The Combination of an *FLT3*-ITD, *NPM1*^{mut}, and an Epigenetic Regulatory Gene Mutation Confers Unique Sensitivity to Quizartinib: Analysis From the QuANTUM-First Trial

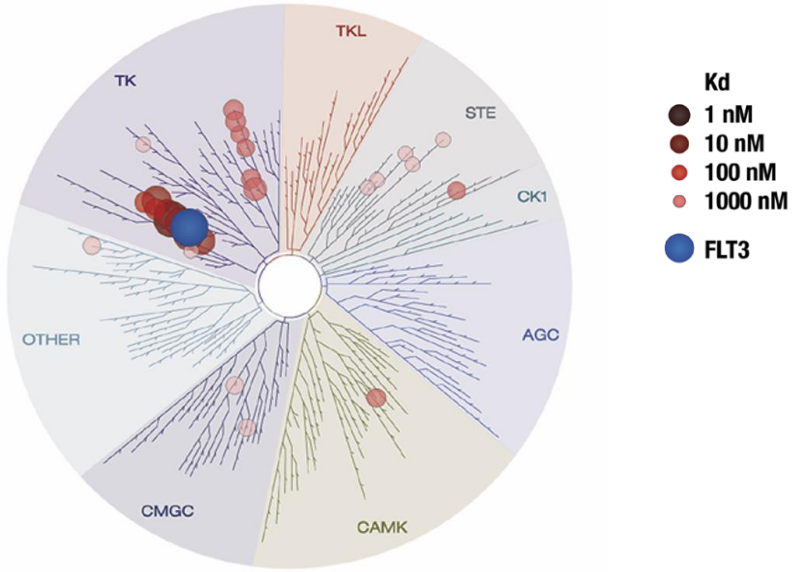
Mark J. Levis,[1] Pau Montesinos,[2] Hee-Je Kim,[3] Radovan Vrhovac,[4] Elzbieta Patkowska,[5] Pavel Zak,[6] Po-Nan Wang,[7] Jorge Cortes,[8] Mikkael A. Sekeres,[9] Herve Dombret,[10] Jianxiang Wang,[11] Richard F. Schlenk,[12] Alexander E. Perl,[13] Giorgio Inghiram,[14] Jaime E. Connolly Rohrbach,[14] Venkat Thodima,[14] Li Liu,[14] Karenza Alexis,[14] Akash Nahar,[14] Kristy Burns,[14] Harry P. Erba[15]

[1]Division of Hematologic Malignancies, Johns Hopkins University, Baltimore, MD, USA; [2]Hematology Department, La Fe University and Polytechnic Hospital, Valencia, Spain; [3]Department of Hematology, Catholic Hematology Hospital, Seoul St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [4]Division of Hematology, University Hospital Centre Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia; [5]Institute of Hematology and Blood Transfusion, Warsaw, Poland; [6]Department of Internal Medicine—Haematology, University Hospital Hradec Kralove, Hradec Kralove, Czechia; [7]Chang Gung Medical Foundation, Linkou, Taiwan; [8]Augusta University Medical Center, Augusta, GA, USA; [9]Sylvester Cancer Center, University of Miami Health System, Miami, FL, USA; [10]Saint Louis Hospital, University of Paris, Paris, France; [11]Institute of Hematology and Blood Diseases Hospital, Tianjin, China; [12]National Center of Tumor Diseases Trial Center, German Cancer Research Center, Department of Internal Medicine V, Heidelberg University Hospital, Heidelberg, Germany; [13]Division of Hematology/Oncology, University of Pennsylvania, Philadelphia, PA, USA; [14]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [15]Duke Cancer Institute, Durham, NC, USA

Background and Objectives

- Approximately 25% of patients with ND AML have *FLT3*-ITD alterations[1,2]
  - *FLT3*-ITD alterations impact survival outcomes, particularly in older patients, irrespective of whether they receive intensive or non-intensive treatment regimens
- The presence of co-mutations can impact prognosis and outcomes for patients with *FLT3*-ITD$^+$ ND AML[1,2]
  - *DNMT3A*^{mut} alters DNA methylation, contributing to the expansion and persistence of pre-leukemic clones[3]
  - *TET2, WT1, IDH1, and IDH2* mutations constitute a complementation group characterized by disordered DNA hydroxymethylation[4]
- Quizartinib is an oral, selective, type II inhibitor of FLT3, with potent binding affinity against FLT3-WT, FLT3-ITDs, and several FLT3 variants with point mutations within the kinase domain
  - Quizartinib is approved in combination with induction + consolidation chemotherapy, then as monotherapy maintenance for patients with *FLT3*-ITD$^+$ ND AML[5]
- In the randomized, phase 3, QuANTUM-First trial (NCT02668653), quizartinib significantly improved OS vs placebo in patients with *FLT3*-ITD$^+$ ND AML[6]
  - Patients < 60 years of age had a more pronounced benefit from quizartinib than patients ≥ 60 years of age

