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QuANTUM-First Trial: *FMS*-Like Tyrosine Kinase 3-Internal Tandem Duplication (*FLT3*-ITD)–Specific Measurable Residual Disease (MRD) Clearance Assessed Through Induction and Consolidation Is Associated with Improved Overall Survival in Newly Diagnosed *FLT3*-ITD+ AML Patients

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QuANTUM-FIRST STUDY

Background: Addition of Quizartinib to Intensive Induction, Consolidation, and Continuation Therapy Improved OS in QuANTUM-First Phase 3 Trial

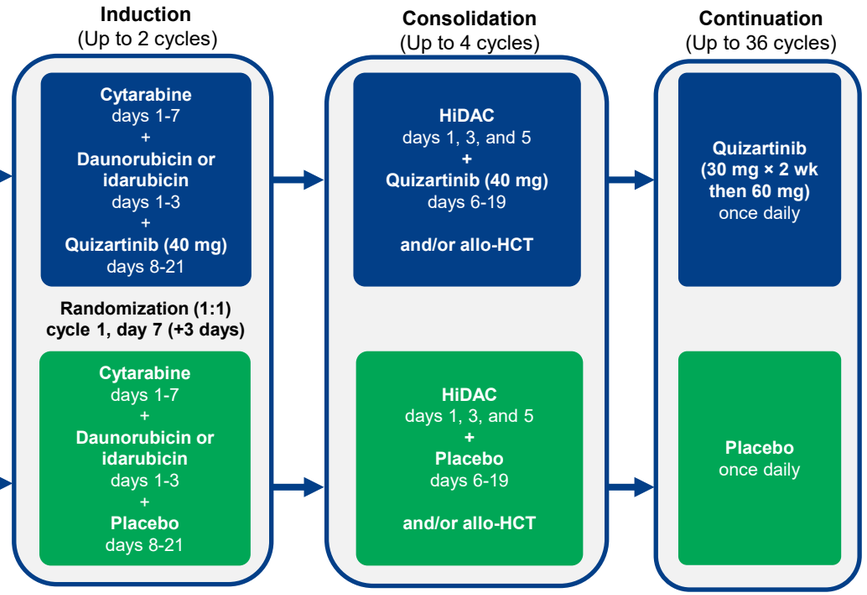
QuANTUM-First Trial Protocol (NCT02668653)[1]

Enrollment dates: Sep 2016 to Aug 2019
Data cutoff: Aug 13, 2021; Sep 30, 2022 (MRD data)

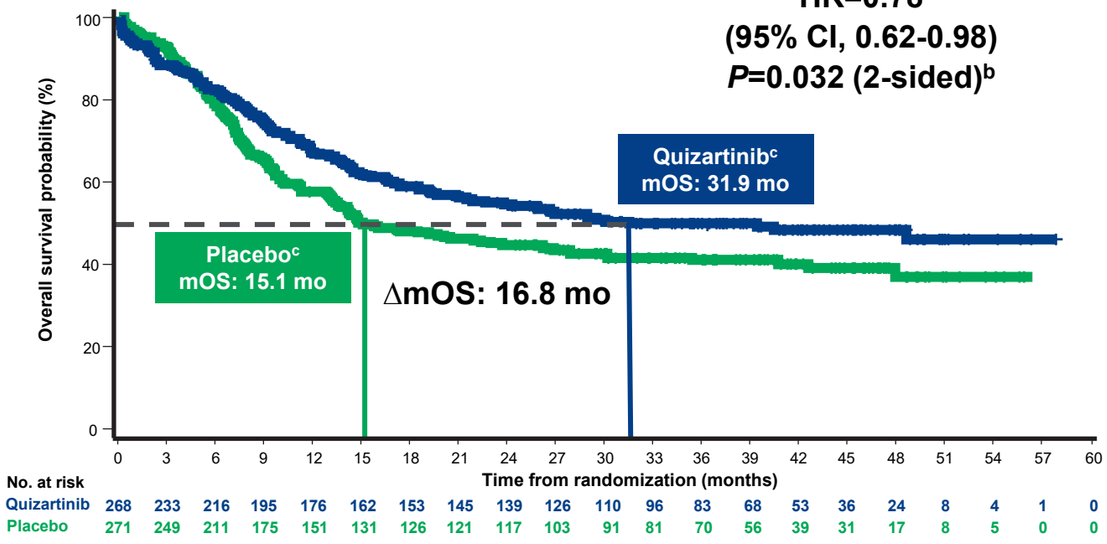
Stratification factors
- **Region**: NA, EU, and Asia/other regions
- **Patient age**: <60 years, ≥60 years
- **WBC**[a]: <40×10^9/L, ≥40×10^9/L

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

Key endpoints[a]
- **Primary endpoint**: OS
- **Secondary endpoints**: EFS, CR, CRc, CR/CRc with MRD− end of induction, safety
- **Exploratory endpoints**: RFS, DoCR



Primary Endpoint: Overall Survival[1]



Rates of CR/CRi per IRC After 1-2 Courses of Induction

	CR (%)	CR/CRi (%)
Quizartinib	54.9	71.6
Placebo	55.4	64.9

- *FLT3*-ITD mutations:
  - Common in AML and are a negative prognostic marker[2-4]
- 3 FDA- and/or EMA-approved FLT3 inhibitors: midostaurin,[5] gilteritinib,[6] and quizartinib[1]
- Quizartinib:
  - Type II inhibitor[1,2] active against *FLT3*-ITD mutations[2,4]
  - More potent and selective than either midostaurin or gilteritinib[2,4]
  - Improved survival when added to induction, consolidation, and continuation therapy of newly diagnosed adults with *FLT3*-ITD+ AML[1]

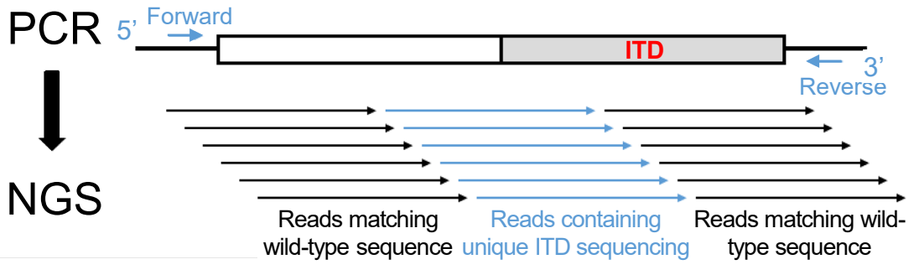
[a]A hierarchical testing procedure was used to test the primary endpoint of OS, followed by EFS, CR, CRc, CR with *FLT3*-ITD MRD negativity, and CRc with *FLT3*-ITD MRD negativity. [b]*P* value was calculated using a stratified log-rank test. [c]Median follow-up time for both arms was 39.2 months. Allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete neutrophil or platelet recovery; DoCR, duration of complete remission; EFS, event-free survival; EMA, European Medicines Agency; EU, European Union; FDA, United States Food and Drug Administration; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; HiDAC, high-dose cytarabine; HR, hazard ratio; IRC, independent review committee; mOS, median overall survival; MRD, measurable residual disease; NA, North America; OS, overall survival; RFS, relapse-free survival; WBC, white blood cell.

