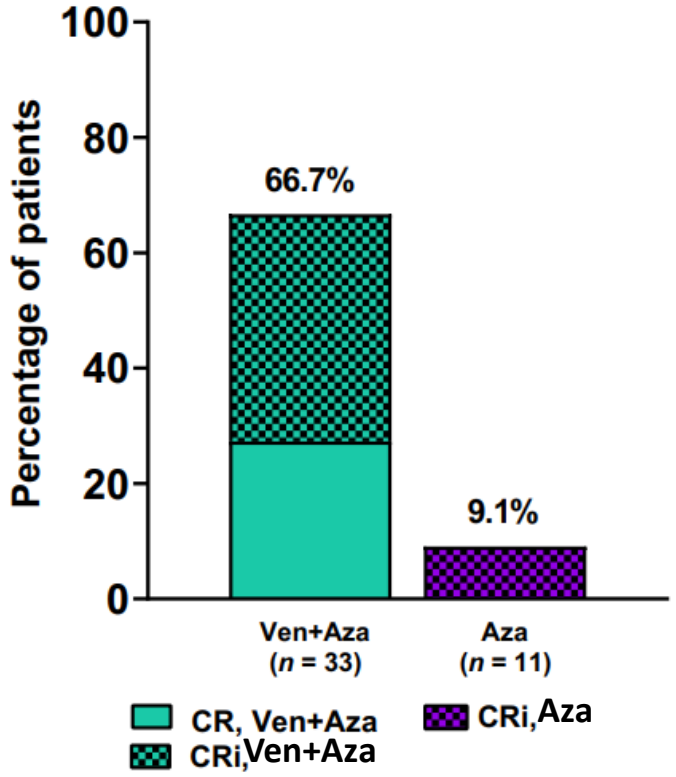
Burd A, et al. *Nature Medicine* 2020; 26: 1852

VEN/AZA in IC-Ineligible m*IDH* AML: Response Rates

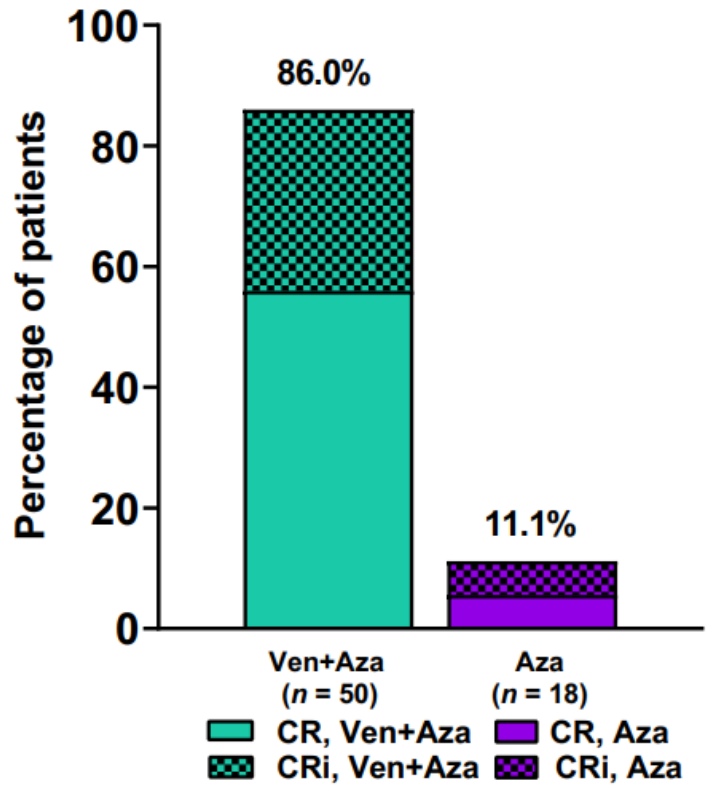
IDH1/2 mutated vs wild type



m*IDH1* VEN/AZA vs AZA



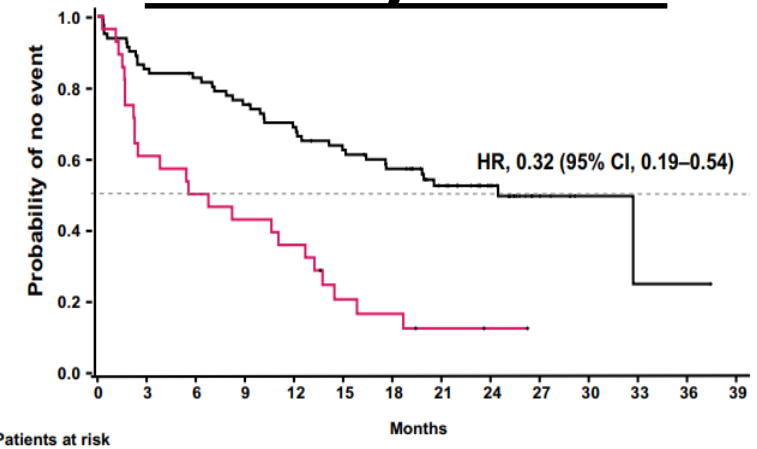
m*IDH2* VEN/AZA vs AZA



Pollyea DA, et al. *Clin Cancer Res.* 2022; 28(13): 2753-2761

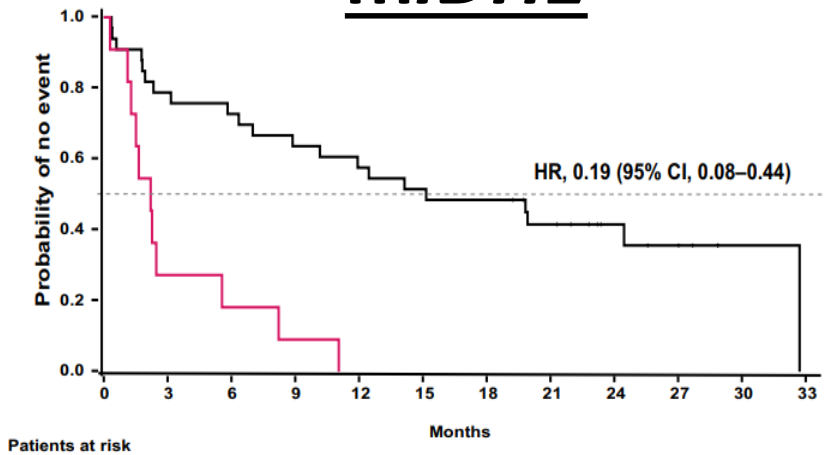
VEN/AZA in IC-Ineligible m*IDH* AML: Overall Survival

m*IDH1*/m*IDH2*



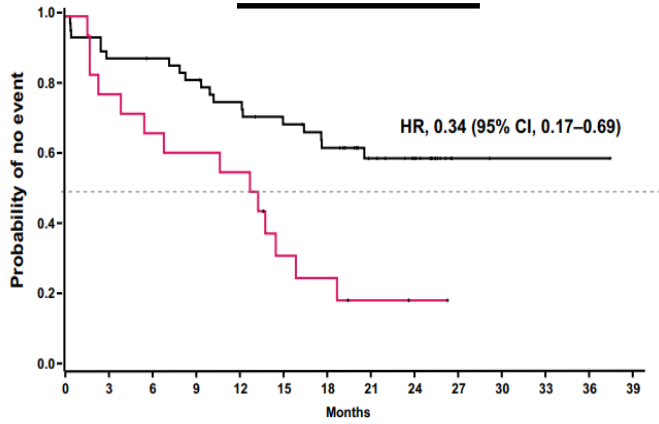
	Events	Survival estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (months) (95% CI)
Ven+Aza (*N* = 81)	39	82.7 (72.5–89.4)	68.8 (57.4–77.7)	52.4 (40.6–62.9)	24.5 (15.2, -)
Aza (*N* = 28)	24	50.0 (30.6–66.6)	35.7 (18.9–53.0)	12.2 (3.2–27.8)	6.2 (2.3–12.7)

m*IDH1*



	Events	Survival estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (months) (95% CI)
Ven+Aza (*N* = 33)	21	72.7 (54.1–84.8)	57.6 (39.1–72.3)	41.6 (24.6–57.7)	15.2 (7.0, -)
Aza (*N* = 11)	11	18.2 (2.9–44.2)	NA	NA	2.2 (1.1–5.6)

m*IDH2*



	Events	Survival estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (months) (95% CI)
Ven Aza (*N* = 50)	19	88.0 (75.2–94.4)	75.6 (61.0–85.3)	59.5 (43.9–72.2)	- (17.6, -)
Aza (*N* = 18)	14	66.7 (40.4–83.4)	55.6 (30.5–74.8)	19.0 (4.8–40.3)	13.0 (3.8–15.8)

	Median OS
Ven+Aza	24.5 months
Aza	6.2 months

	Median OS
Ven+Aza	15.2 months
Aza	2.2 months

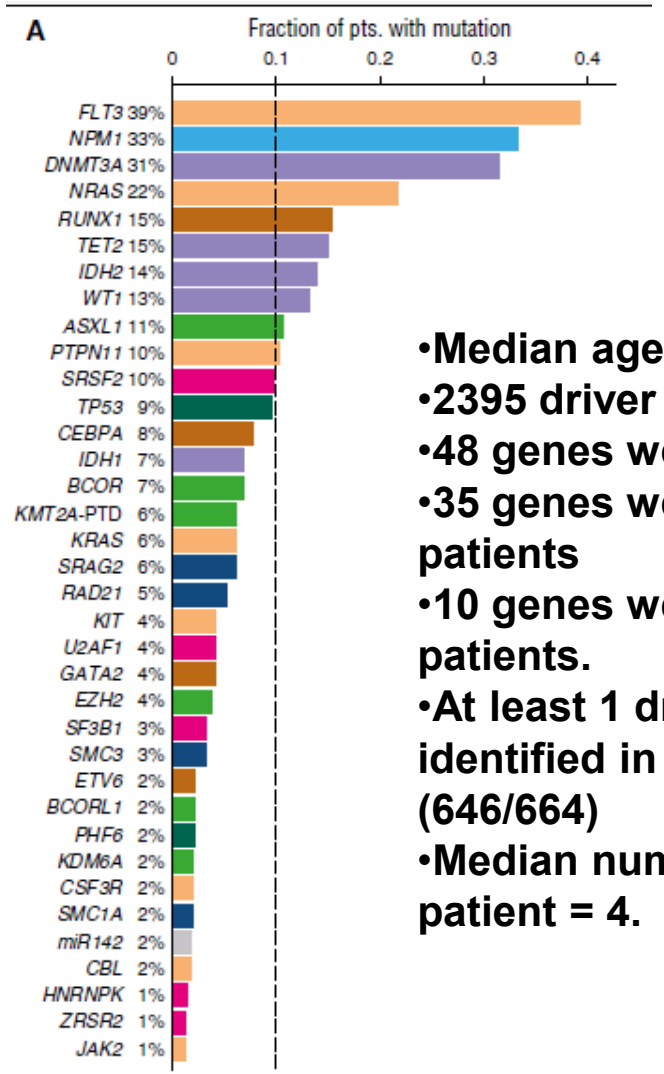
	Median OS
Ven+Aza	Not Reached
Aza	13.0 months