Kinase selectivity profiling of quizartinib



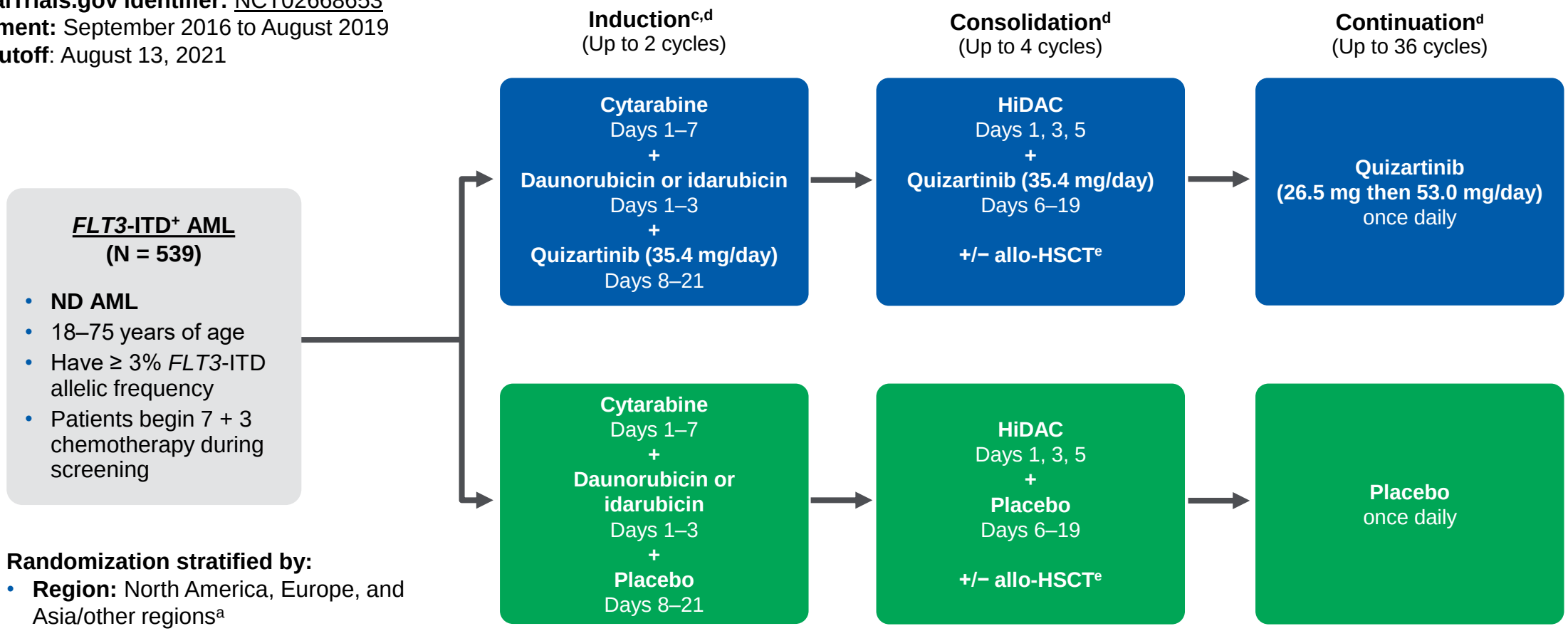
Hypothesis: The presence of co-mutations in *NPM1* and an epigenetic regulator (*DNMT3A*, *TET2*, *WT1*, *IDH1*, or *IDH2*) may identify a subgroup of patients with *FLT3*-ITD$^+$ AML who particularly benefit from quizartinib

DNMT3A, DNA (cytosine-5)-methyltransferase 3A; FLT3, FMS-like tyrosine kinase 3; *IDH*, isocitrate dehydrogenase; ITD, internal tandem duplication; mut, mutation; ND AML, newly diagnosed acute myeloid leukemia; *NPM1*, nucleophosmin 1; OS, overall survival; *TET2*, Tet methylcytosine dioxygenase 2; WT, wild-type; *WT1*, Wilms' tumor 1.

1. Döhner H, et al. *Blood* 2017;129:424–447. 2. Papaemmanuil E, et al. *N Engl J Med* 2016;374:2209–2221. 3. Chan SM, Majeti R. *Int J Hematol* 2013;98:648–657. 4. Rampal R, et al. *Cell Rep* 2014;9:1841–1855.
5. VANFLYTA® (quizartinib) [prescribing information]. Basking Ridge, NJ: Daiichi Sankyo Inc.; 2023. 6. Erba HP, et al. *Lancet* 2023;401:1571–1583.

QuANTUM-First Study Design

ClinicalTrials.gov identifier: NCT02668653
Enrollment: September 2016 to August 2019
Data cutoff: August 13, 2021



Randomization stratified by:
- **Region:** North America, Europe, and Asia/other regions[a]
- **Age:** < 60 years, ≥ 60 years
- **WBC[b]:** < 40 × 10^9/L, ≥ 40 × 10^9/L

[a]Including Australia and South America. [b]WBC count was measured at the time of AML diagnosis. [c]During Cycle 2 of the induction phase, the 7 + 3 or the 5 + 2 chemotherapy regimen may be administered, and quizartinib/placebo started on Day 8 or 6, respectively. [d]A fourth phase is the long-term follow-up phase, which begins upon completion of 36 cycles of study drug (quizartinib/placebo) in the continuation phase or permanent discontinuation of study drug in any phase. [e]Per institutional policies.
allo-HSCT, allogeneic hematopoietic stem cell transplantation; HiDAC, high-dose cytarabine; WBC, white blood cell.

Baseline Mutational Analyses

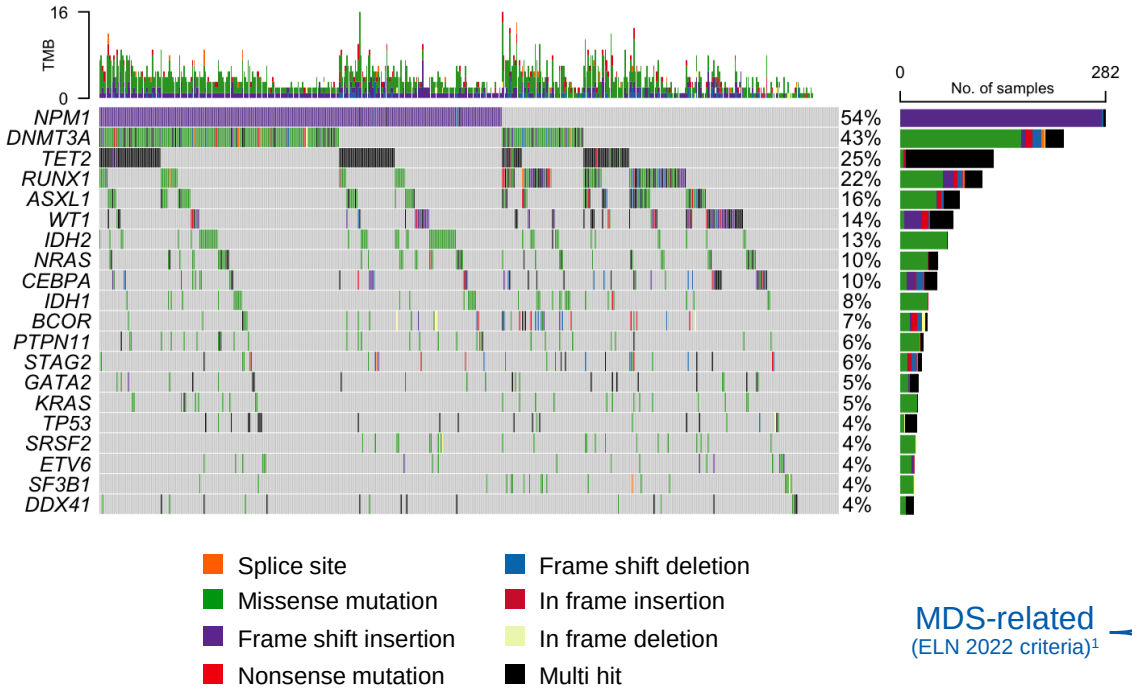
- Gene mutations were assessed by central laboratory testing using bone marrow and peripheral blood samples collected at screening (baseline)
- Mutational statuses of 38 AML-related genes were analyzed via next-generation sequencing using a customized Archer VARIANTPlex Core Myeloid panel
  - A gene was considered mutated if it exhibited ≥ 1 somatic mutation with a VAF ≥ 2.7%
- Exploratory analyses were conducted to assess the effect of individual gene mutations on OS, composite CR (CRc; CR + CRi) rate, and RFS[a]:
  - **OS (primary study endpoint):** time from randomization until death
  - **CRc rate (secondary endpoint):** proportion achieving CR or CRi by end of induction (IWG 2003 criteria[1])
  - **RFS (exploratory endpoint):** time from randomization until relapse or death in patients achieving CR/CRi