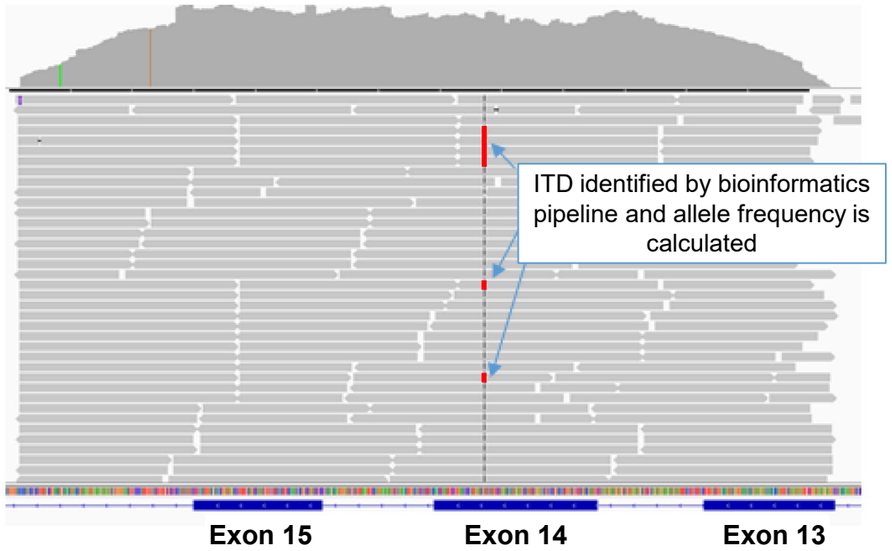
1. Erba H, et al. *Lancet.* 2023;401(10388):1571-1583. 2. Aikawa T, et al. *Oncotarget.* 2020;11(11):943-955. 3. Levis M. *Hematology Am Soc Hematol Educ Program.* 2013;2013:220-226. 4. Pratz KW, et al. *Blood.* 2010;115(17):1425-1432. 5 .Stone RM, et al. *N Engl J Med.* 2017;377(5):454-464. 6. Perl AE, et al. *N Engl J Med.* 2019;381(18):1728-1740.

Measurable Residual Disease (MRD) and QuANTUM-First

- MRD:
  - Key prognostic factor in AML[1-3]
  - Conventional PCR for *FLT3*-ITD less useful due to insensitivity (~1%)[2]
- PCR-NGS is sensitive and specific for *FLT3*-ITD MRD (targeting exons 14-15)[2,4]:
  - PCR amplification step[2]
  - Amplicons analyzed by NGS[2]
  - Developed specifically for this trial[2,4]
  - LLOQ=10^{-4}
  - LLOD=2×10^{-6}
  - Often identifies multiple ITD sequences

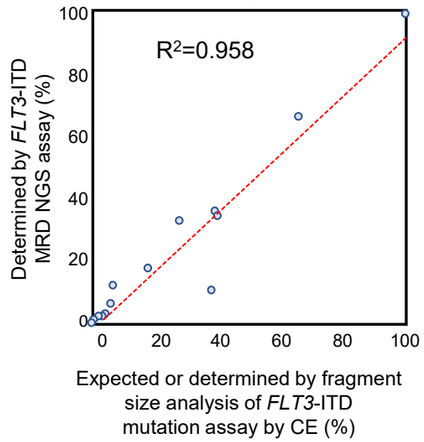
Schema for *FLT3*-ITD MRD Assay





Ultra-deep sequencing of the region (Illumina SBS)

MRD Assay Linearity



AML, acute myeloid leukemia; CE, capillary electrophoresis; CR, complete remission; CRc, composite complete remission; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; ITD, internal tandem duplication; LLOD, lower limit of detection; LLOQ, lower limit of quantification; MRD, measurable residual disease; NGS, next-generation sequencing; PCR, polymerase chain reaction.

1. Jongen-Lavrencic M, et al. *N Engl J Med*. 2018;378(13):1189-1199. 2. Levis M, et al. *Blood Adv*. 2018;2(8):825-831. 3. Döhner H, et al. *Blood*. 2022;140(12):1345-1377. 4. Levis M, et al. *Blood*. 2020;135(1):75-78.

MRD, Long ITD Inserts, and Possibly Multiple ITDs Negatively Impact Survival

- A retrospective *FLT3*-ITD PCR-NGS MRD analysis of 161 newly diagnosed *FLT3*-ITD+ patients with AML enrolled in phase 3 HOVON-SAKK clinical trials[1]
  - MRD after 2 cycles of intensive chemotherapy was associated with increased relapse risk and reduced OS[1]
- Distal ITD insertion sites are associated with long ITD insert size.[2] In the RATIFY trial, patients with the most distal ITD insertion site (TKD1) had a significantly inferior OS compared with patients with more proximal insertion sites (JMD)[3]
  - The negative impact conferred by the most distal ITD insertion sites was not improved by midostaurin treatment[3]
- Retrospective UK cooperative group data suggested multiple *FLT3*-ITDs worsen survival, but follow-up studies did not confirm this.[4,5] A limitation of these studies was the low-sensitivity PCR assay used, which cannot detect low-level VAF *FLT3*-ITDs easily seen by PCR-NGS

	FLT3-ITD MRD+ (n=47)	*FLT3*-ITD MRD– (n=114)	HR (95% CI)	*P* value
4-year CIR	75%	33%	3.70 (2.31-5.94)	*P*<0.001
4-year OS	31%	57%	2.47 (1.59-3.84)	*P*<0.001

	TKD1 sole (n=84)		JMD sole (n=251)		*P* value
4-year OS	29%		44%		*P*=0.032
	TKD1 sole (n=84)		**JMD sole (n=251)**		
	Midostaurin (n=55)	**Placebo (n=29)**	**Midostaurin (n=119)**	**Placebo (n=132)**	
4-year OS	32%	26%	48%	40%	
***P* value**	*P*=0.256		*P*=0.047		

AML, acute myeloid leukemia; CIR, cumulative incidence of relapse; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; HR, hazard ratio; ITD, internal tandem duplication; JMD, juxtamembrane domain; MRD, measurable residual disease; NGS, next-generation sequencing; OS, overall survival; PCR, polymerase chain reaction; TKD1, tyrosine kinase domain-1; UK, United Kingdom; VAF, variant allele frequency.