Pollyea DA, et al. *Clin Cancer Res.* 2022; 28(13): 2753-2761

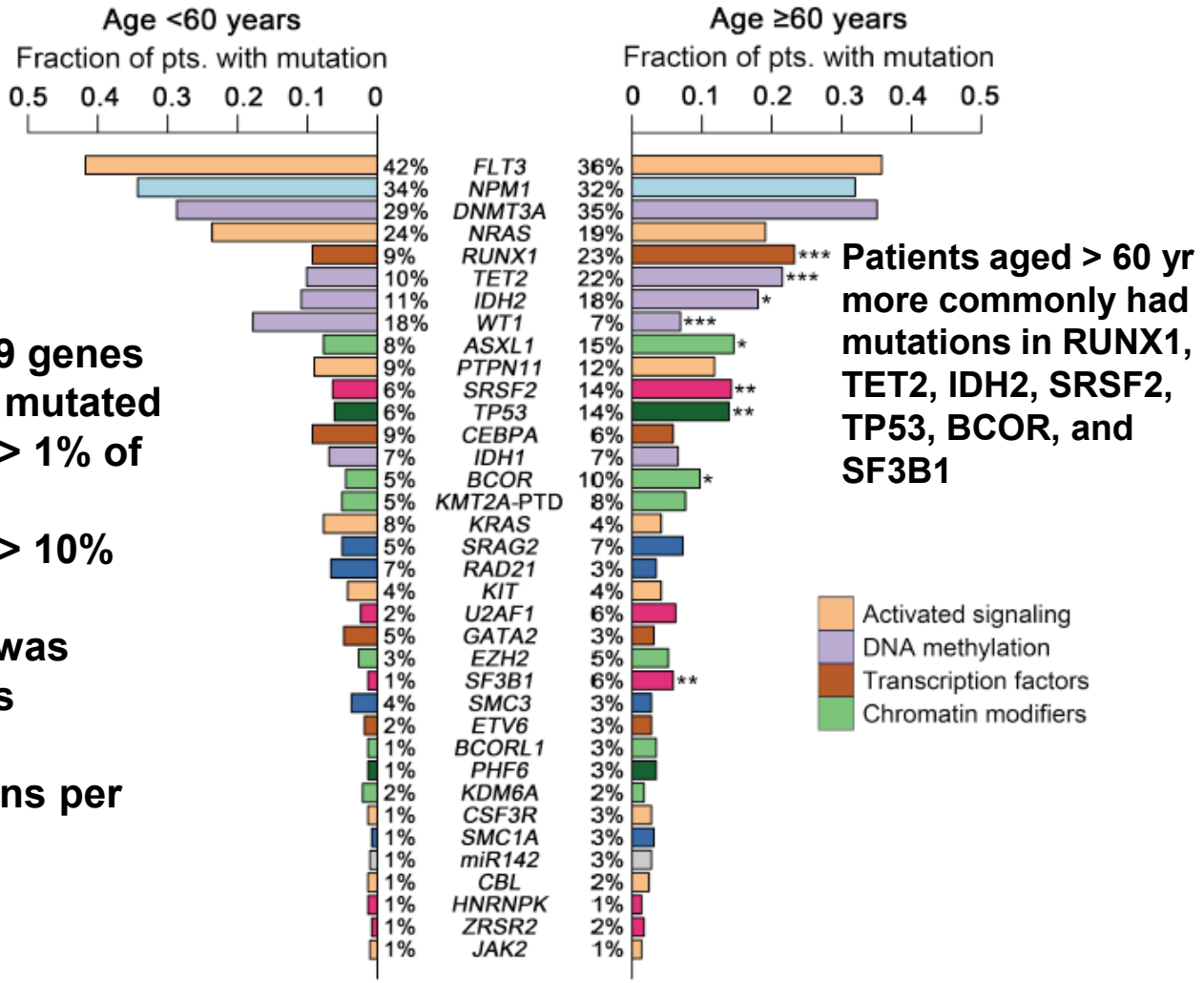
VEN/AZA vs IVO/AZA in IC-Ineligible m*IDH1* AML

	VEN/AZA	IVO/AZA
Mutation agnostic	Yes	No
Response Rate	CR/CRi 67%	CR/CRh 53%
Time to response	1 month	4 month
Median overall survival	15 months	24 months
Options in second line	IVO (if m*IDH1* present)	VEN/HMA
Toxicity	Myelosuppression, Tumor lysis syndrome	Differentiation syndrome, QT prolongation
Ease of administration	Dose modifications for cytopenias	

Mutational Profile in AML (664 Patients)



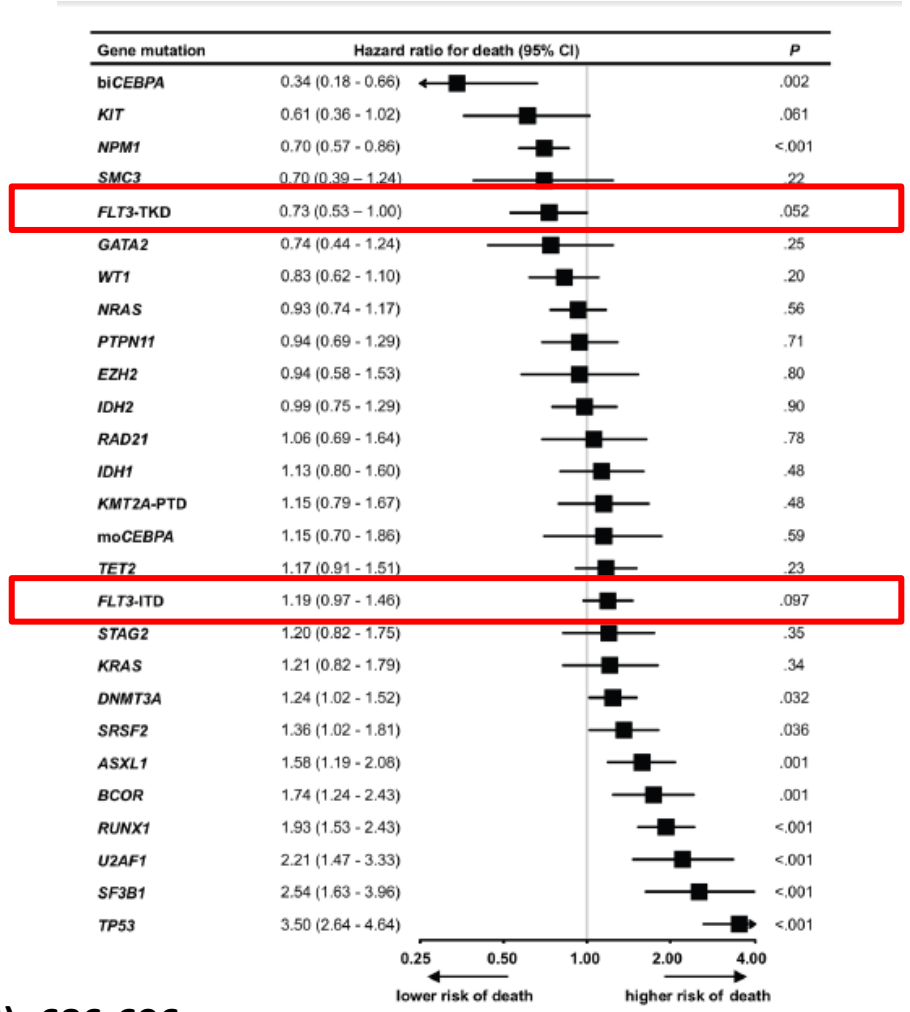
- Median age: 57 yrs
- 2395 driver mutations in 59 genes
- 48 genes were recurrently mutated
- 35 genes were mutated in > 1% of patients
- 10 genes were mutated in > 10% patients.
- At least 1 driver mutation was identified in 97% of patients (646/664)
- Median number of mutations per patient = 4.



Patients aged > 60 yr more commonly had mutations in RUNX1, TET2, IDH2, SRSF2, TP53, BCOR, and SF3B1

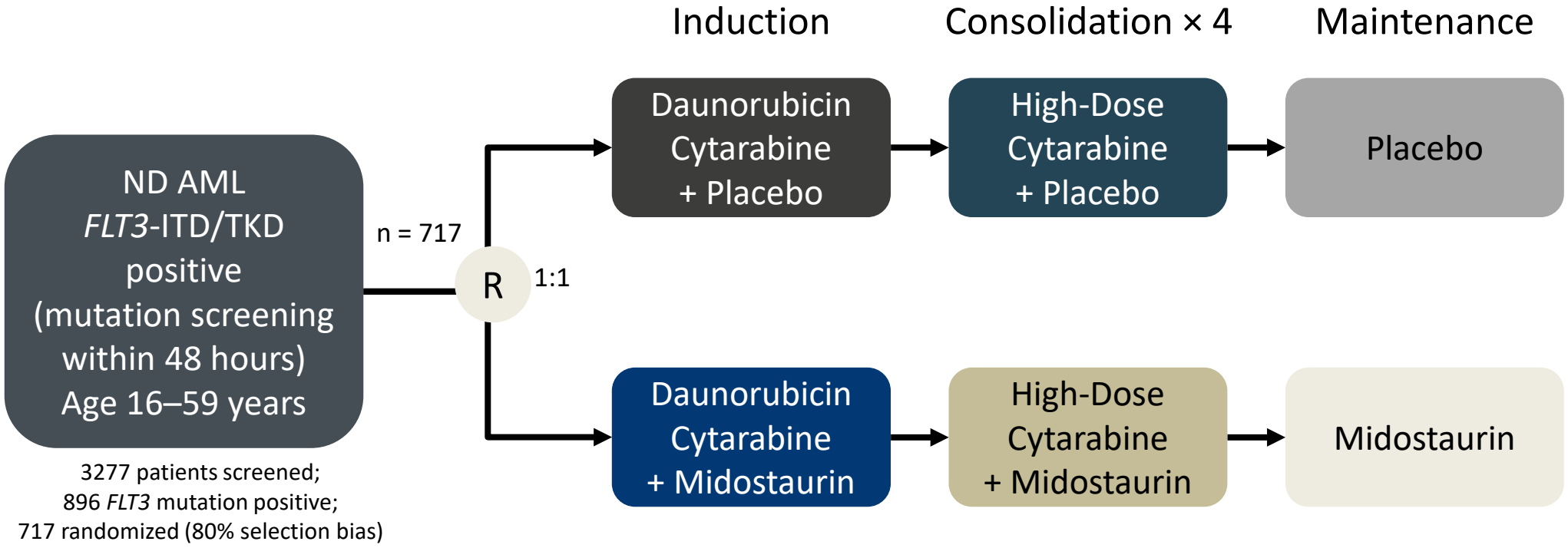
Metzeler KH, et al. *Blood* 2016; 128 (5): 686-696

Effect of Single Gene Mutations on Overall Survival in AML



Metzeler KH, et al. *Blood* 2016; 128 (5): 686-696

RATIFY (CALGB 10603): Chemotherapy + Midostaurin or Placebo in Newly Diagnosed Patients <60 Years With *FLT3*-Mutated AML



Collaboration with 13 international cooperative groups; 225 sites from 17 countries

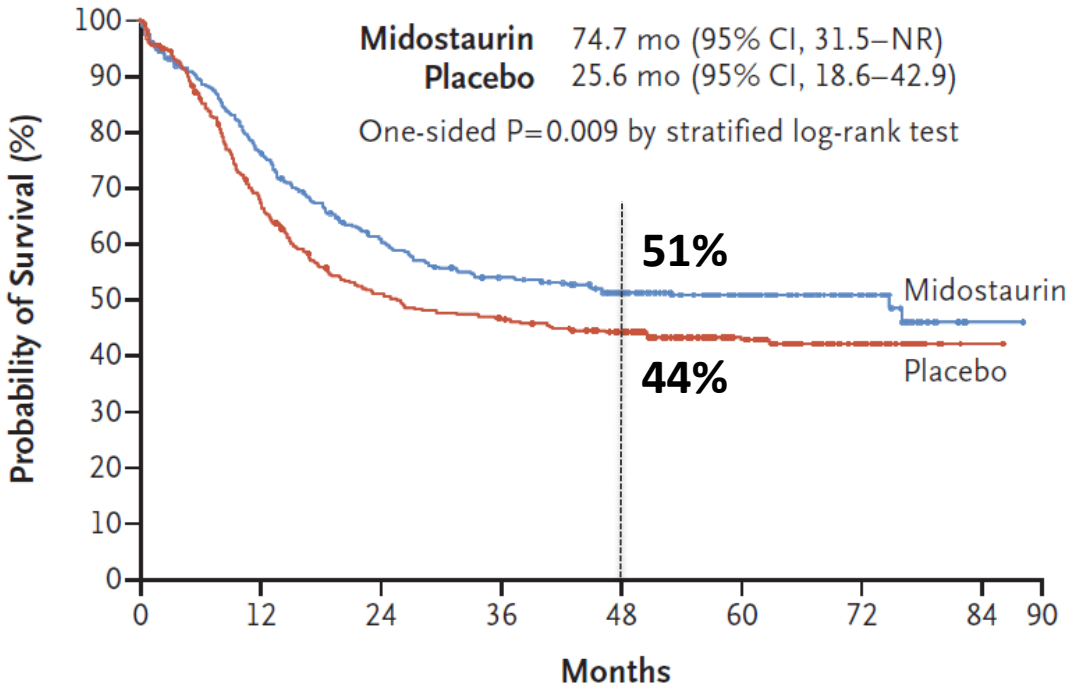
Alliance, SWOG, ECOG, NCIC CTG, GIMEMA, EORTC, AMLSG, SAL, OSHO, PETHEMA, CETLAM