[a]OS and RFS are summarized by treatment group using the Kaplan–Meier method, with the HR and 95% CI for treatment groups estimated using unstratified Cox proportional hazard models. CRc rates are based on IRC assessment and summarized by treatment group, with point estimates and associated two-sided 95% CIs constructed using the Clopper–Pearson method.

CI, confidence interval; CR, complete remission; CRc, composite CR; CRi, CR with incomplete hematologic recovery; HR, hazard ratio; IRC, independent review committee; IWG, International Working Group; RFS, relapse-free survival; VAF, variant allele frequency.

1. Cheson BD, et al. *J Clin Oncol* 2003;21:4642–4649.

Mutational Frequencies at Baseline



Baseline mutation frequency

Prognostically relevant

MDS-related (ELN 2022 criteria)[1]

	Quizartinib (N = 258) n (%)	Placebo (N = 260) n (%)
RUNX1	51 (20)	62 (24)
ASXL1	39 (15)	43 (17)
BCOR	14 (5)	24 (9)
STAG2	12 (5)	17 (7)
SRSF2	9 (3)	13 (5)
SF3B1	10 (4)	10 (4)
U2AF1	5 (2)	10 (4)
ZRSR2	6 (2)	5 (2)
EZH2	4 (2)	7 (3)
KRAS	16 (6)	8 (3)
NRAS	27 (10)	25 (10)
TP53	10 (4)	13 (5)

Most common

	Quizartinib (N = 258) n (%)	Placebo (N = 260) n (%)
NPM1	142 (55)	140 (54)
DNMT3A	112 (43)	113 (43)
TET2	61 (24)	67 (26)
RUNX1	51 (20)	62 (24)
ASXL1	39 (15)	43 (17)
WT1	36 (14)	37 (14)
IDH2	30 (12)	35 (13)
NRAS	27 (10)	25 (10)
CEBPA	27 (10)	24 (9)
IDH1	20 (8)	19 (7)
BCOR	14 (5)	24 (9)
PTPN11	13 (5)	19 (7)
STAG2	12 (5)	17 (7)

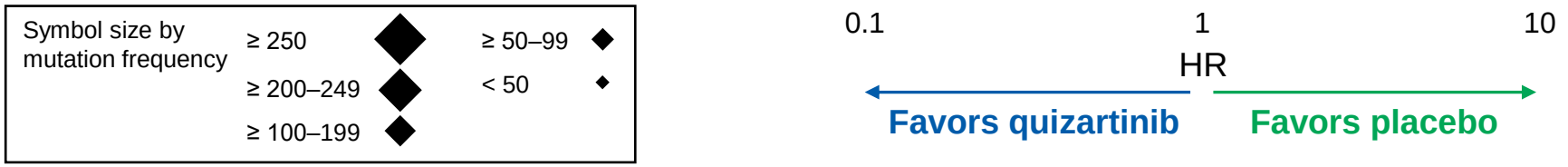
- In addition to *FLT3*-ITD, mutations were detected in 96.5% (500/518) of analyzed samples
- *NPM1* and *DNMT3A* were co-mutated in 33.6% (168/500) of patients
- An *NPM1* mutation in combination with any mutation in *DNMT3A*, *TET2*, *WT1*, *IDH1*, or *IDH2* was detected in 50.2% (251/500) of patients

ELN, European LeukemiaNet; MDS, myelodysplastic syndromes

1. Döhner H, et al. *Blood* 2022;140:1345–1377.

Impact of Most Common Individual Baseline Mutations on OS

Gene mutation	Quizartinib N/mOS	Placebo N/mOS	HR (95% CI)
NPM1	**142/NE**	**140/15.1**	**0.64 (0.46–0.89)**
DNMT3A	**112/40.4**	**113/9.6**	**0.55 (0.39–0.78)**
TET2	**61/NE**	**67/11.3**	**0.60 (0.37–0.97)**
RUNX1	51/16.8	62/13.4	0.93 (0.58–1.47)
ASXL1	39/16.5	43/42.5	1.70 (0.94–3.05)
WT1	36/24.2	37/16.0	0.77 (0.41–1.43)
IDH2	30/28.9	35/35.4	0.82 (0.42–1.61)
NRAS	27/31.9	25/28.3	0.97 (0.46–2.04)
CEBPA	27/NE	24/47.8	0.79 (0.33–1.90)
IDH1	20/NE	19/7.2	0.43 (0.18–1.04)
BCOR	14/NE	24/19.8	0.41 (0.15–1.12)
PTPN11	13/NE	19/8.1	0.45 (0.17–1.17)
STAG2	12/11.9	17/18.5	0.97 (0.37–2.58)



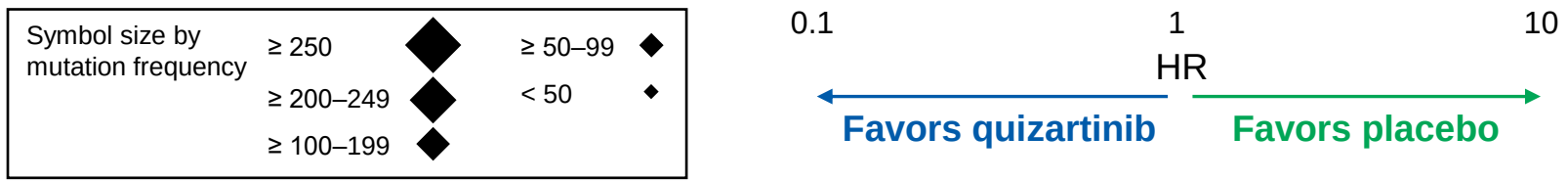
- OS benefits with quizartinib vs placebo persisted across most subgroups defined by individual gene mutations
- Substantial OS benefits were observed for quizartinib in patients with *NPM1*, *DNMT3A*, or *TET2* mutations
- No individual mutation fully favored placebo for OS (ie, both 95% CIs > 1)

mOS, median OS; NE, not estimatable.