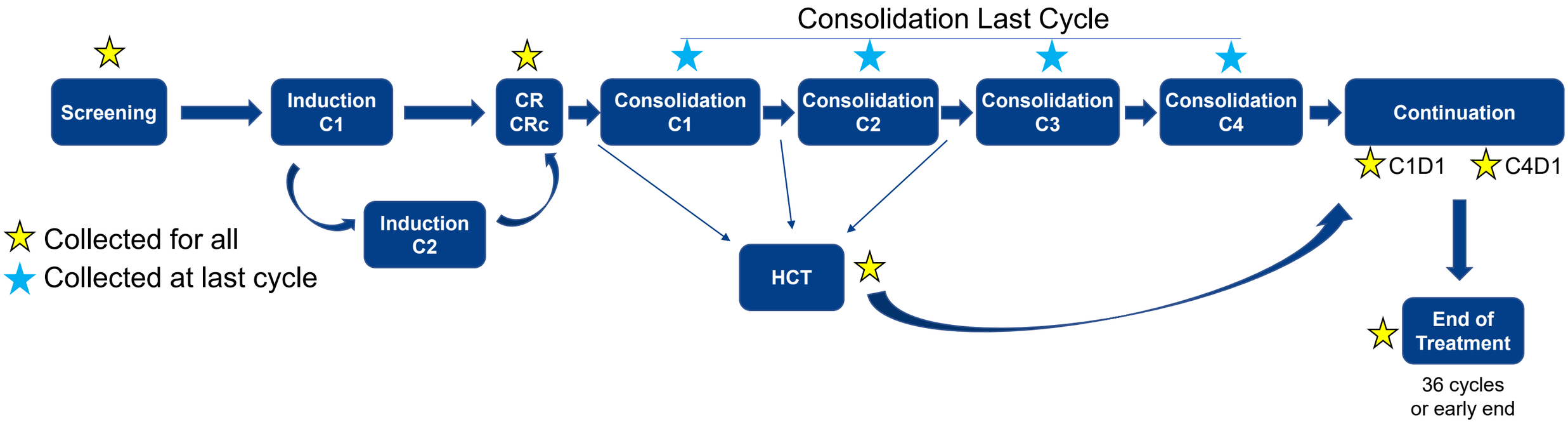
1. Grob T, et. al. *J Clin Oncol.* 2023;41(4):756-765. 2. Kayser S, et al. *Blood.* 2009;114(12):2386-2392. 3. Rucker FG, et al. *Leukemia.* 2022;36(1):90-99. 4. Kottaridis PD, et al. *Blood*. 2001;98(6):1752-1759. 5. Gale RE, et al. *Blood.* 2008;111(5):2776-2784.

Aims

- Using samples from QuANTUM-First analyzed for *FLT3*-ITD MRD by PCR-NGS, we sought to answer the following:
  - Do deeper remissions, defined as having lower *FLT3*-ITD MRD at defined therapy time points, correlate with survival?
  - Does the addition of quizartinib to intensive chemotherapy result in lower levels of *FLT3*-ITD MRD (eg, deeper remissions)?
  - Does ITD length at diagnosis impact the outcome and if so, what is the impact of quizartinib on these outcomes?
  - Does the presence of multiple ITD clones at diagnosis impact the outcome, and if so, what is the impact of quizartinib on these outcomes?

FLT3-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; ITD, internal tandem duplication; MRD, measurable residual disease; NGS, next-generation sequencing; PCR, polymerase chain reaction.

Sample Acquisition/Collection



- Assay used for MRD analysis:
  - *FLT3*-ITD mutations were obtained from 800 ng to 1100 ng of genomic DNA and cross-validated against enrollment ITD sequences
  - VAF (*FLT3*-ITD/total *FLT3*) calculated
  - Two cutoffs for MRD were used:
    - 10^{-4} leukemia cells (predefined/per protocol, based on the assay LLOQ)
    - Zero/undetectable (post hoc analysis)
- Statistical methods:
  - Comparison of the *FLT3*-ITD MRD VAF between treatment arms across time points was made using a Wilcoxon rank-sum test
  - Comparisons of OS by ITD length and number of ITD inserts were made using unstratified Cox regression analysis
  - All *P* values were not adjusted for multiplicity

C, cycle; D, day; CR, complete remission; CRc, composite complete remission; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; ITD, internal tandem duplication; LLOQ, lower limit of quantification; MRD, measurable residual disease; OS, overall survival; VAF, variant allele frequency.

Baseline Characteristics of Patients With CRc by the End of induction

Patient characteristics	Patients who achieved CRc by the end of induction (N=368; 192 with Quiz, 176 with PBO)	
	With available MRD data (N=321)[a]	
	Quizartinib (N=162)	Placebo (N=159)
Age, years		
Median (range)	56 (23-75)	55 (20-75)
<60 years, n (%)	99 (61.1)	96 (60.4)
≥60 years, n (%)	63 (38.9)	63 (39.6)
60-64 years, n (%)	20 (12.3)	25 (15.7)
≥65 years, n (%)	43 (26.5)	38 (23.9)
Sex, n (%)		
Male	73 (45.1)	65 (40.9)
Female	89 (54.9)	94 (59.1)
ECOG PS, n (%)		
0	53 (32.7)	56 (35.2)
1	83 (51.2)	82 (51.6)
2	26 (16.0)	21 (13.2)
Mutated *NPM1,* n (%)	99 (61.1)	102 (64.2)
Mutated *CEBPA*, n (%)	37 (22.8)	39 (24.5)
***FLT3*-ITD/total *FLT3*, n (%)**		
≥3% to ≤25%	57 (35.2)	50 (31.4)
>25% to ≤50%	85 (52.5)	88 (55.3)
>50%	20 (12.3)	21 (13.2)
>25%	105 (64.8)	109 (68.6)
Unknown	0	0
MRD sample collection, n (%)		
Peripheral blood	16 (9.9)	11 (6.9)
Bone marrow aspirate	161 (99.4)	158 (99.4)

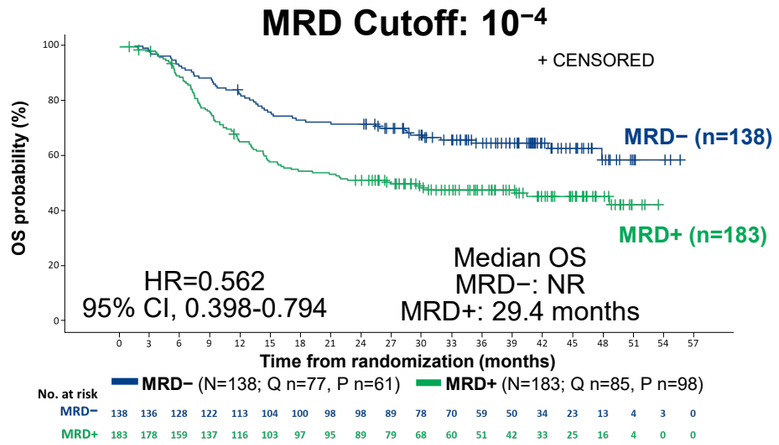
[a]MRD data are available for 321 out of 368 patients achieving CRc after 1 or 2 courses of induction (47 patients had no MRD data).; *CEBPA*, CCAAT enhancer-binding protein alpha; ECOG PS, ECOG PS, Eastern Cooperative Oncology Group performance status; CRc, composite complete remission; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; MRD, measurable residual disease; *NPM1*, nucleophosmin 1.