9 academic *FLT3* screening laboratories worldwide

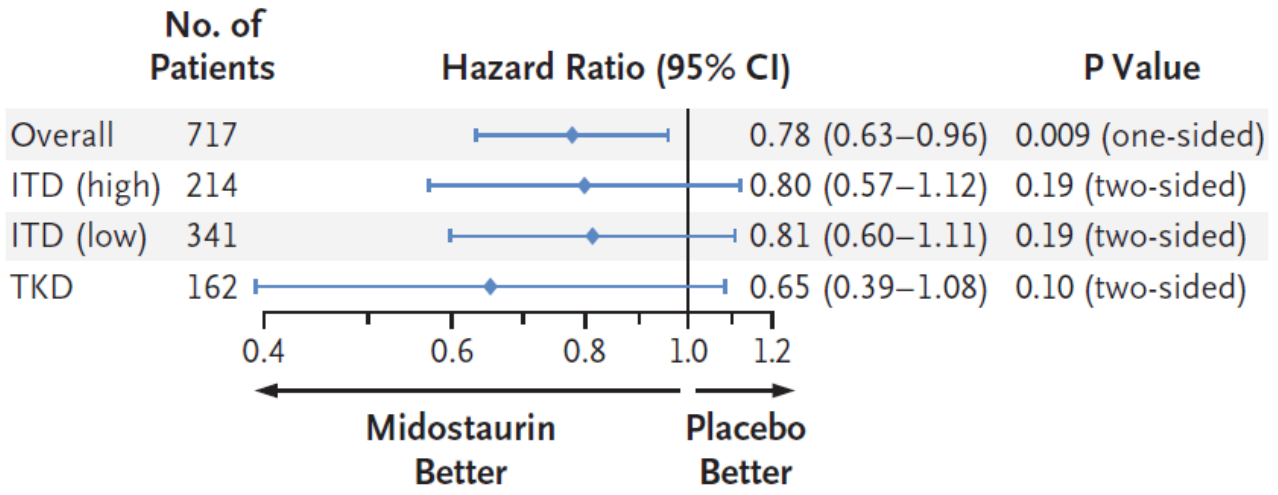
Stone RM, et al. *N Engl J Med.* 2017;377:454-464.

RATIFY (CALGB 10603): Overall Survival

Median OS

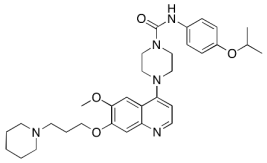
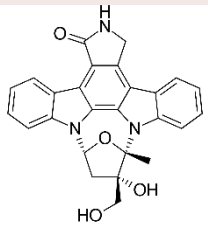
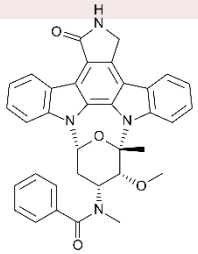
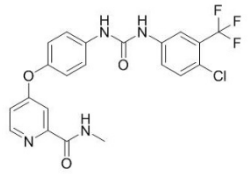
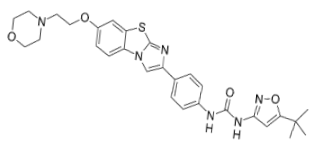
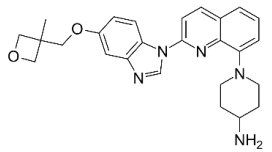
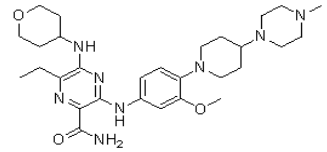


OS Subgroup Analysis



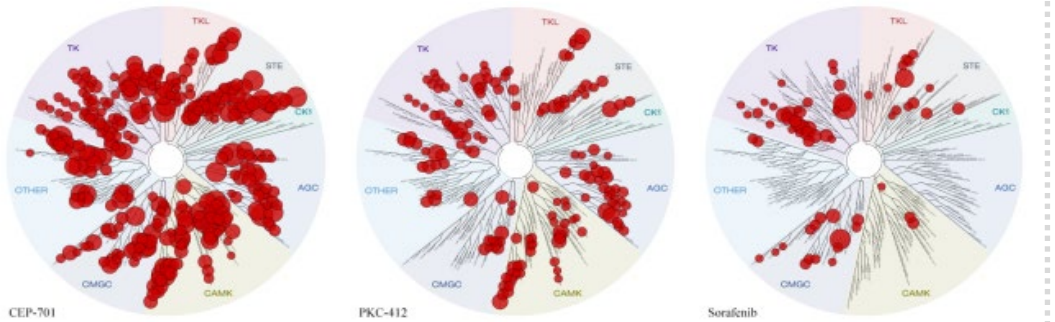
Stone RM, et al. *N Engl J Med.* 2017;377:454-464.

Potency and Selectivity of FLT3 Inhibitors

FLT3 inhibitors	Tandutinib	Lestaurtinib	Midostaurin	Sorafenib	Quizartinib	Crenolanib	Gilteritinib
FLT3 inhibition (IC50, nM)[a]	220	3	< 10	58	1.1	0.15	1.6
Inhibits *FLT3*	ITD	ITD and TKD	ITD and TKD	ITD	ITD	ITD and TKD	ITD and TKD
Structure							
Other targets[b,c]	*PDGFRβ, KIT,*	*Multiple kinases, including JAK2,3 TRK A/B/C*	*Multiple kinases, including PKC, SYK, Flk-1, AKT, KIT, Fgr, SRC, PDGFRβ, VEGFR1/2*	*Multiple kinases, including RAF, VEGFR1/2/3, PDGFRβ, KIT, RET*	*KIT, PDGFRβ, CSF1R, RET*	*PDGFRβ*	*LTK, ALK, AXL*

c. Larrosa-Garcia M, et al. *Mol Cancer Ther*. 2017;16:991-1001.

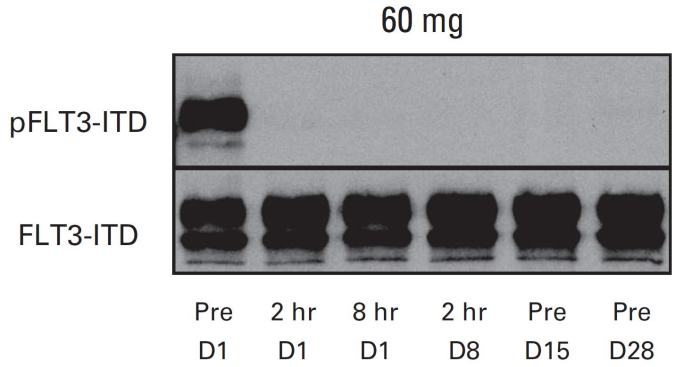
Quizartinib (AC220): A Highly Potent and Selective FLT3 Inhibitor

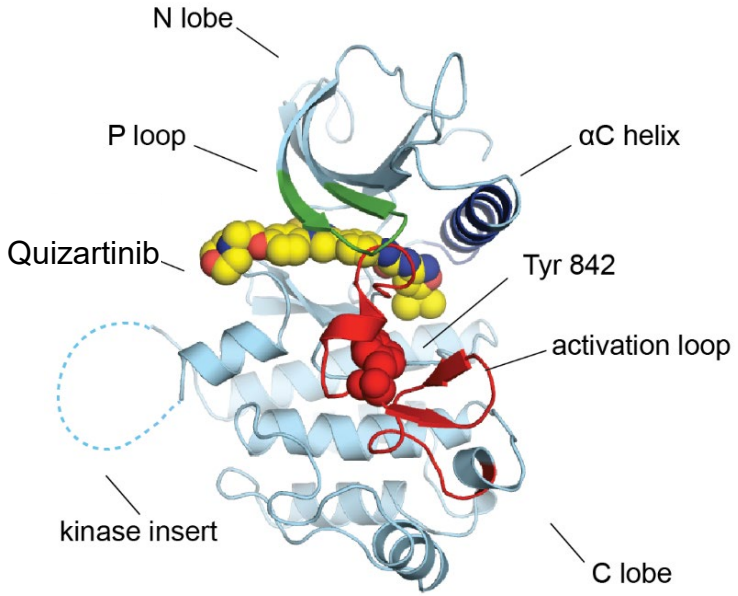


Lestaurtinib[1] **Midostaurin[1]** **Sorafenib[1]** **Quizartinib[1]**

First-generation multikinase inhibitors[2]

Second-generation FLT3 inhibitor[3]





Quizartinib properties

- **Type II FLT3 inhibitor, maintains inactive conformation. Active on ITD+ cells only.**
- **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]**

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.

Quizartinib Prolonged Survival vs Placebo Plus Intensive Induction and Consolidation Therapy Followed by Single-Agent Continuation in Patients Ages 18-75 Years With Newly Diagnosed *FLT3*-ITD+ AML

Harry P. Erba,[1] Pau Montesinos,[2] Radovan Vrhovac,[3] Elzbieta Patkowska,[4] Hee-Je Kim,[5] Pavel Zak,[6] Po-Nan Wang,[7] Tsvetomir Mitov,[8] James Hanyok,[9] Li Liu,[9] Aziz Benzohra,[9] Arnaud Lesegretain,[9] Jorge Cortes,[10] Alexander Perl,[11] Mikkael Sekeres,[12] Hervé Dombret,[13] Sergio Amadori,[14] Jianxiang Wang,[15] Mark Levis,[16] Richard F. Schlenk[17]

[1]Duke Cancer Institute, Durham, NC, USA; [2]La Fe University and Polytechnic Hospital, Valencia, Spain; [3]University Hospital Centre Zagreb, Zagreb, Croatia; [4]Institute of Hematology and Blood Transfusion, Warsaw, Poland; [5]Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea; [6]University Hospital Hradec Kralove, Hradec Kralove, Czechia; [7]Chang Gung Medical Foundation, Linkou, Taiwan; [8]Daiichi Sankyo UK Ltd, Uxbridge, United Kingdom; [9]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [10]Augusta University Medical Center, Augusta, GA, USA; [11]University of Pennsylvania, Philadelphia, PA, USA; [12]Sylvester Cancer Center, University of Miami Health System, Miami, FL, USA; [13]Saint Louis Hospital, University of Paris, Paris, France; [14]Tor Vergata Polyclinic Hospital Rome, Rome, Italy; [15]Institute of Hematology and Blood Diseases Hospital, Tianjin, China; [16]Johns Hopkins University, Baltimore, MD, USA; [17]Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany

QuANTUM-FIRST STUDY

AML, acute myeloid leukemia; FLT3, fms related receptor tyrosine kinase 3; ITD+, internal tandem duplication positive.