Impact of MDS-Related Gene Mutations on OS

MDS-related (ELN 2022 criteria)[1]

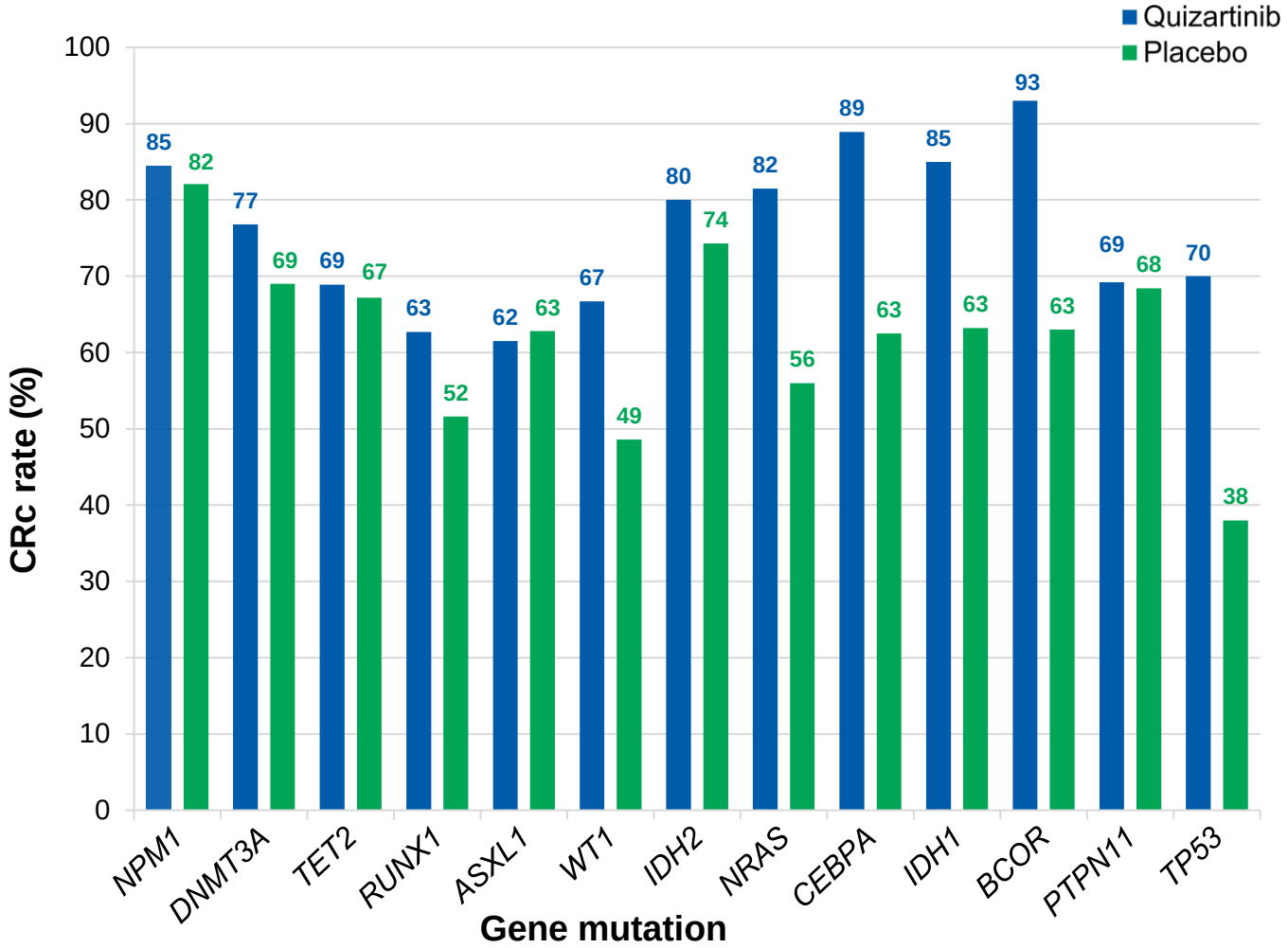
Gene mutation	Quizartinib N/mOS	Placebo N/mOS	HR (95% CI)
RUNX1	51/16.8	62/13.4	0.93 (0.58–1.47)
ASXL1	39/16.5	43/42.5	1.70 (0.94–3.05)
BCOR	14/NE	24/19.8	0.41 (0.15–1.12)
STAG2	12/11.9	17/18.5	0.97 (0.37–2.58)
SRSF2	9/14.5	13/27.8	1.55 (0.59–4.07)
SF3B1	10/9.2	10/6.6	0.66 (0.27–1.66)
U2AF1	5/9.0	10/5.0	0.83 (0.27–2.52)
ZRSR2	6/NE	5/13.8	0.66 (0.13–3.32)
EZH2	4/NE	7/13.8	0 (0–NE)
KRAS	16/22.4	8/7.0	0.62 (0.22–1.79)
NRAS	27/31.9	25/28.3	0.97 (0.46–2.04)
TP53	10/19.7	13/10.2	0.66 (0.24–1.85)



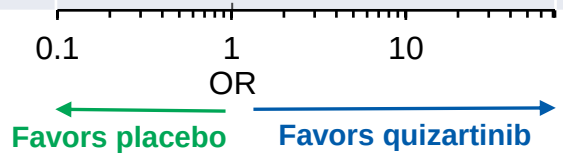
- Small patient numbers and wide CIs limit the interpretability of the results
- The OS HR for patients with any MDS-related gene mutation was 0.998 (95% CI, 0.72–1.39)

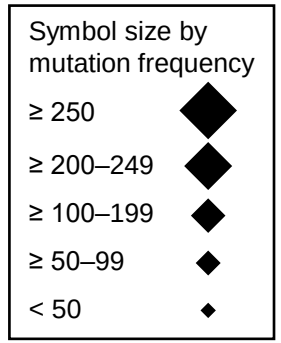
1. Döhner H, et al. *Blood* 2022;140:1345–1377.