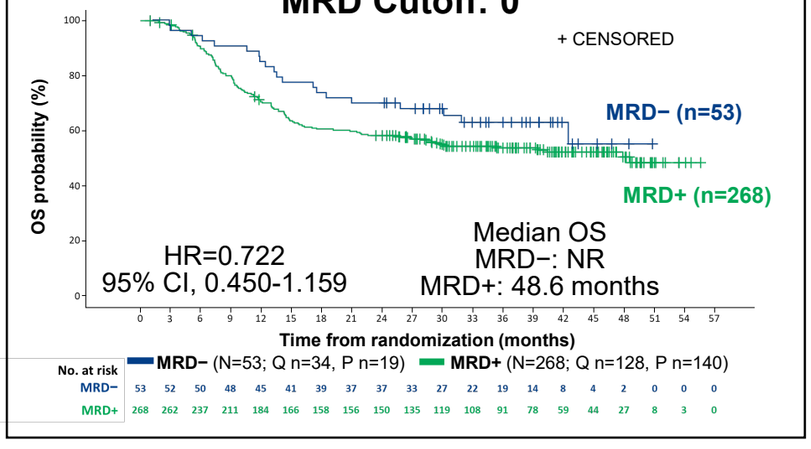
FLT3-ITD MRD Reduction Predicts Overall Survival Across Therapy Time Points

MRD cutoff: 10^{-4}

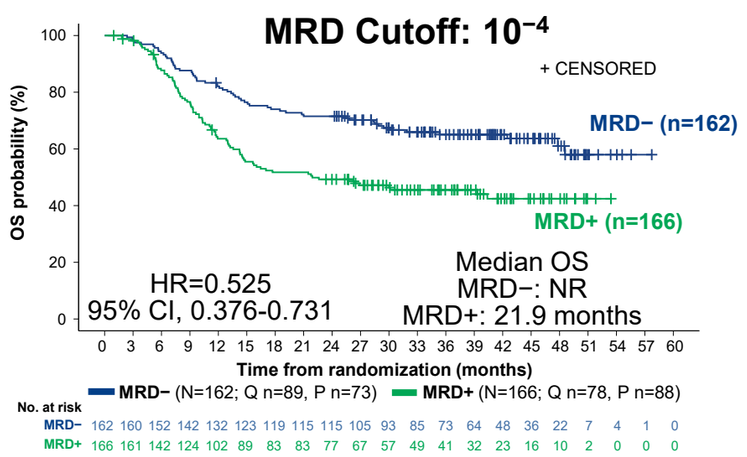
MRD cutoff: 0

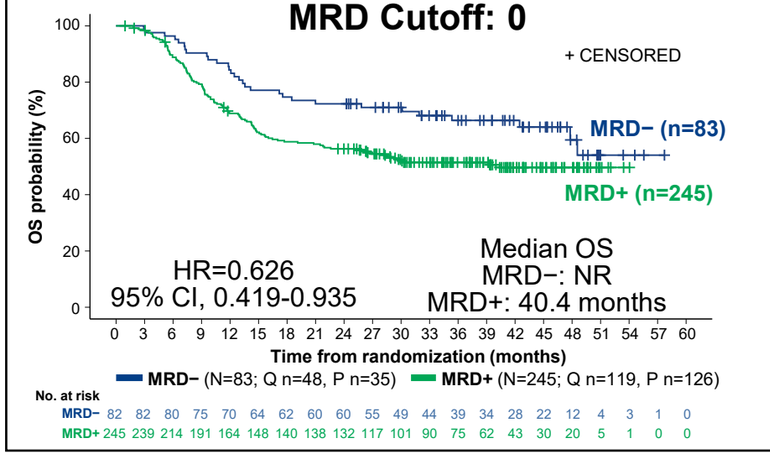
CRc After Induction
(1 or 2 cycles)



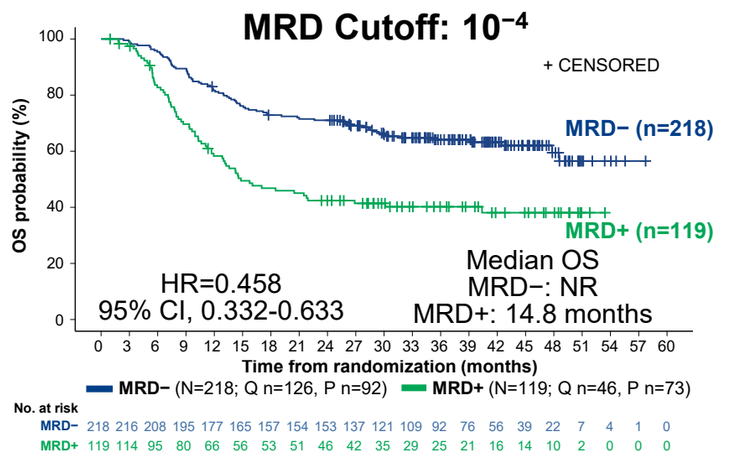


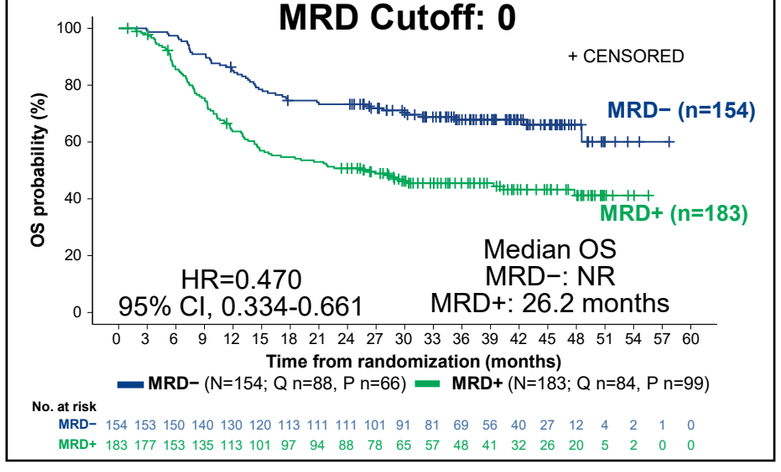
After 2 Cycles of CTx[a]
(CRc after induction × 2 cycles or
CRc after induction #1 + consol. #1)





After Last Consolidation Cycle[b]
(up to 4 cycles)

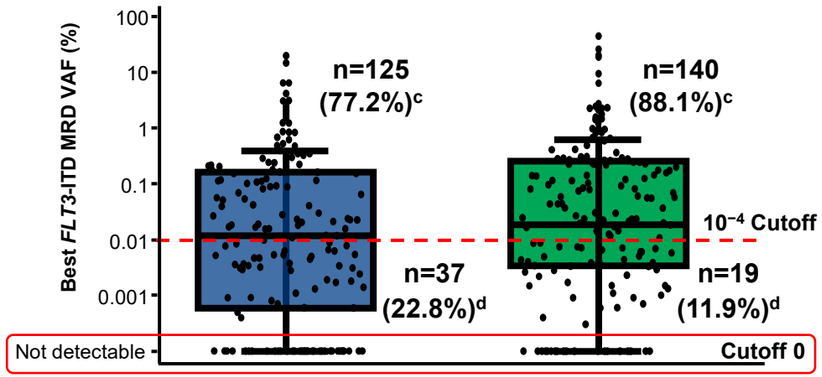




Post hoc analysis. [a]Defined as 2 cycles of induction CTx or 1 cycle of induction CTx + 1 cycle of consolidation cCTx. [b]Include samples up to end of consolidation; if there was no MRD data for the last consolidation cycle, the earlier available MRD status was used, including from induction. CRc, composite complete remission; CTx, chemotherapy; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; HR, hazard ratio; MRD, measurable residual disease; NR, not reached; OS, overall survival; P, placebo; Q, quizartinib.