QuANTUM-First Phase 3 Trial (NCT02668653): Quizartinib Plus Standard Induction Chemotherapy and Consolidation Followed by Single-Agent Quizartinib

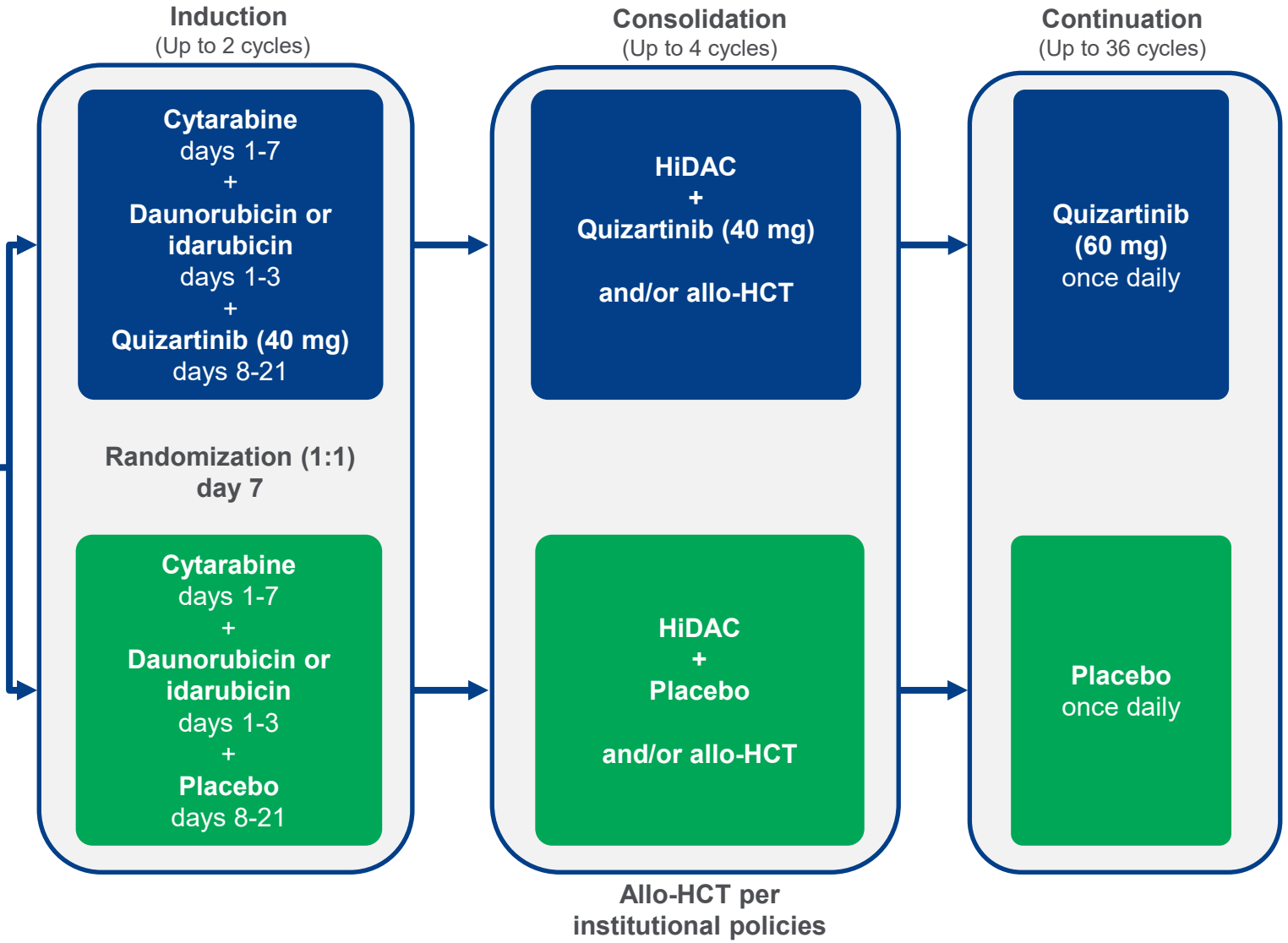
Enrollment dates: September 2016 to August 2019
Data cutoff: August 13, 2021

Stratification factors
- **Region**: NA, EU, and Asia/other regions
- **Patient age**: <60 years, ≥60 years
- **WBC**[a]: <40×10^9/L, ≥40×10^9/L

- Newly diagnosed *FLT3*-ITD+ AML
- 18-75 years of age
- ≥3% *FLT3*-ITD allelic frequency
- Patients begin 7+3 chemotherapy during screening

Selected endpoints
- **Primary endpoint**: OS
- **Secondary endpoints**: EFS, CR/CRc, Safety
- **Exploratory endpoints**: RFS, DoCR

A hierarchical testing procedure was used to test the primary endpoint of OS, followed by EFS, CR and CRc.



AML, acute myeloid leukemia; CR, complete remission; CRc, composite complete remission; DoCR, duration of complete remission; EFS, event-free survival; EU, Europe; HiDAC, high-dose cytarabine; NA, North America, OS, overall survival; RFS, relapse-free survival; WBC, white blood cell.
[a] WBC count was measured at the time of AML diagnosis.

Baseline Patient Characteristics

Patient Characteristics	Quizartinib (N=268)[a]	Placebo (N=271)[a]
Age, years		
Median (range)	56 (23-75)	56 (20-75)
≥60 years, %	39.9	40.2
Sex, n %		
Male	46.3	44.6
Female	53.7	55.4
Race, %		
Asian	29.9	28.8
Black or African American	0.7	1.8
American Indian or Alaska Native	0	0.4
White	59.3	60.1
Other	10.1	8.9
Region, %		
North America	6.0	6.6
Europe	60.8	60.1
Asia/other regions	33.2	33.2

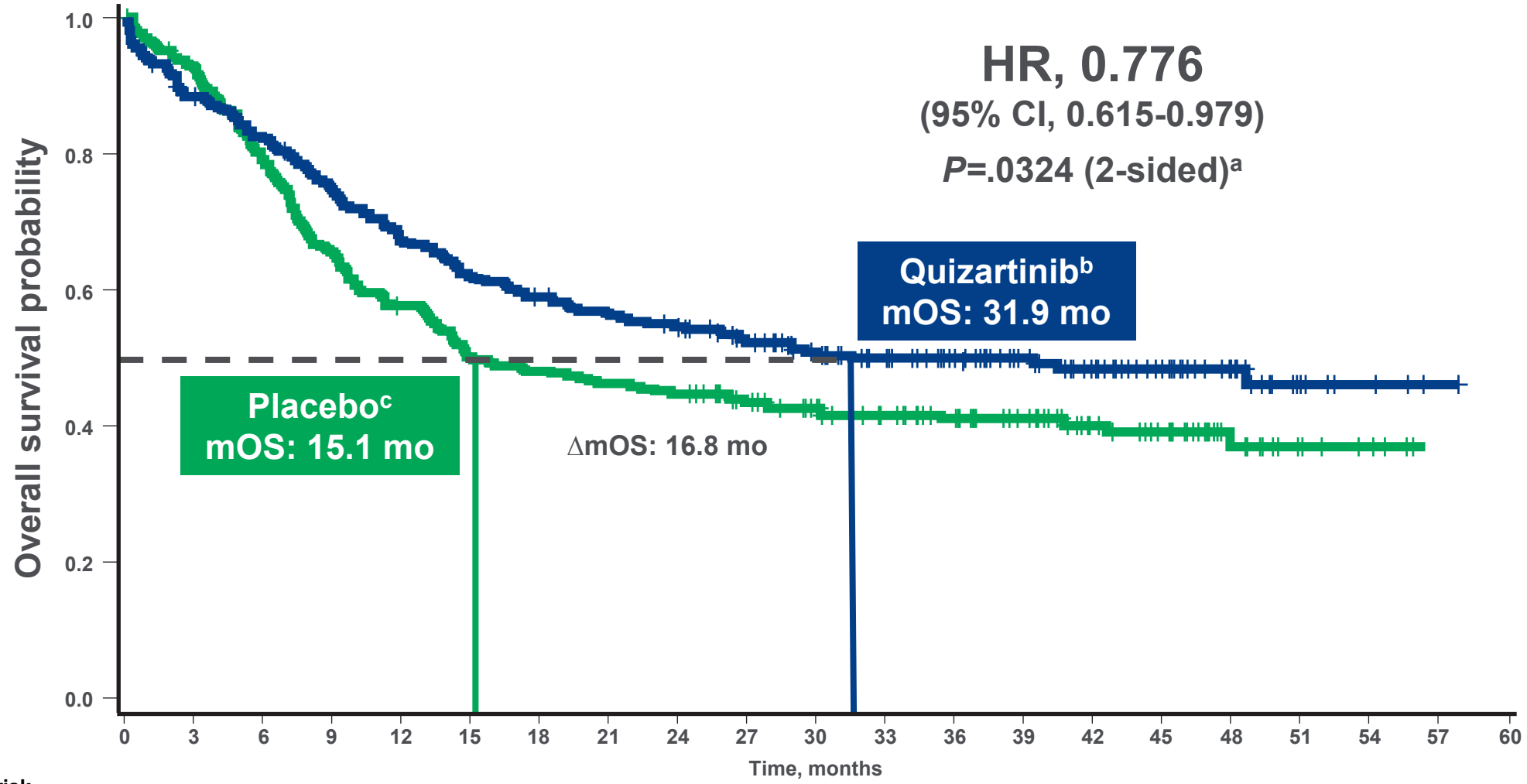
ITT, intention to treat.
[a] Three patients in the ITT set were randomized but not treated.

Baseline Disease Characteristics

Disease Characteristics	Quizartinib (N=268)[a]	Placebo (N=271)[a]
ECOG performance status, %[b]		
0	32.5	36.2
1	50.0	50.2
2	17.5	13.3
Cytogenetic risks, %		
Favorable	5.2	7.0
Intermediate	73.5	71.2
Unfavorable	7.1	10.0
Unknown	14.2	11.4
Missing	0	0.4
Mutated *NPM1*	53.0	51.7
***FLT3*-ITD/total *FLT3*, %[c,d]**		
≥3% to ≤25%	35.1	36.2
>25% to ≤50%	53.4	50.9
>50%	11.2	12.9
WBC count at diagnosis of AML, %		
<40×10^9/L	50.4	50.6
≥40×10^9/L	49.6	49.4

AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; FLT3, fms related receptor tyrosine kinase 3; ITD, internal tandem duplication; *NPM1*, nucleophosmin; WBC, white blood cell.
[a] Three patients in the ITT set were randomized but not treated in each arm. [b] One patient in the placebo group was missing an ECOG status. [c] Variant allele frequency was assessed by central lab testing. [d] One patient with unknown *FLT3*-ITD/total *FLT3* was positive per local laboratory testing.

Primary Endpoint: Overall Survival

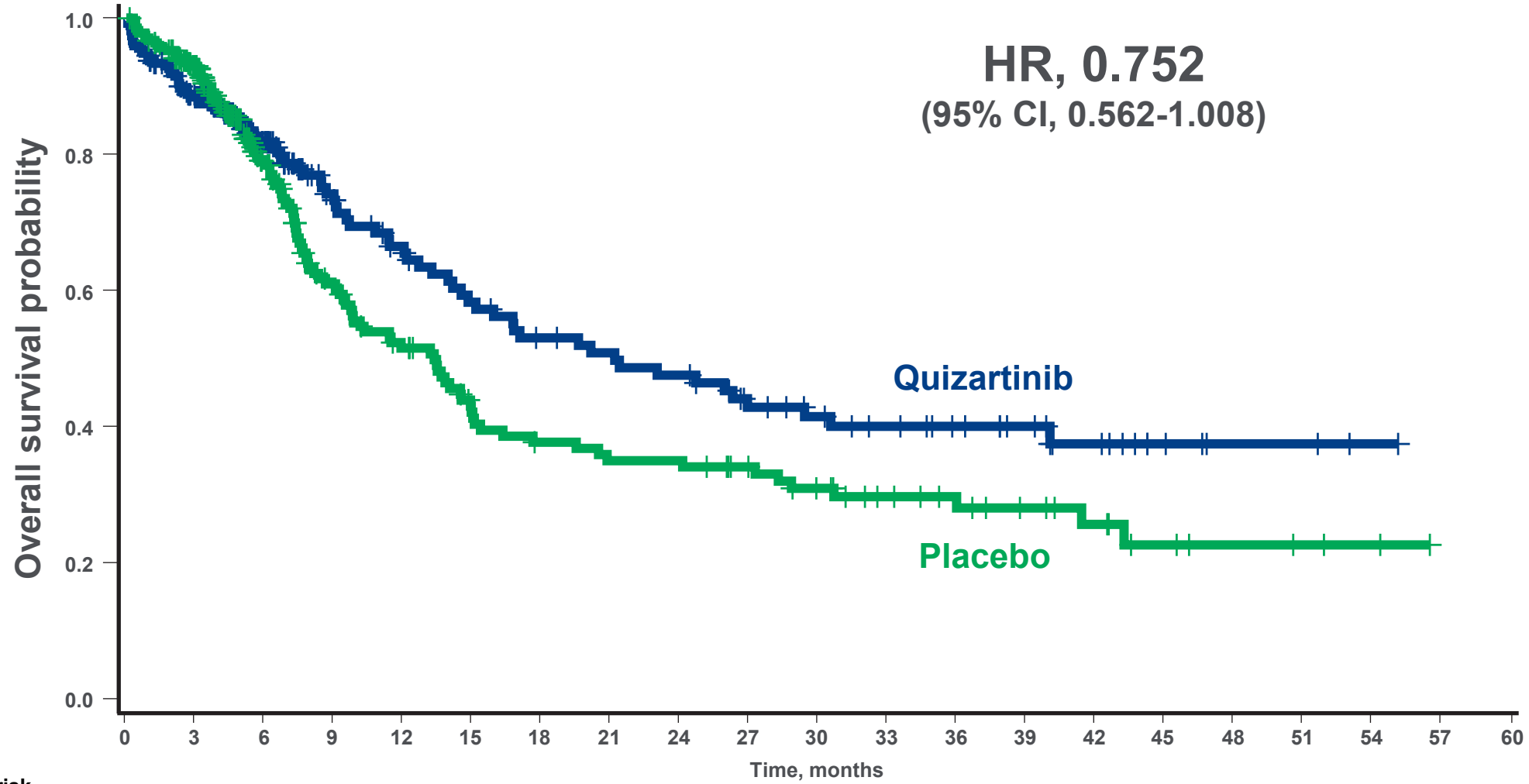


No. at risk																					
Quizartinib	268	233	216	195	176	162	153	145	139	126	110	96	83	68	53	36	24	8	4	1	0
Placebo	271	249	211	175	151	131	126	121	117	103	97	81	70	56	39	31	17	8	5	0	0

HR, hazard ratio; mOS, median overall survival.