CRc Rates by Individual Baseline Gene Mutation



Gene mutation	CRc OR (95% CI)	OR (95% CI)
NPM1		1.19 (0.63–2.22)
DNMT3A		1.48 (0.82–2.69)
TET2		1.08 (0.51–2.27)
RUNX1		1.58 (0.74–3.36)
ASXL1		0.95 (0.39–2.32)
WT1		2.11 (0.82–5.44)
IDH2		1.39 (0.43–4.47)
NRAS		3.46 (0.99–12.1)
CEBPA		**4.80 (1.12–20.6)**
IDH1		3.31 (0.71–15.4)
BCOR		7.80 (0.87–70.1)
PTPN11		1.04 (0.23–4.77)



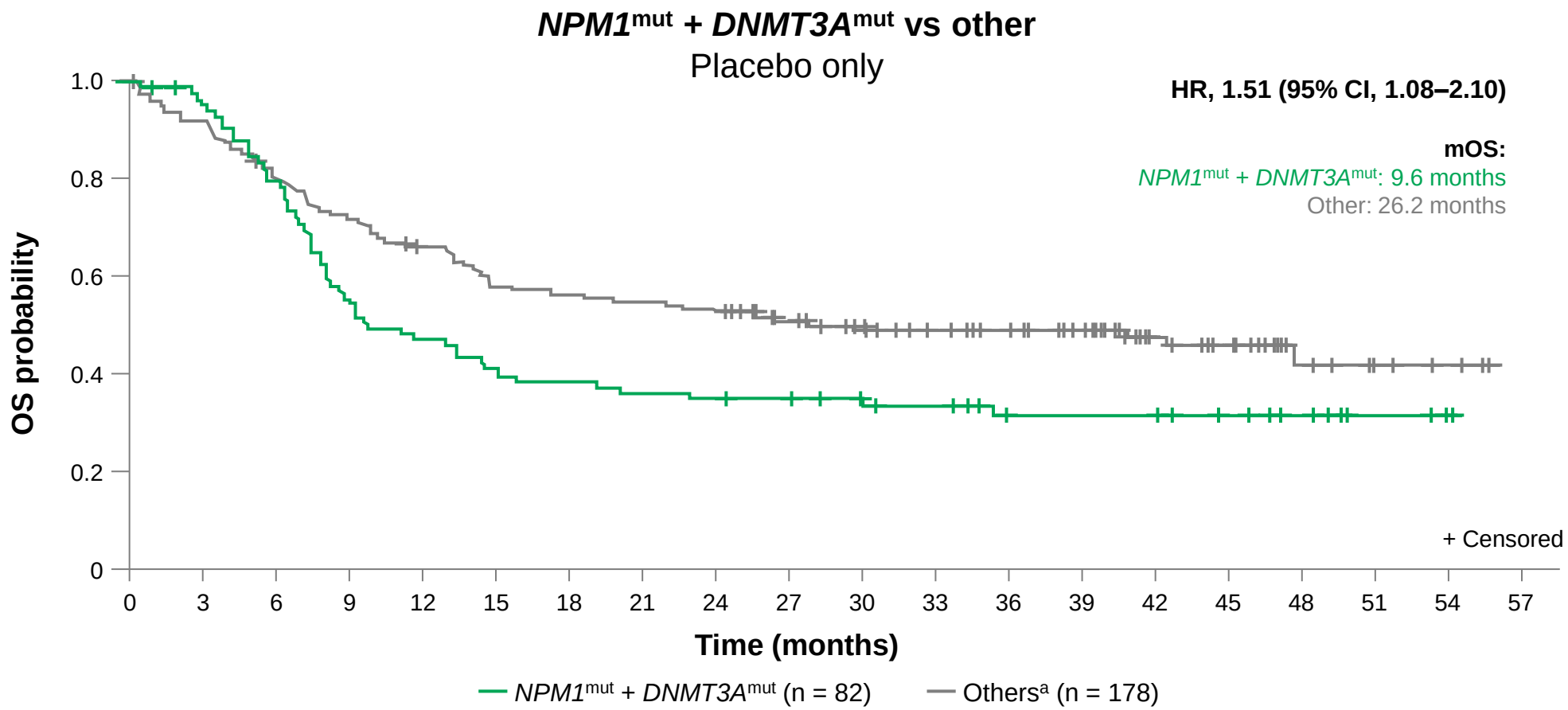


- No individual baseline mutation appeared to confer primary resistance to quizartinib

OR, odds ratio.

Placebo Arm: OS for Patients With *NPM1*^{mut} + *DNMT3A*^{mut}

- In the placebo arm, patients with the triple mutation of *FLT3*-ITD + *NPM1*^{mut} + *DNMT3A*^{mut} had a poorer OS vs patients without the triple mutation