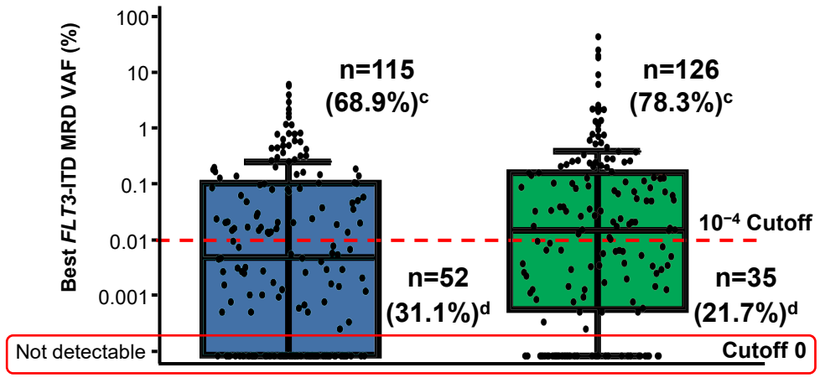
Across the Treatment Course, Quizartinib Leads to Deeper Responses and More Frequently Eliminates Detectable MRD Than Placebo

CRc After Induction
(1 or 2 cycles)



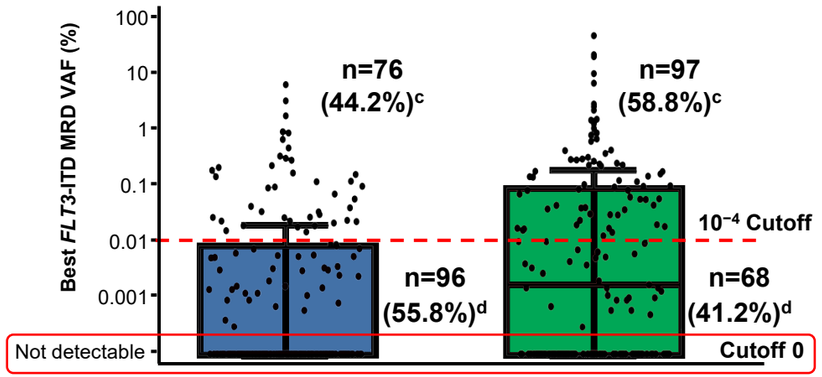
Median = 0.01% quizartinib vs 0.03% placebo
Nominal *P* value (2-sided) = 0.0251

After 2 Cycles of CTx[a]
(CRc after induction × 2 cycles or
CRc after induction #1 + consolidation #1)

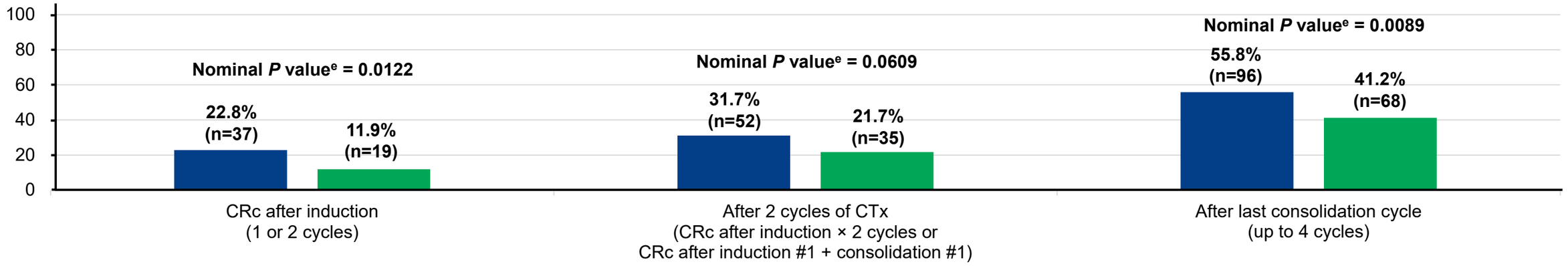


Median = 0.0054% quizartinib vs 0.0171% placebo
Nominal *P* value (2-sided) = 0.0540

After Last Consolidation Cycle[b]
(up to 4 cycles)



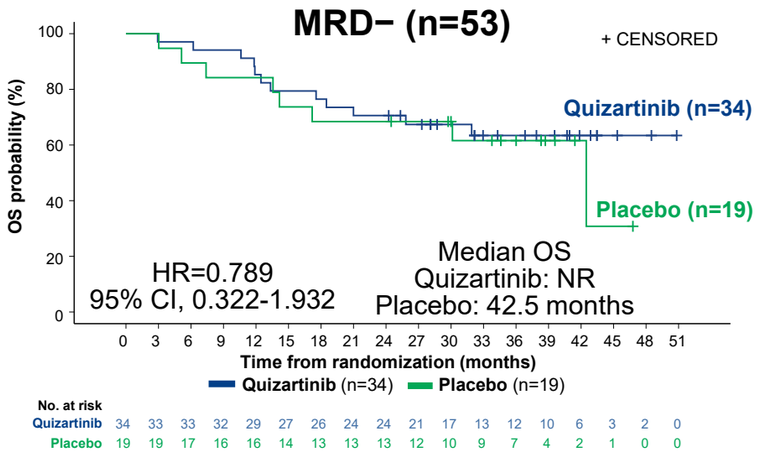
Median = 0% quizartinib vs 0.0017% placebo
Nominal *P* value (2-sided) = 0.0006

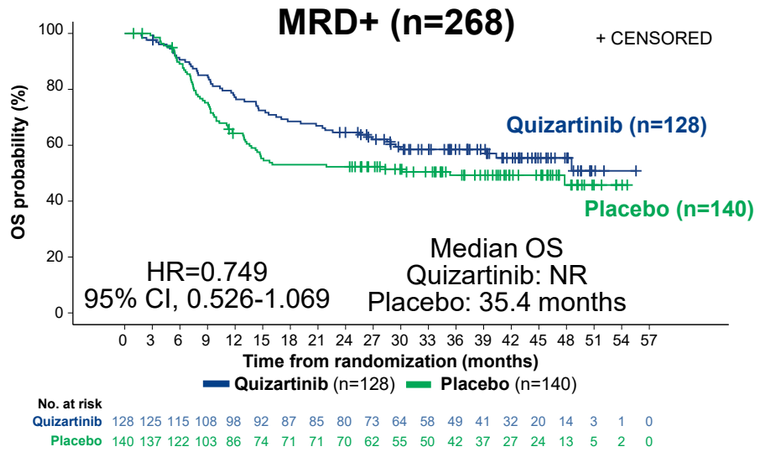


Post hoc analysis. [a]Defined as 2 cycles of induction CTx or 1 cycle of induction CTx + 1 cycle of consolidation CTx. [b]Include samples up to end of consolidation, including from induction. [c]Percentage of patients with *FLT3*-ITD MRD VAF>0 among CRc patients with MRD data. [d]Percentage of patients with *FLT3*-ITD MRD VAF=0 among CRc patients with MRD data. [e]Fisher's exact test. CRc, composite complete remission; CTx, chemotherapy; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; MRD, measurable residual disease; VAF, variant allele frequency.