[a] *P* value was calculated using a stratified log-rank test. [b] Median follow-up time for quizartinib arm, 39.2 months. [c] Median follow-up time for placebo arm, 39.2 months.

Sensitivity Analysis: OS Censored for Allo-HCT

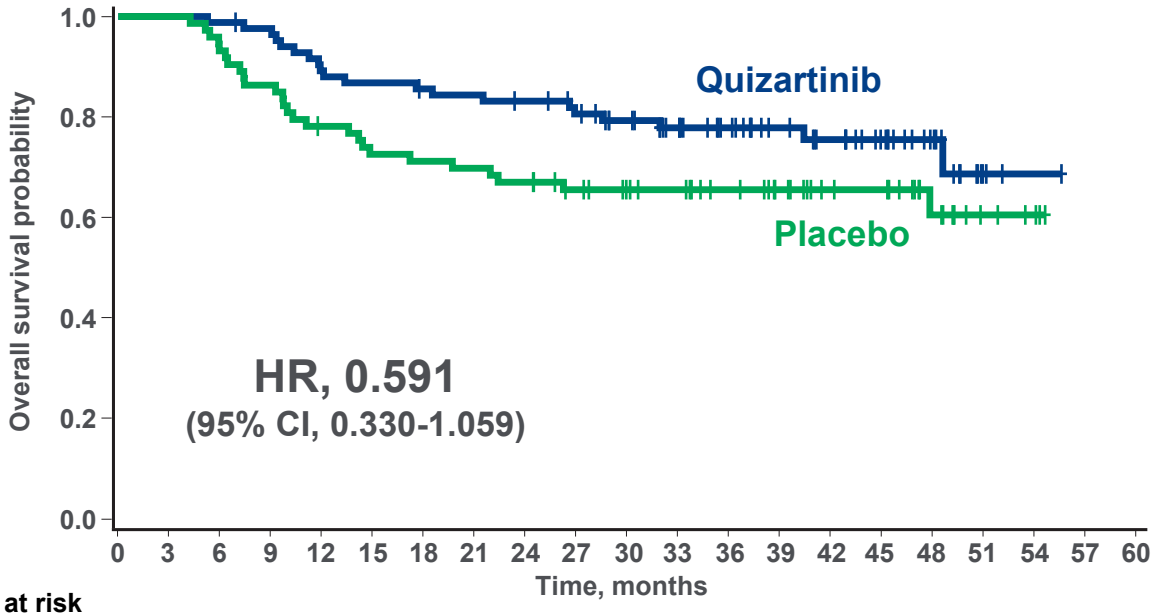


No. at risk																					
Quizartinib	268	212	111	73	62	54	48	43	41	33	27	24	20	16	10	5	3	2	1	0	0
Placebo	271	222	114	76	62	44	40	37	36	30	25	19	16	13	8	5	4	2	1	0	0

Allo-HCT, allogeneic hematopoietic cell transplantation; HR, hazard ratio; mOS, median overall survival; OS, overall survival.

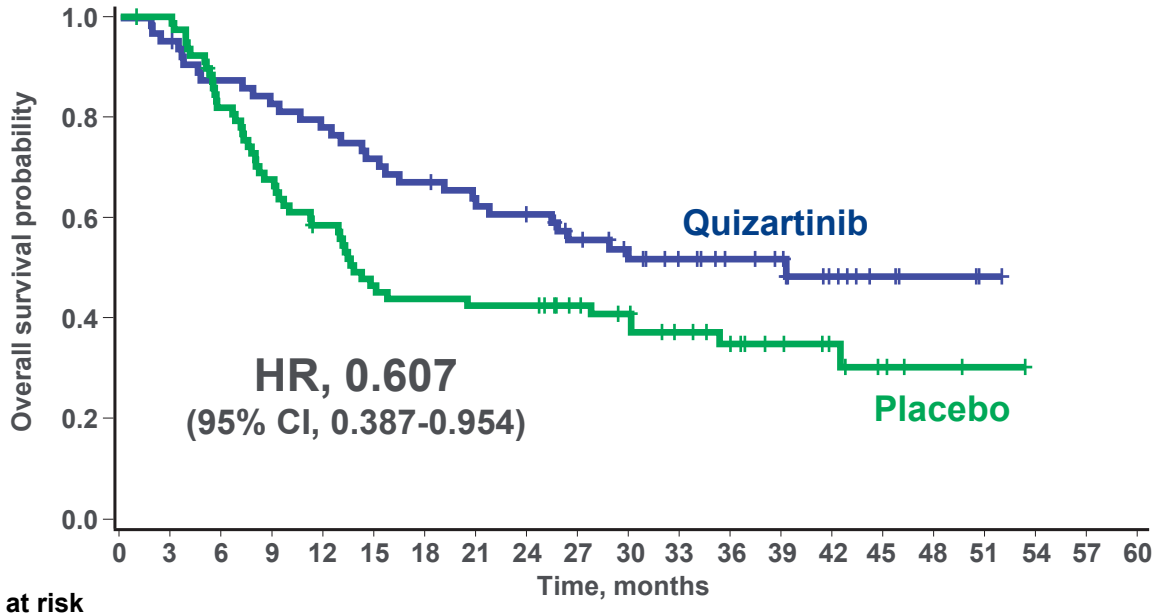
Post-hoc Analysis: OS in Patients Who Achieved CR[a]

OS – Patients With CR Who Received Allo-HCT in CR1



No. at risk																					
Quizartinib	84	84	83	81	74	72	70	69	67	63	57	50	42	34	29	22	14	3	1	0	0
Placebo	73	73	68	63	56	52	51	50	48	43	39	37	32	27	21	20	12	5	3	0	0

OS – Patients With CR NOT Receiving Allo-HCT in CR1



No. at risk																					
Quizartinib	63	60	54	51	48	44	41	37	35	30	25	21	17	15	9	5	3	1	0	0	0
Placebo	77	76	61	50	42	33	31	30	30	25	22	17	14	10	7	4	2	1	0	0	0

- Subgroup analysis for descriptive purposes only

Allo-HCT, allogeneic hematopoietic cell transplantation; CR, complete remission; HR, hazard ratio; IRC, independent review committee; OS, overall survival.
[a] By end of induction by IRC.

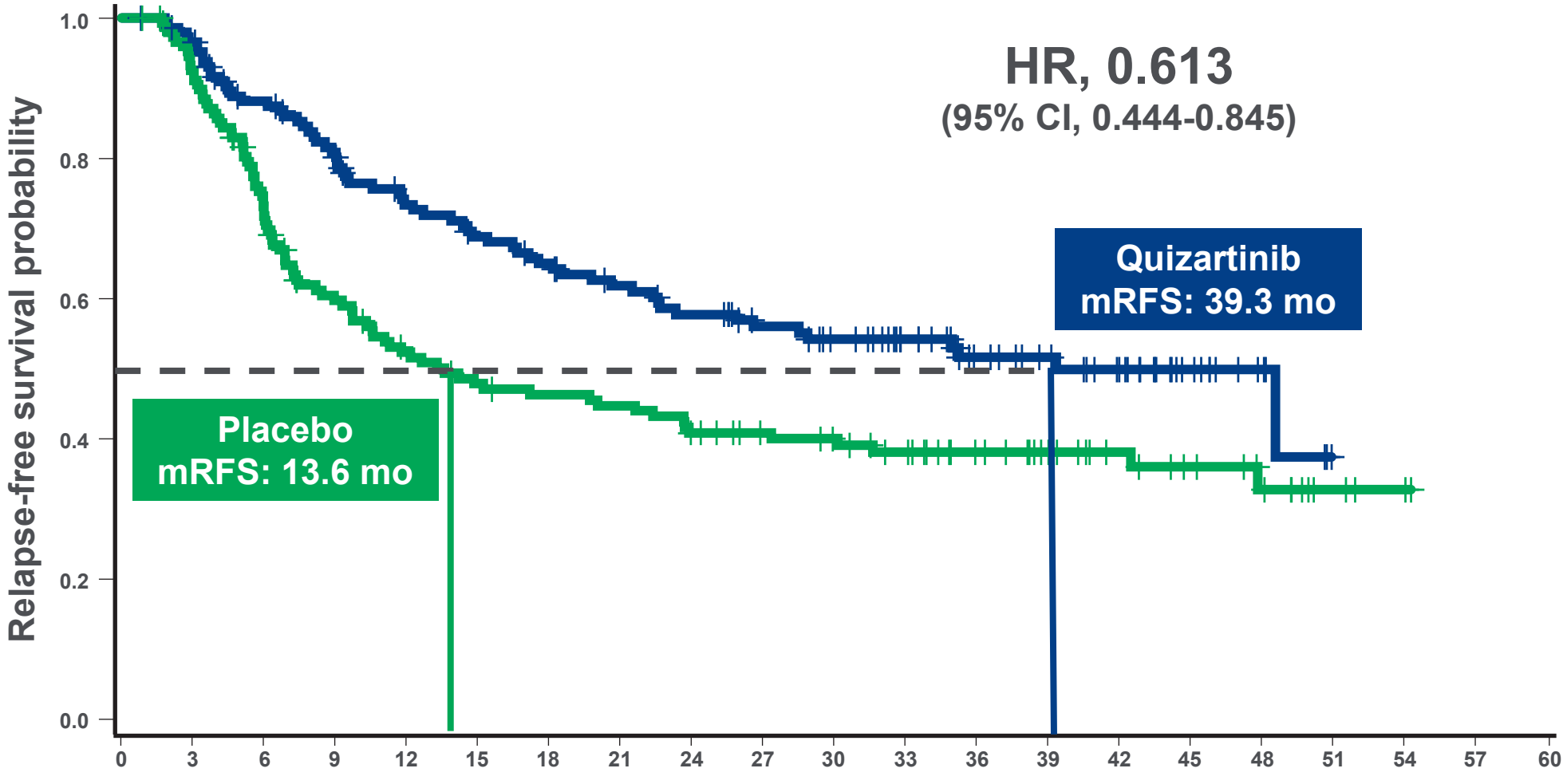
Response and Duration of CR[a]

Parameter	Quizartinib (N=268)	Placebo (N=271)
CRc		
%	71.6	64.9
95% CI	(65.8-77.0)	(58.9-70.6)
CR		
%	54.9	55.4
95% CI	(48.7-60.9)	(49.2-61.4)
CRi		
%	16.8	9.6
95% CI	(12.5-21.8)	(6.4-13.7)
Duration of CR		
Median, months	38.6	12.4
95% CI	(21.9-NE)	(8.8-22.7)

CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete neutrophil or platelet recovery; IRC, independent review committee; NE, not evaluable.

[a] By end of induction by IRC.