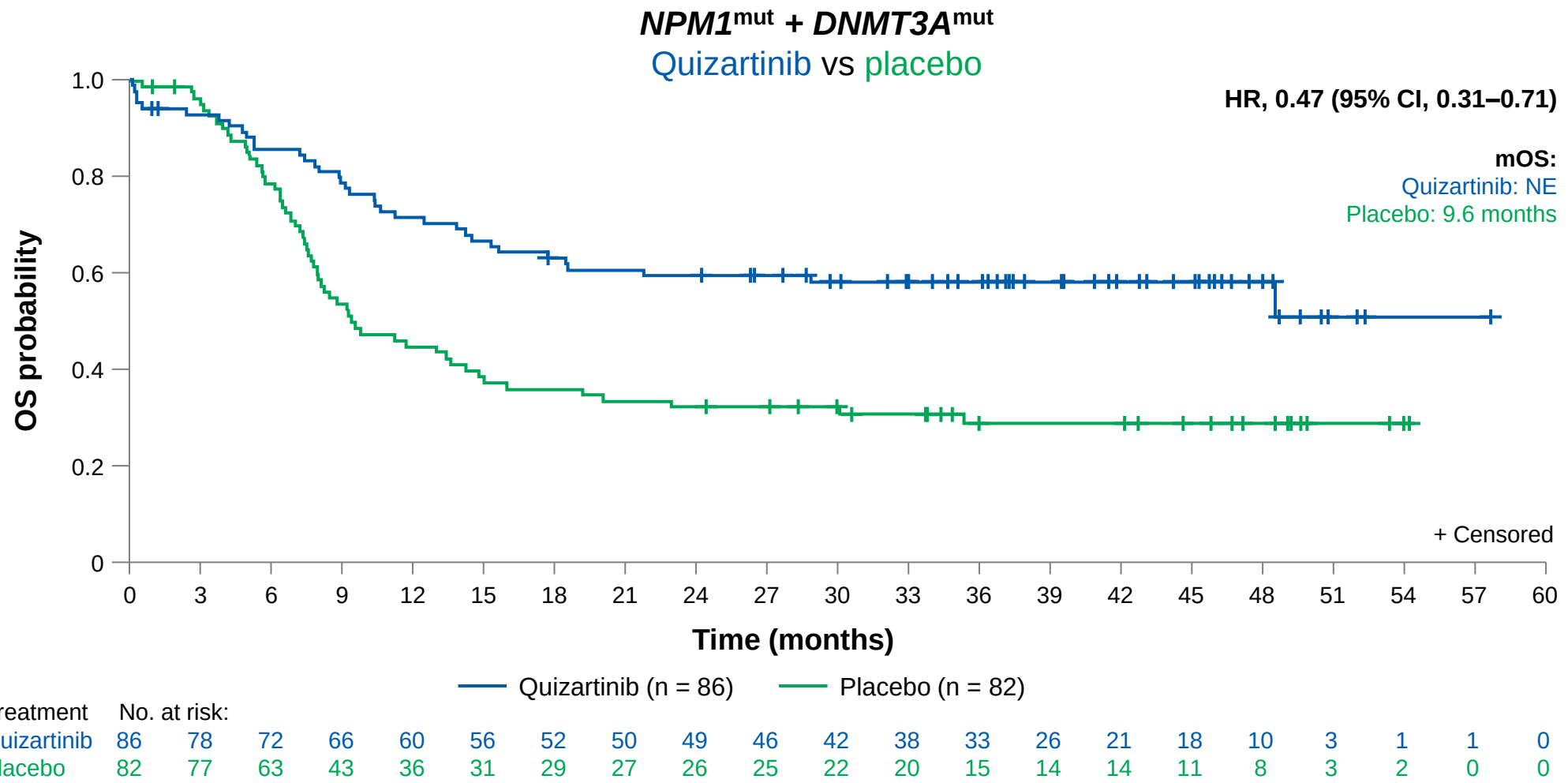


Mutation status	No. at risk:																			
NPM1^{mut} + *DNMT3A*^{mut}	82	77	63	43	36	31	29	27	26	25	22	20	15	14	14	11	8	3	2	1
Others[a]	178	162	140	125	112	97	94	91	88	76	68	60	55	42	25	20	9	5	3	0

[a]Includes *NPM1*^{mut} + *DNMT3A*^{WT}, *NPM1*^{WT} + *DNMT3A*^{mut}, or *NPM1*^{WT} + *DNMT3A*^{WT}.

OS for Patients With *NPM1*^{mut} + *DNMT3A*^{mut}

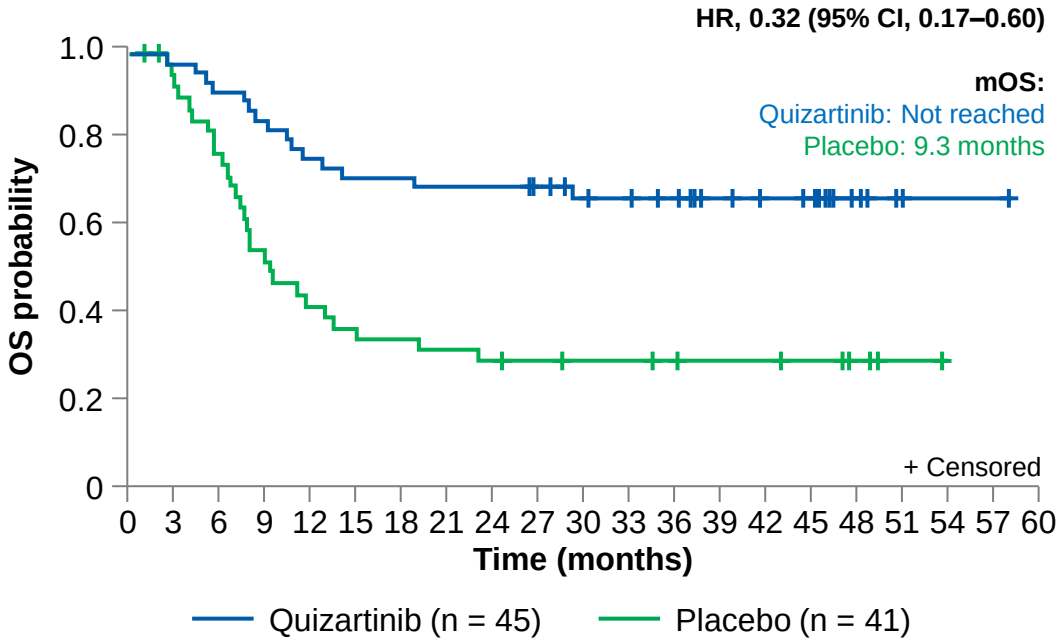
- The OS benefit with quizartinib was most pronounced in patients with the *FLT3*-ITD + *NPM1*^{mut} + *DNMT3A*^{mut} triple mutation



OS for Patients With *NPM1*^{mut} + *DNMT3A*^{mut} by Age

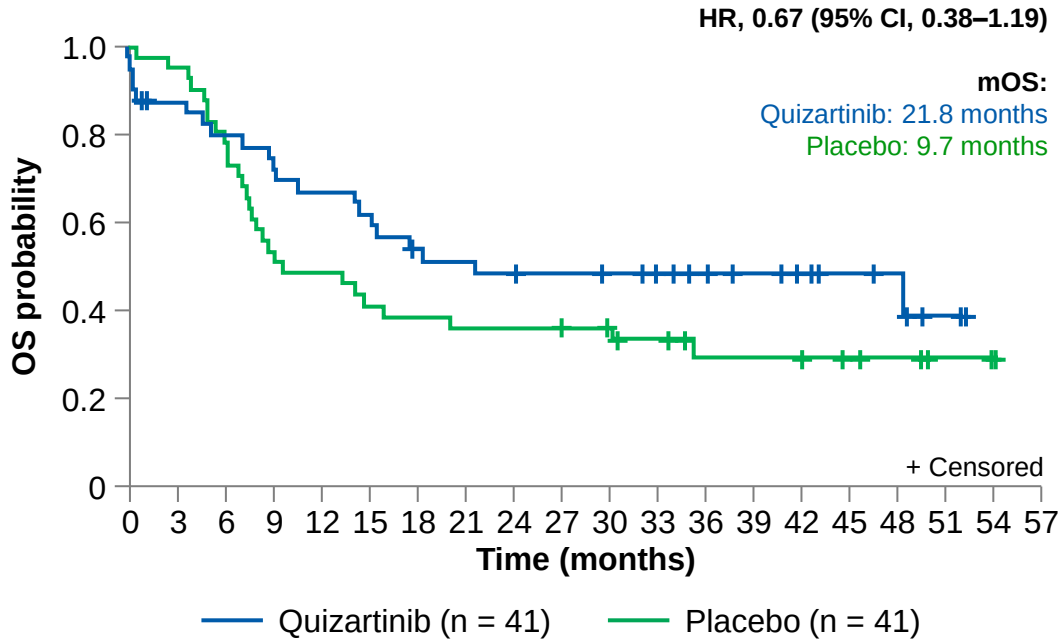
- A substantial OS benefit was observed with quizartinib for patients with *NPM1*^{mut} + *DNMT3A*^{mut} regardless of age