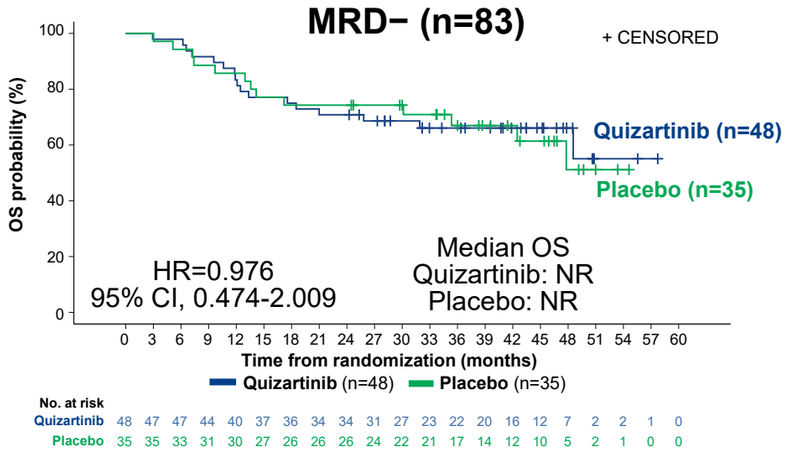
FLT3-ITD MRD Reduction Predicts Survival Across Therapy Time Points (Cutoff 0)

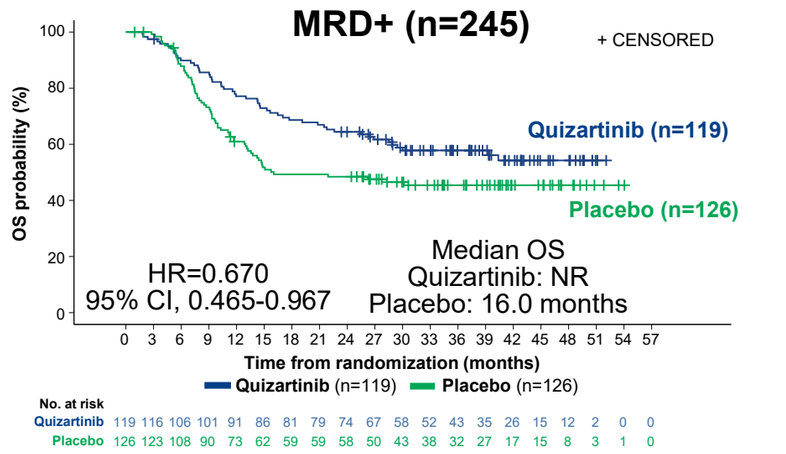
CRc After Induction
(1 or 2 cycles)



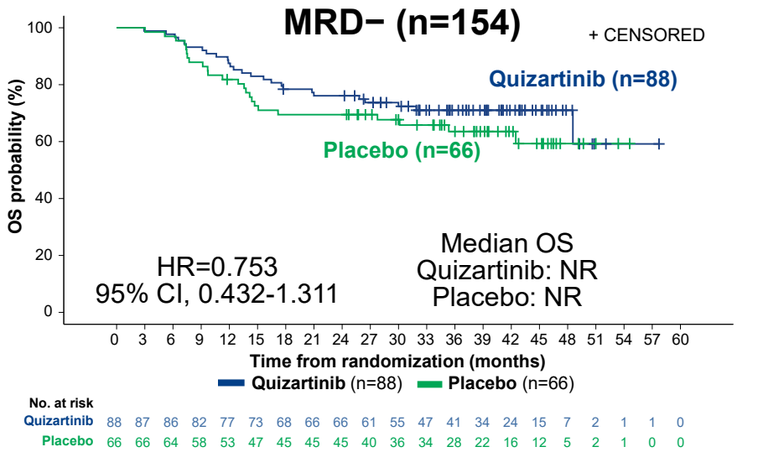


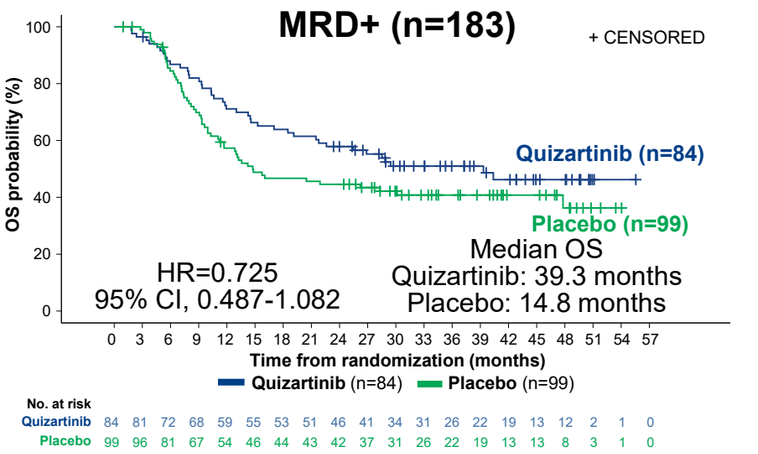
After 2 Cycles of CTx[a]
(CRc after induction × 2 cycles or
CRc after induction #1 + consolidation #1)





After Last Consolidation Cycle[b]
(up to 4 cycles)



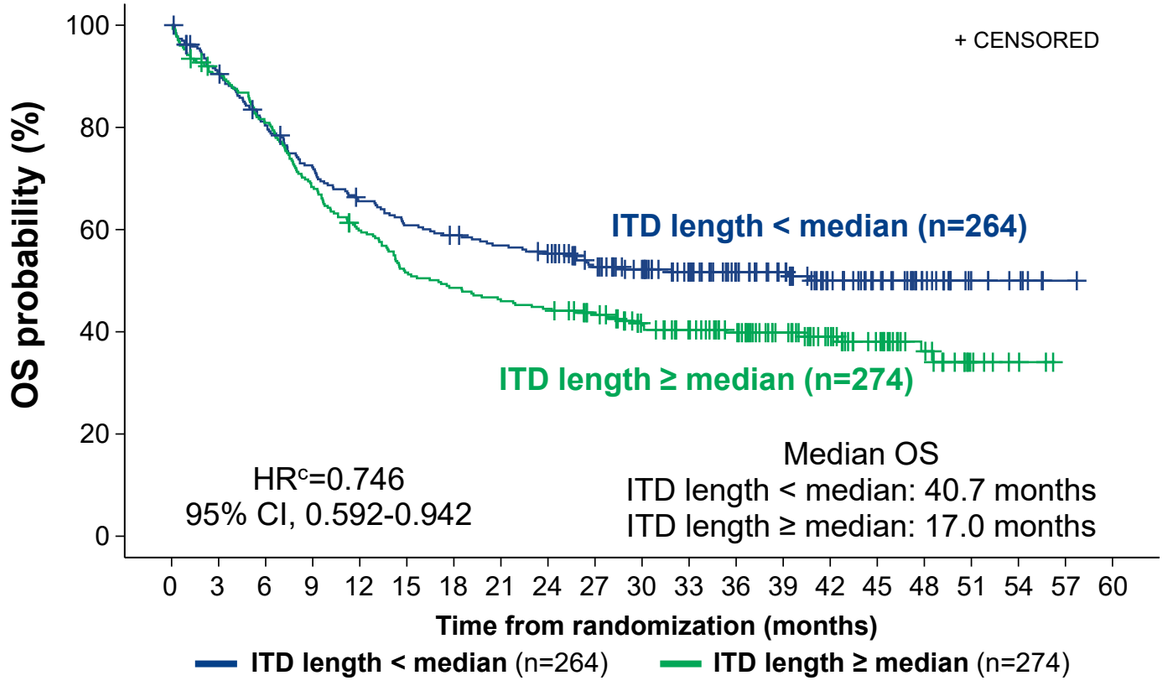


Post hoc analysis. [a]Defined as 2 cycles of induction CTx or 1 cycle of induction CTx + 1 cycle of consolidation CTx. [b]Include samples up to end of consolidation; if there was no MRD data for the last consolidation cycle, the earlier available MRD status was used, including from induction. CRc, composite complete remission; CTx, chemotherapy; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; HR, hazard ratio; MRD, measurable residual disease; NR, not reached; OS, overall survival.