Exploratory Endpoint: Relapse-Free Survival in CR Patients

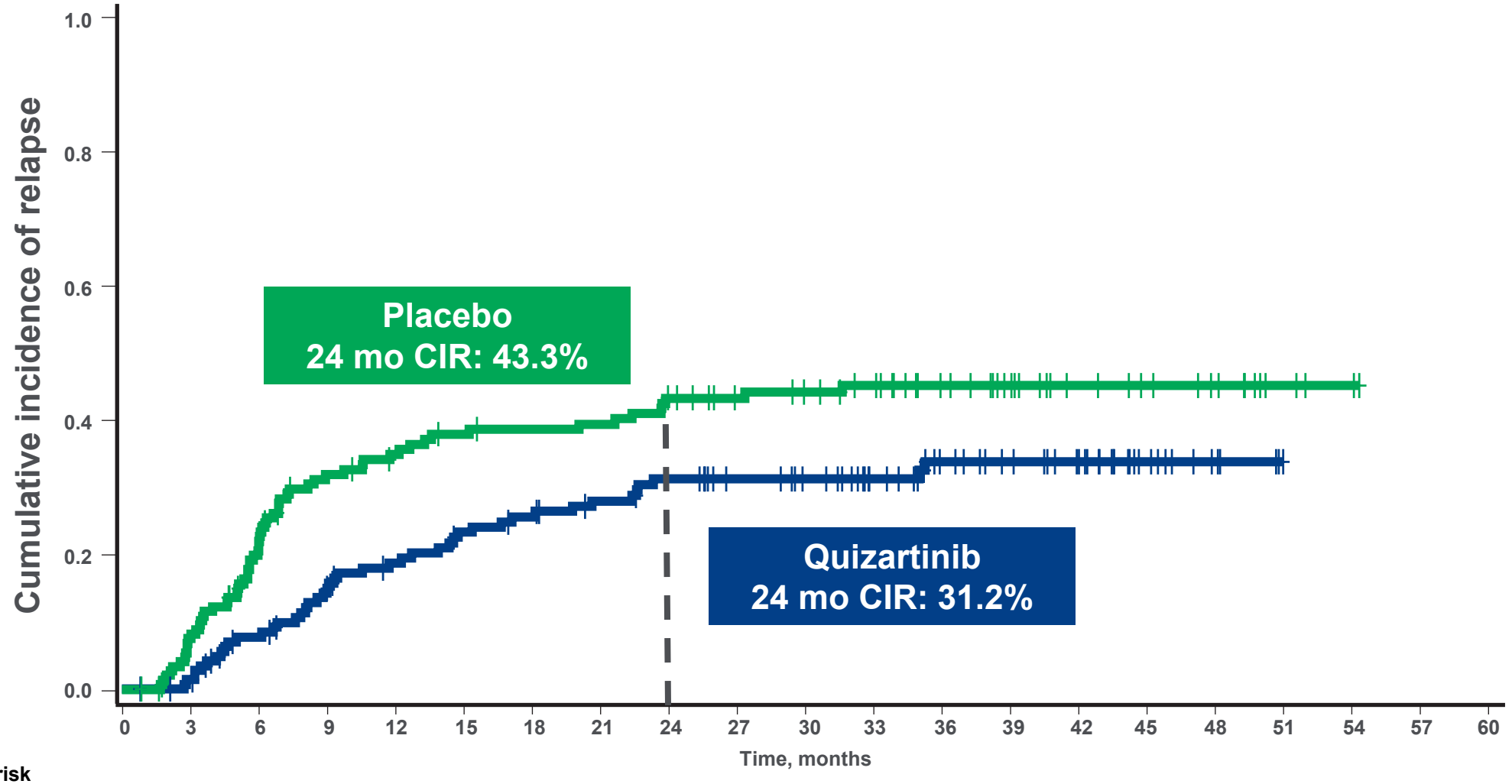


No. at risk																					
Quizartinib	147	140	123	111	97	90	84	77	71	63	57	48	36	31	24	13	6	0	0	0	0
Placebo	150	136	103	82	70	63	60	58	52	47	44	39	31	24	18	14	10	4	2	0	0

CR, complete remission; HR, hazard ratio; IRC, independent review committee; mRFS, median relapse-free survival.

[a] By end of induction by IRC.

Post-Hoc Analysis: Cumulative Incidence of Relapse in CR Patients



No. at risk																					
Quizartinib	147	140	123	111	97	90	84	77	71	63	57	48	36	31	24	13	6	0	0	0	0
Placebo	150	136	103	82	70	63	60	58	52	47	44	39	31	24	18	14	10	4	2	0	0

CIR, cumulative incidence of relapse; CR, complete remission; IRC, independent review committee.

[a] By end of induction by IRC.

Summary of Treatment Emergent Adverse Events (TEAEs)

Patients, %	Quizartinib (N=265)[a]	Placebo (N=268)[a]
Overview of adverse events		
TEAEs	99.6	98.9
Grade ≥3 TEAEs	92.1	89.6
TEAEs associated with fatal outcome	11.3	9.7
SAEs	54.0	45.9
Dose modifications[b]		
TEAEs associated with discontinuation	20.4	8.6
TEAEs associated with dose interruption	34.0	20.1
TEAEs associated with dose reduction	18.9	6.3
Summary of death		
Deaths within 30 days of study drug initiation	5.7	3.4
Deaths within 60 days of study drug initiation	7.5	4.9

- Median treatment duration: 10.7 weeks for quizartinib and 9.5 weeks for placebo
- Overall treatment exposure: 208 total patient-years for quizartinib and 174 total patient-years for placebo

SAE, Serious Adverse Event; TEAE, Treatment Emergent Adverse Event.

[a] Three patients in each group were not treated and not included in the safety analysis. [b] Patients may have been included in >1 category.

Summary of TEAEs Occurring in ≥20% of Patients

TEAEs, %	Quizartinib (N=265)[a]		Placebo (N=268)[a]	
Hematologic adverse events	All Grades	Grade ≥3	All Grades	Grade ≥3
Febrile neutropenia	44.2	43.4	42.2	41.0
Neutropenia	20.4	18.1	10.1	8.6
Non-hematologic adverse events	All Grades	Grade ≥3	All Grades	Grade ≥3
Pyrexia	42.3	4.5	40.7	4.9
Diarrhea	37.0	3.8	35.1	3.7
Hypokalemia	35.1	18.9	35.8	16.4
Nausea	34.0	1.5	31.3	1.9
Headache	27.5	0	19.8	0.7
Rash	26.0	3.0	24.6	1.1
Vomiting	24.5	0	19.8	1.5
Stomatitis	21.5	4.5	20.9	3.0
Constipation	21.1	0.4	25.7	0

TEAE, Treatment Emergent Adverse Event.

[a] Three patients in each group were not treated and not included in the safety analysis.

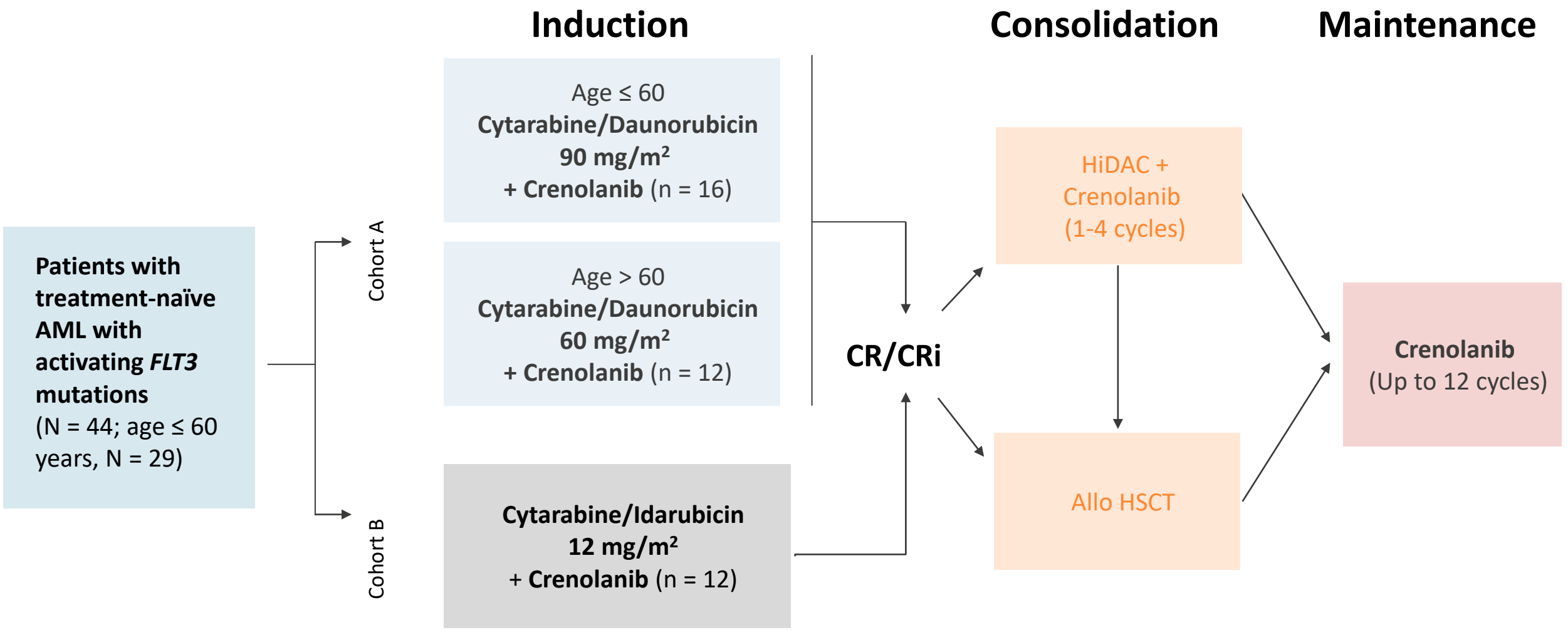
QT Prolongation by Central ECG and Select Cardiac Events by TEAE

Parameter	Quizartinib (N=265)	Placebo (N=268)
QTcF interval based on central ECG data (ms), %		
New > 450 ms	34.3	17.9
New > 480 ms	7.5	2.2
New > 500 ms	2.3	0.7
QTcF increase from baseline > 30 ms	55.1	32.5
QTcF increase from baseline > 60 ms	10.1	4.9
Select cardiac events by TEAE (PT), %		
ECG QT prolonged	13.6	4.1
Cardiac arrest/ventricular fibrillation	0.8	0
Ventricular tachycardia	0.4	0.4

- Two patients (0.8%) treated with quizartinib had cardiac arrest (grade 4 [n=1], grade 5 [n=1]), with recorded ventricular fibrillation in the setting of severe hypokalemia
- One patient (0.4%) died in their sleep (PT ‘death’) in the quizartinib arm
- Two patients (0.8%) discontinued quizartinib due to QT prolongation

ECG, electrocardiogram; PT, preferred term; QTcF, corrected QT interval by Fridericia’s formula; TEAE, Treatment Emergent Adverse Event.

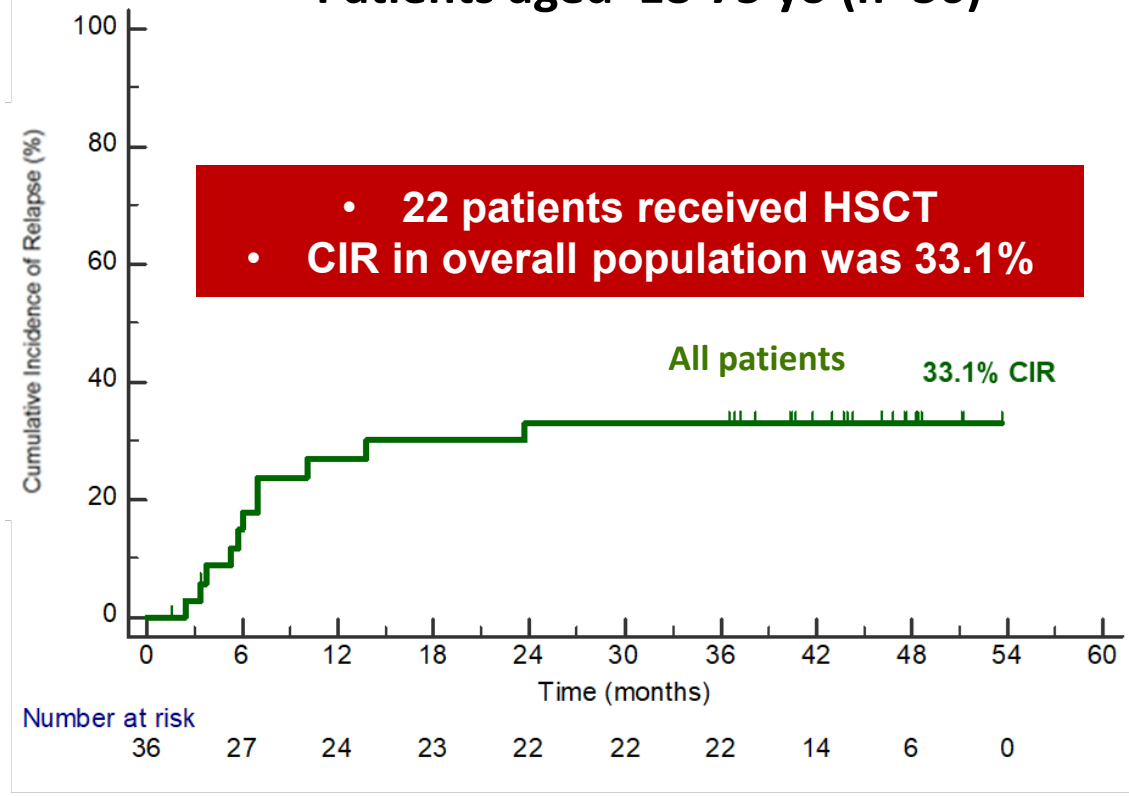
Crenolanib + Intensive Chemotherapy in *FLT3*m AML: *Study Design*



Wang ES, et al. *J Clin Oncol*. 2022;40(16 Suppl): Abstract 7007.