***NPM1*^{mut} + *DNMT3A*^{mut}**
< 60 years of age
Quizartinib vs placebo



Treatment	No. at risk																			
Quizartinib	45	44	41	37	34	32	32	31	31	29	26	24	21	16	13	12	5	1	1	1	0
Placebo	41	38	30	21	16	14	13	12	11	10	9	9	8	7	7	6	4	1	0	0	0

***NPM1*^{mut} + *DNMT3A*^{mut}**
≥ 60 years of age
Quizartinib vs placebo



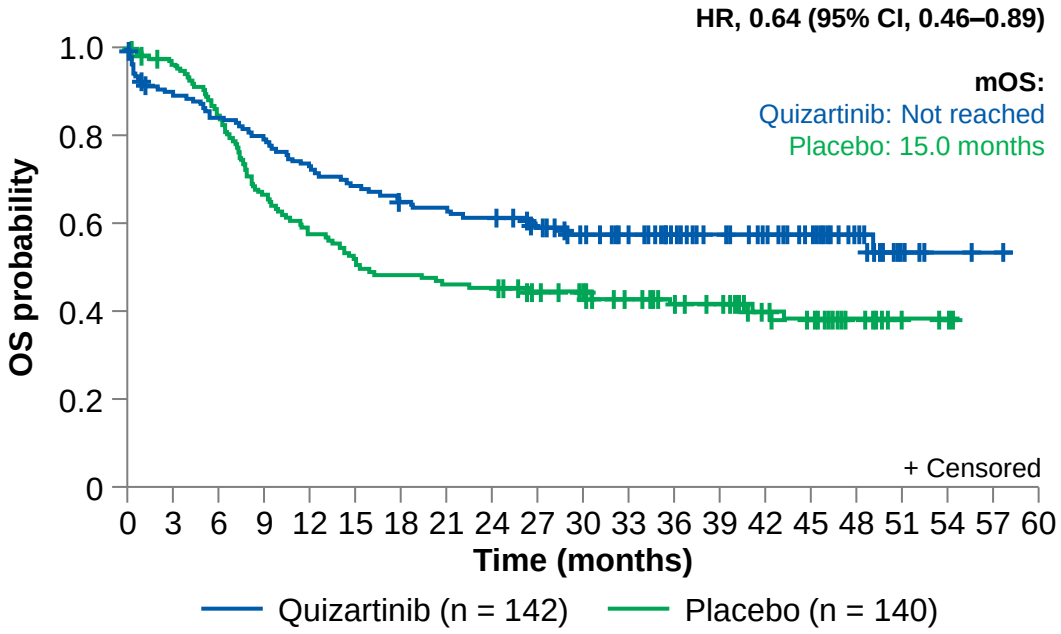
Treatment	No. at risk																			
Quizartinib	41	34	31	29	26	24	20	19	18	17	16	14	12	10	8	6	5	2	0	0
Placebo	41	38	30	21	16	14	13	12	11	10	9	9	8	7	7	6	4	1	0	0

OS for Patients With *NPM1*^{mut} + a Mutated Epigenetic Regulator

- A substantial OS benefit was observed in patients with *NPM1*^{mut}
- Patients with the triple mutation of *FLT3*-ITD + *NPM1*^{mut} + a mutated epigenetic regulator had a greater OS vs patients with *NPM1*^{mut} alone

NPM1^{mut}

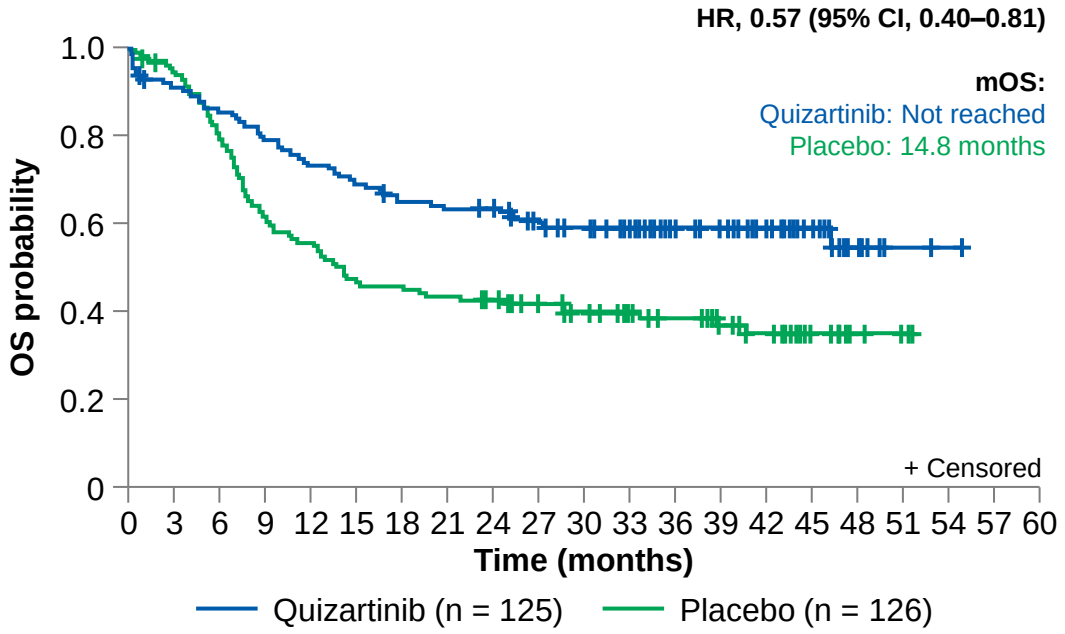
Quizartinib vs placebo



Treatment	No. at risk																			
Quizartinib	142	125	118	110	101	96	90	86	85	78	70	61	52	44	36	26	16	5	2	1	0
Placebo	140	132	114	91	79	69	66	63	62	55	51	43	36	32	24	20	10	3	2	0	0

NPM1^{mut} + [_DNMT3A_^{mut}, _TET2_^{mut}, _WT1_^{mut}, _IDH1_^{mut}, or _IDH2_^{mut}]