Long ITD Insertions Are Associated With Worse Survival

Median ITD insertion length = 54 bp

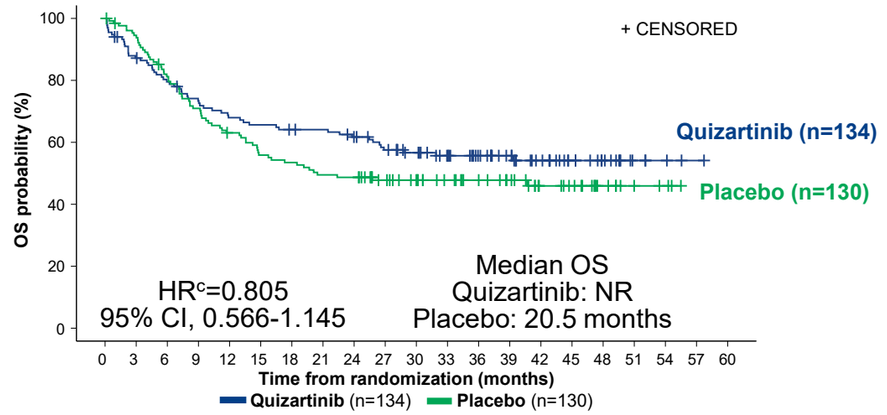
OS by *FLT3*-ITD Length[a] Regardless of Treatment Arm (N=538)



No. at risk

ITD length < median	264	236	207	185	167	155	149	143	137	120	107	93	80	67	49	36	22	9	6	1	0
ITD length ≥ median	274	245	219	185	160	138	130	123	119	109	94	84	73	57	43	31	19	7	3	0	0

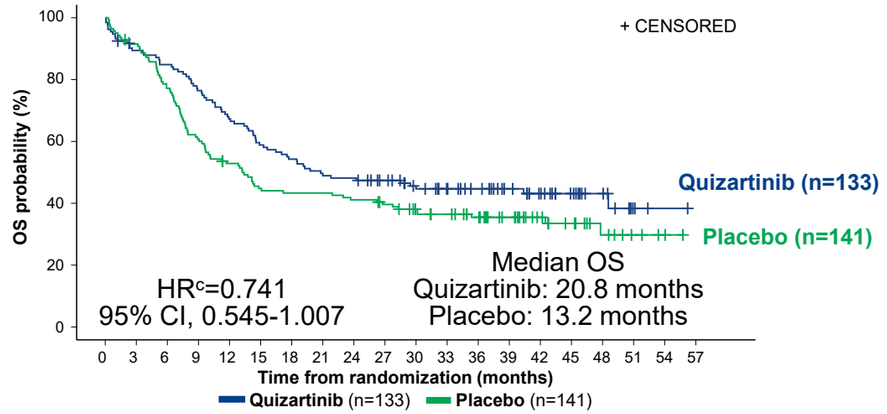
Patients[a] With *FLT3*-ITD Length < Median Length[b] (n=264)



No. at risk

Quizartinib	134	115	104	95	88	85	82	81	76	69	62	54	46	38	29	19	13	5	3	1	0
Placebo	130	121	103	90	79	70	67	62	61	51	45	39	34	29	20	17	9	4	3	0	0

Patients[a] With *FLT3*-ITD Length ≥ Median Length[b] (n=274)



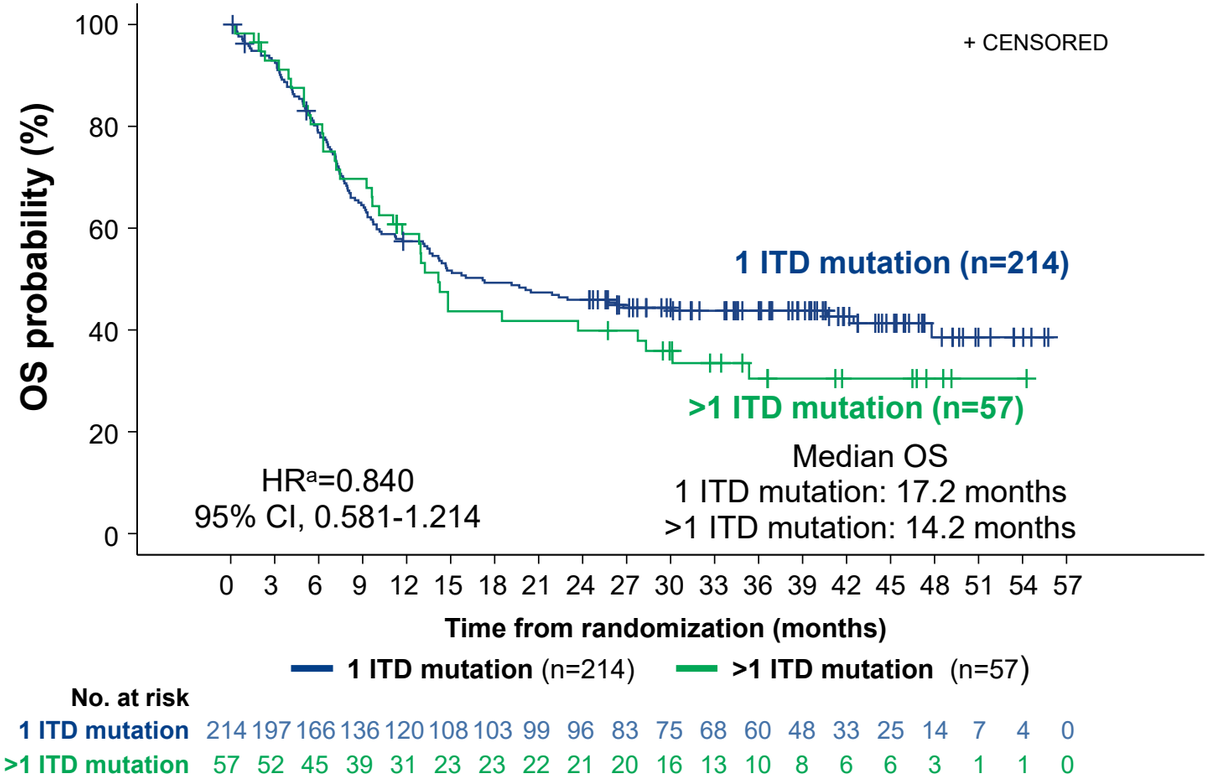
No. at risk

Quizartinib	133	117	111	100	88	77	71	64	63	57	48	42	37	30	24	17	11	3	1	0
Placebo	141	128	108	85	72	61	59	59	56	52	46	42	36	27	19	14	8	4	2	0

Post hoc analysis. [a]Patients may have only 1 ITD length or >1 ITD length. [b]Median ITD length (54 bp) is calculated based on enrollment assay data (Navigate BioPharma *FLT3*-ITD Mutation Assay). [c]Unstratified Cox regression analysis.
FLT3-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; HR, hazard ratio; ITD, internal tandem duplication; NR, not reached; OS, overall survival.