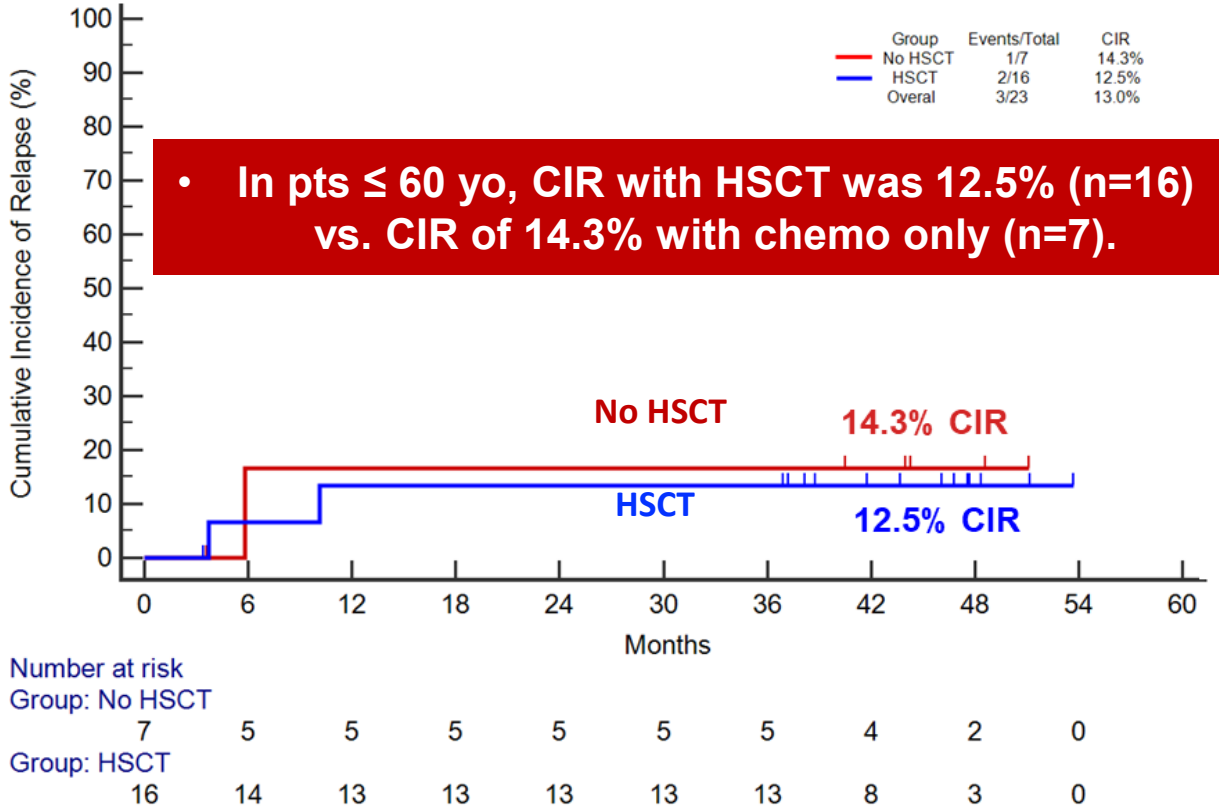
Crenolanib + Intensive Chemotherapy in *FLT3*m AML:
Cumulative Incidence of Relapse

Patients aged 18-75 yo (n=36)



- 22 patients received HSCT
- CIR in overall population was 33.1%

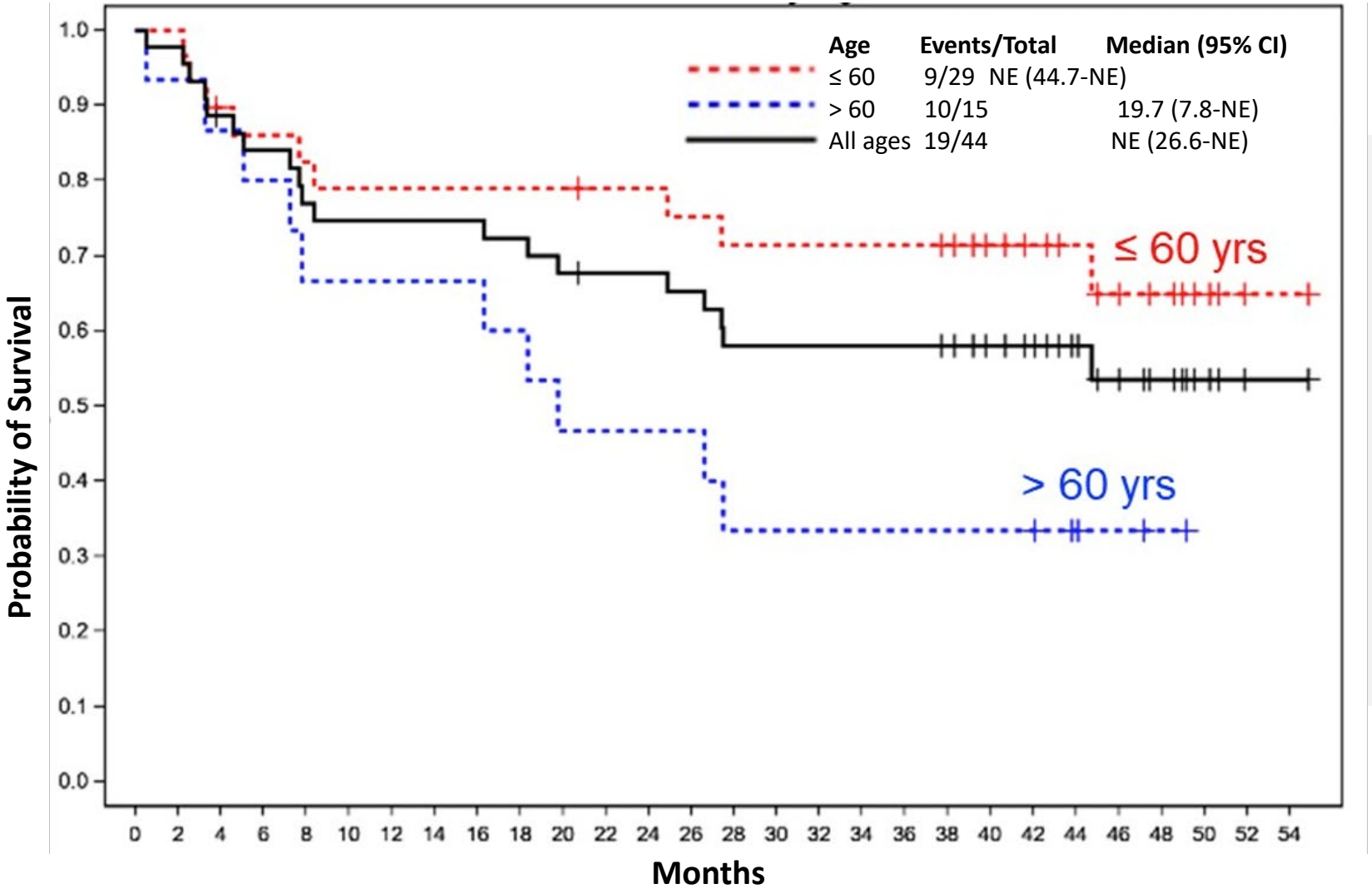
Patients aged ≤ 60 yo (n=23)



- In pts ≤ 60 yo, CIR with HSCT was 12.5% (n=16) vs. CIR of 14.3% with chemo only (n=7).

Wang ES, et al. *J Clin Oncol*. 2022;40(16 Suppl): Abstract 7007.

Crenolanib + Intensive Chemotherapy in *FLT3*m AML: *Overall Survival by Age*

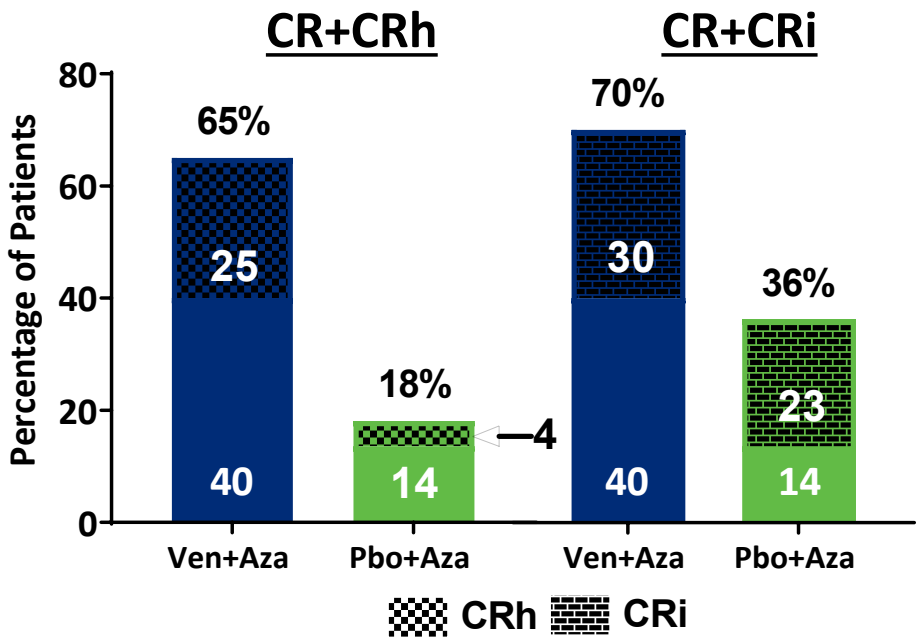


- At 45-mo follow-up, median OS not reached; 56.8% of patients alive
- Estimated 3-year OS 71%

Wang ES, et al. *J Clin Oncol*. 2022;40(16 Suppl): Abstract 7007.

VIALE A: Response and Survival in FLT3m+ AML

40 FLT3m+ pts (28 ITD) in AZA/VEN, 22 (13 ITD) in AZA/PBO



Median treatment duration of 7 mo
median time to CR/CRh of 1 m (0.8-4.8 mo)
Median DOR of CRh 18.3 mo (17.4 in ITD)
Median OS 13.3 mo/11.5 ITD

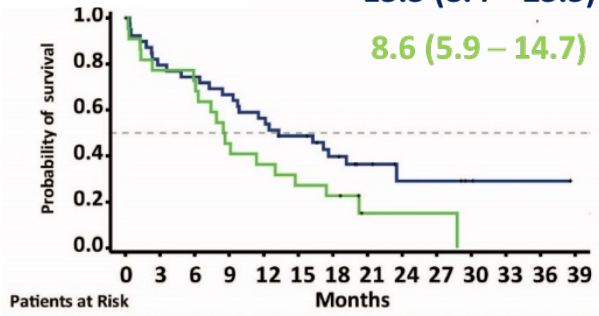
A.

FLT3mut

Median OS, months (95% CI)

13.3 (8.4 – 23.5)

8.6 (5.9 – 14.7)



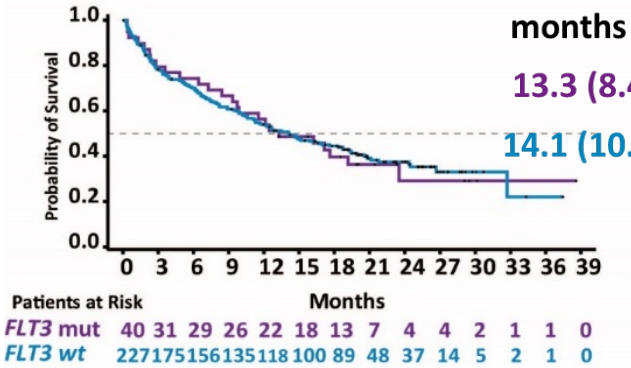
B.