Quizartinib vs placebo



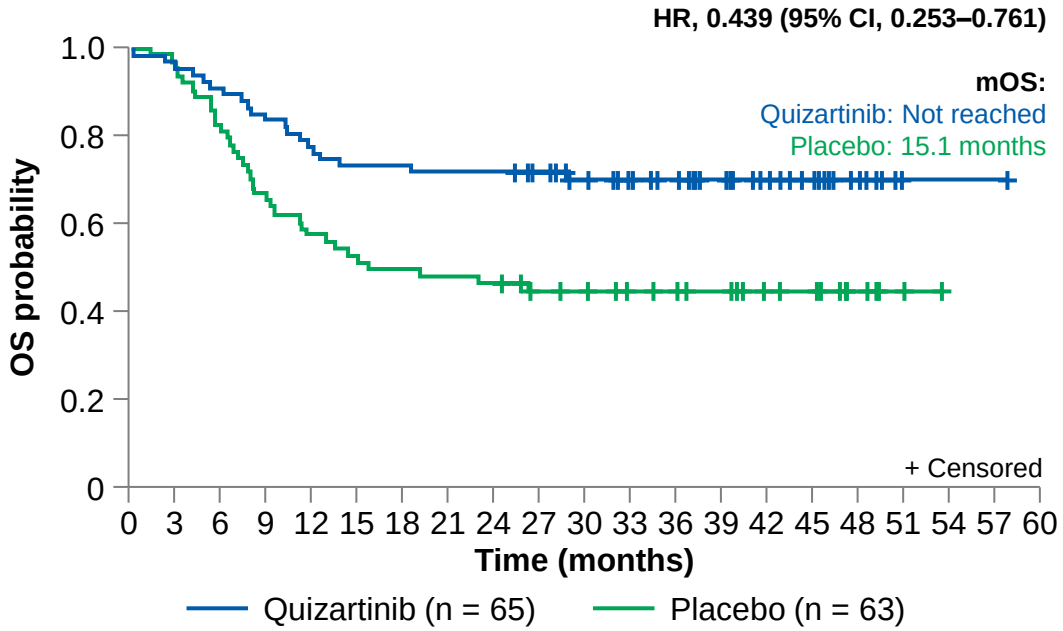
Treatment	No. at risk																			
Quizartinib	125	112	106	99	92	87	81	78	77	70	63	57	49	42	35	25	15	5	2	1	0
Placebo	126	119	102	80	70	61	58	55	54	48	45	37	31	28	21	17	9	3	2	0	0

OS for Patients With *NPM1*^{mut} + a Mutated Epigenetic Regulator by Age

- Quizartinib conferred an OS benefit in patients with *NPM1*^{mut} + a mutated epigenetic regulator, regardless of age

NPM1^{mut} **+ [*DNMT3A*^{mut} , *TET2*^{mut}, *WT1*^{mut}, *IDH1*^{mut}, or *IDH2*^{mut}]**
< 60 years of age

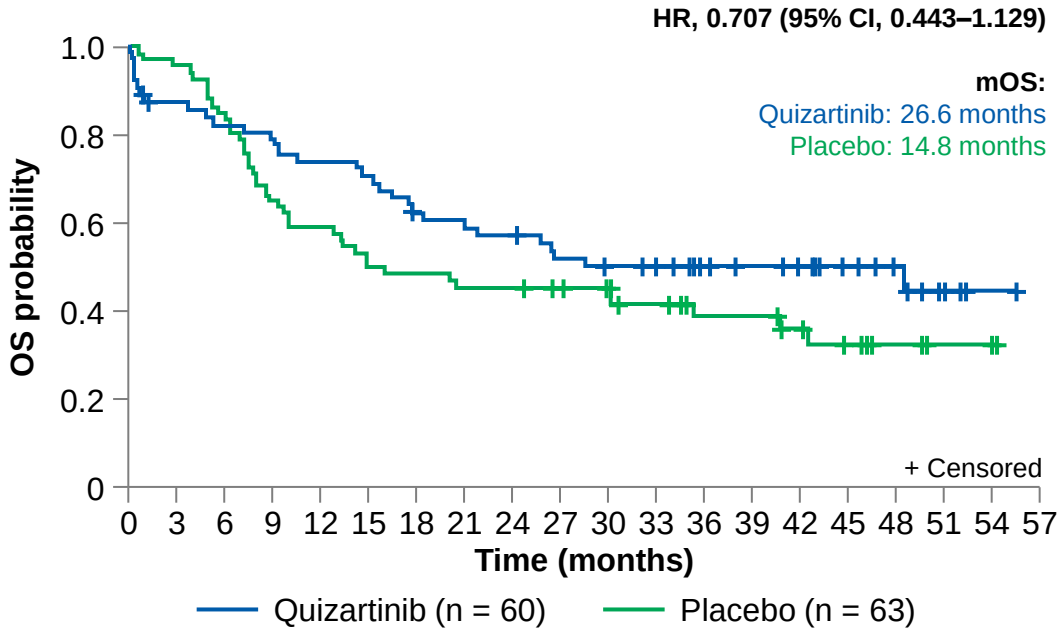
Quizartinib vs placebo



Treatment	No. at risk																			
Quizartinib	65	62	59	54	50	47	47	46	46	43	38	34	30	25	20	14	7	1	1	1	0
Placebo	63	59	49	40	34	31	29	28	27	23	22	19	18	15	11	10	5	1	0	0	0

NPM1^{mut} **+ [*DNMT3A*^{mut} , *TET2*^{mut}, *WT1*^{mut}, *IDH1*^{mut}, or *IDH2*^{mut}]**
≥ 60 years of age

Quizartinib vs placebo



Treatment	No. at risk																			
Quizartinib	60	50	47	45	42	40	34	32	31	27	25	23	19	17	15	11	8	4	1	0
Placebo	63	60	53	40	36	30	29	27	27	25	23	18	13	13	10	7	4	2	2	0

Conclusions

- In the QuANTUM-First trial, *NPM1* (54%) and *DNMT3A* (43%) were commonly co-mutated with *FLT3*-ITD at baseline and provided a substantial OS benefit with quizartinib treatment
- Quizartinib survival benefits persisted across patient subgroups defined by the presence of common gene mutations, and no individual baseline mutation appeared to confer primary resistance to quizartinib
- Patients with the triple mutation of *FLT3*-ITD + *NPM1* + *DNMT3A* particularly benefited from quizartinib, irrespective of age
- *FLT3*-ITD, in combination with an *NPM1* mutation and a mutation in any epigenetic regulatory gene (*DNMT3A*, *TET2*, *WT1*, *IDH1*, or *IDH2),* may represent a biologically distinct sub-entity of AML that is "FLT3-addicted" and particularly susceptible to quizartinib FLT3 inhibition, regardless of age

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