FLT3mut vs. wt in Ven+Aza

Median OS, months (95% CI)

13.3 (8.4 – 23.5)

14.1 (10.6 – 18.7)



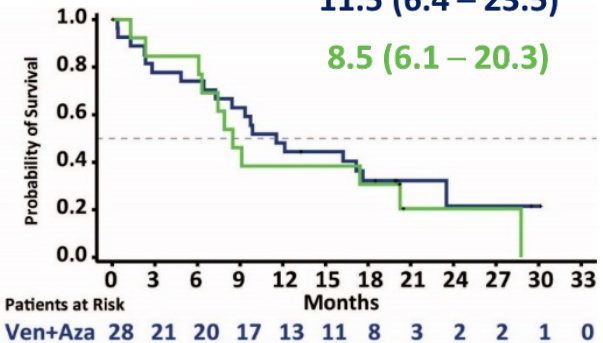
C.

FLT3-ITD

Median OS, months (95% CI)

11.5 (6.4 – 23.5)

8.5 (6.1 – 20.3)



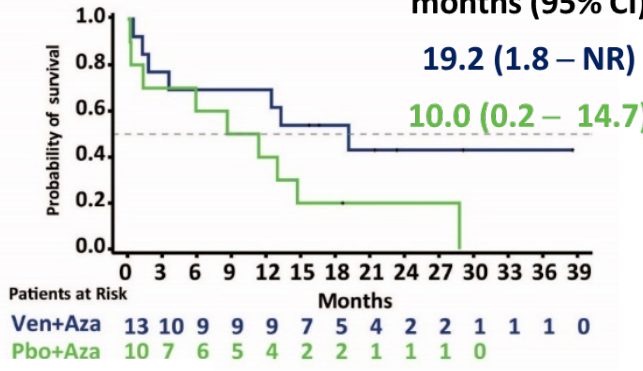
D.

FLT3-TKD

Median OS, months (95% CI)

19.2 (1.8 – NR)

10.0 (0.2 – 14.7)

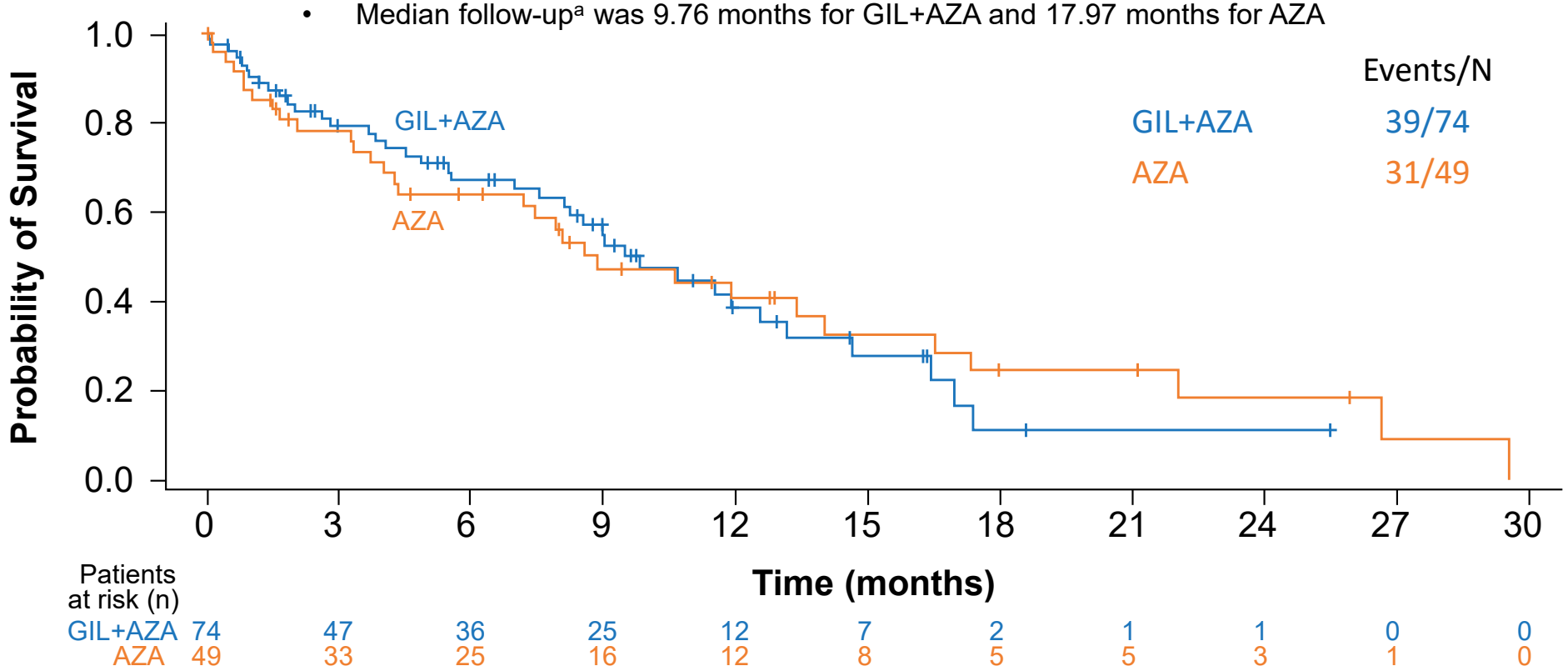


VIALE-A: In all patients (not just FLT3) with composite complete remission, MRD neg occurred in 23.4% (95% CI, 18.6 to 28.8)
MRD assessed by flow cytometry, with negativity defined according to ELN guidelines

Konopleva M et al. ASH 2020

Phase III Study of GLIT/AZA vs AZA in *FLT3*m AML
LACEWING: Overall Survival

- Median follow-up[a] was 9.76 months for GIL+AZA and 17.97 months for AZA



	Events/N	Median (95% CI)
GIL+AZA	39/74	9.82 (7.56, 12.55) months
AZA	31/49	8.87 (4.34, 14.03) months

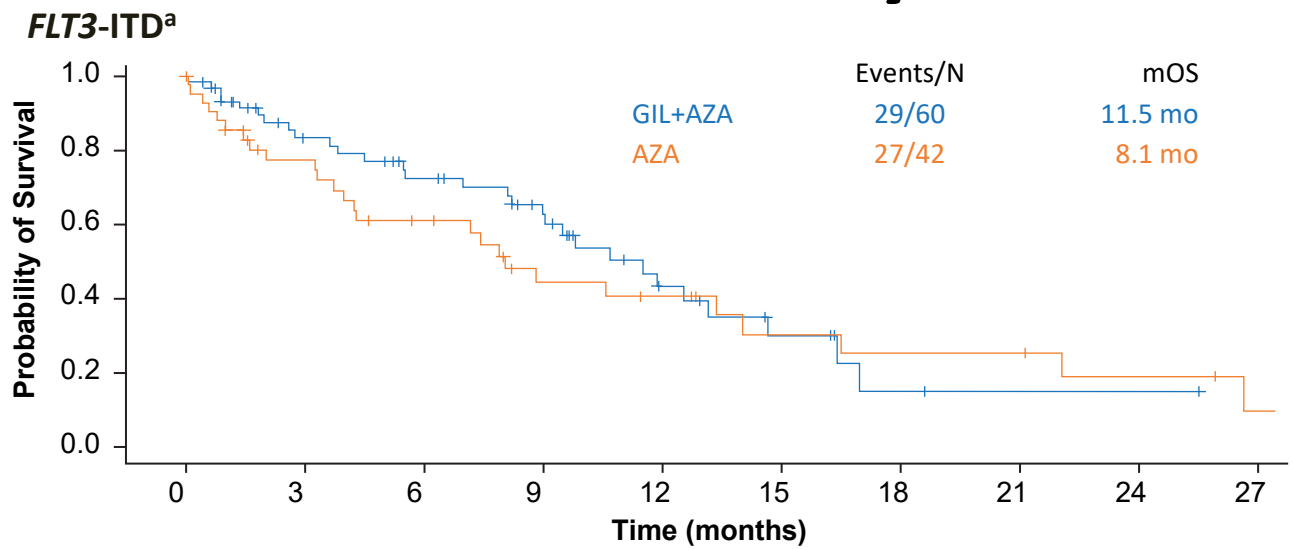
HR=0.916 (0.529, 1.585)
P=0.753

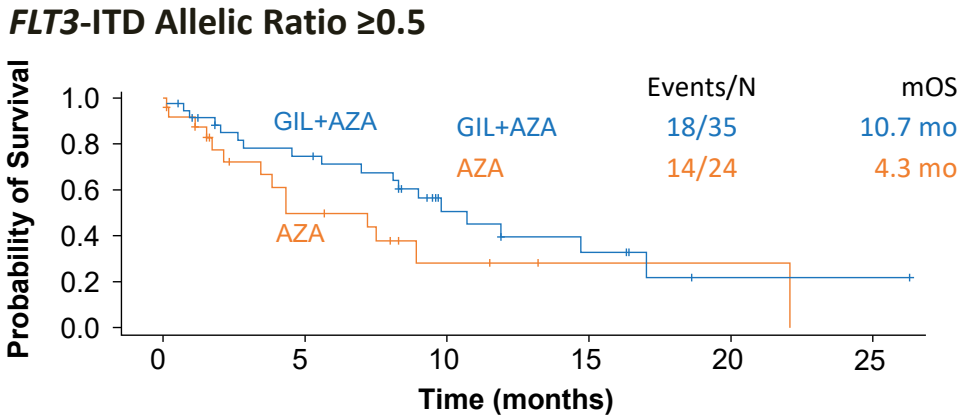
The intention-to-treat population included all randomized patients.
[a]Based on reverse Kaplan-Meier estimates.
Abbreviations: AZA, azacitidine; CI, confidence interval; GIL+AZA, gilteritinib plus azacitidine; HR, hazard ratio.

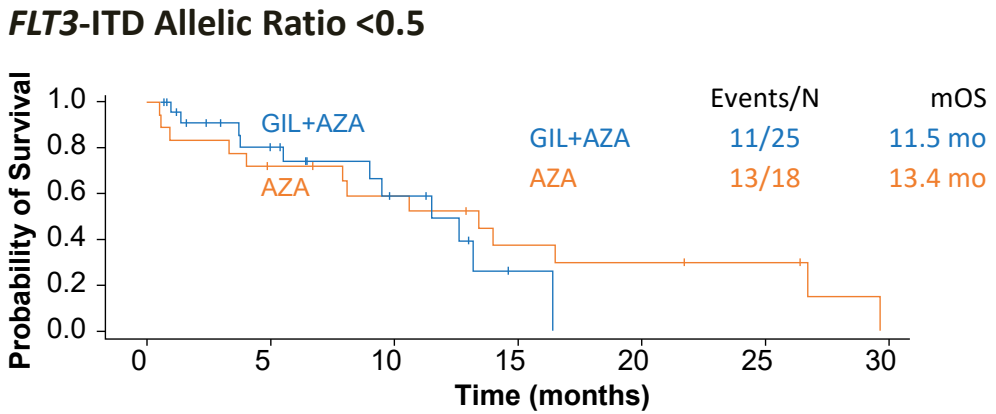
Wang ES, et al. ASH 2021, Abstract 700.

Data cutoff date: August 26, 2020

LACEWING: Overall Survival by Baseline *FLT3* ITD AR







[a]Includes patients ITD alone and ITD with TKD mutations.

Abbreviations: AZA, azacitidine; CI, confidence interval; *FLT3*, FMS-like tyrosine kinase 3; GIL+AZA, gilteritinib plus azacitidine; HR, hazard ratio; ITD, internal tandem duplication; mOS, median overall survival; TKD, tyrosine kinase domain.

Wang ES, et al. ASH 2021, Abstract 700.

Data cutoff date: August 26, 2020

QuANTUM-First: Conclusions

- In the pivotal phase 3 QuANTUM-First trial, quizartinib improved OS when combined with standard induction and consolidation therapy and continued for up to 3 years as a single agent in patients ages 18-75 with newly diagnosed *FLT3*-ITD+ AML
  - Clinically meaningful improvements in RFS, reduced CIR, and longer duration of CR may underpin the OS benefit
- Safety of quizartinib combined with intensive chemotherapy and as continuation monotherapy was generally manageable, with no new safety signals
- These data have the potential to change the standard of care for the treatment of adult patients with newly diagnosed *FLT3*-ITD+ AML

Q&A