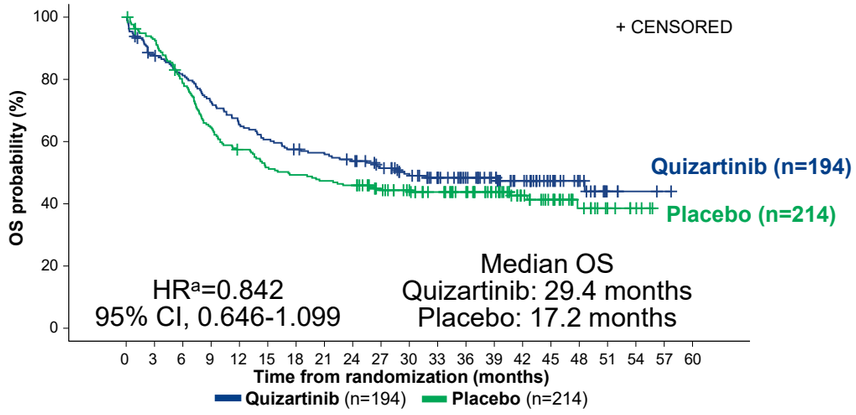
Multiple ITDs Are Associated With Worse Survival, and Quizartinib Can Improve OS in Patients With Multiple ITDs

OS by Number of *FLT3*-ITDs per Patient (N=271): Placebo Arm



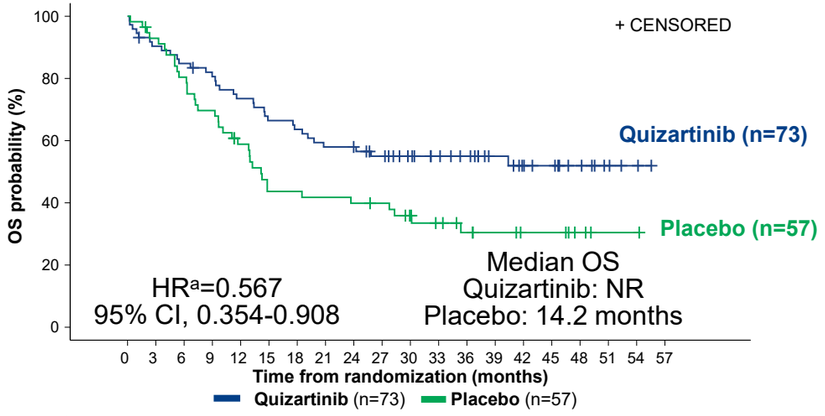
No. at risk																			
1 ITD mutation	214	197	166	136	120	108	103	99	96	83	75	68	60	48	33	25	14	7	4	0
>1 ITD mutation	57	52	45	39	31	23	23	22	21	20	16	13	10	8	6	6	3	1	1	0

Patients With 1 *FLT3*-ITD Mutation (n=264)



No. at risk																				
Quizartinib	194	167	154	138	124	115	108	104	99	90	79	69	59	50	39	24	16	4	2	1	0
Placebo	214	197	166	136	120	108	103	99	96	83	75	68	60	48	33	25	14	7	4	0	0

Patients With >1 *FLT3*-ITD Mutation (n=130)



No. at risk																			
Quizartinib	73	65	61	57	52	47	45	41	40	36	31	27	24	18	14	12	8	4	2	0
Placebo	57	52	45	39	31	23	23	22	21	20	16	13	10	8	6	6	3	1	1	0

Post hoc analysis. [a]Unstratified Cox regression analysis.
FLT3-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; HR, hazard ratio; ITD, internal tandem duplication; NR, not reached; OS, overall survival.

Conclusions

- These findings demonstrate the potential prognostic utility of *FLT3*-ITD–specific MRD measurements in the clinical management of patients with *FLT3*-ITD+ AML
- Elimination of detectable *FLT3*-ITD MRD is associated with longer OS compared with intensive chemotherapy with or without quizartinib
- Therapy with quizartinib is associated with deeper responses and more frequently eliminates detectable MRD than placebo after induction, after 2 cycles of chemotherapy, and after consolidation
- The presence of multiple ITDs or long ITD inserts at diagnosis did not negatively impact the survival benefits of quizartinib
- Our data suggest that some of the long-term OS benefits conferred by quizartinib derive from an early, deep, and sustained reduction of the *FLT3*-ITD+ leukemia burden

AML, acute myeloid leukemia; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; ITD, internal tandem duplication; MRD, measurable residual disease.

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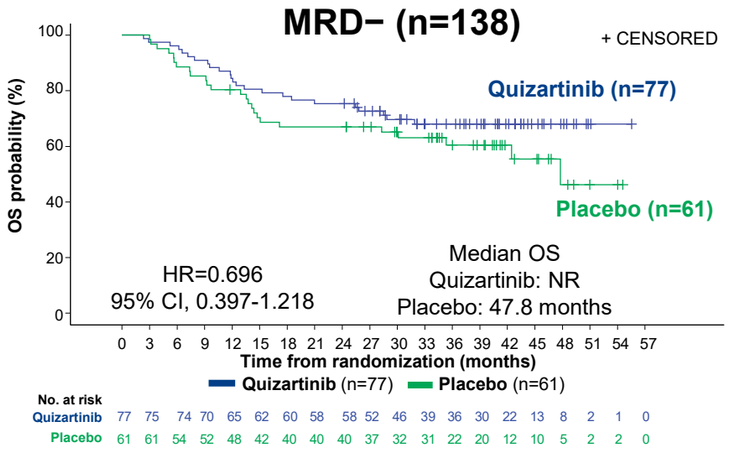
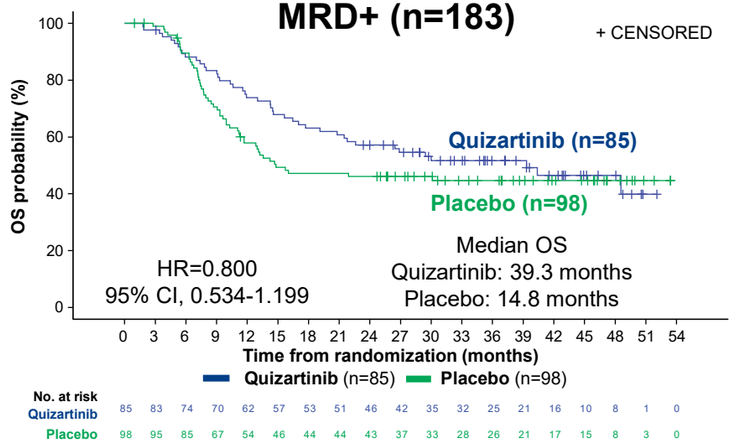
BACKUP SLIDES

QuANTUM-FIRST STUDY

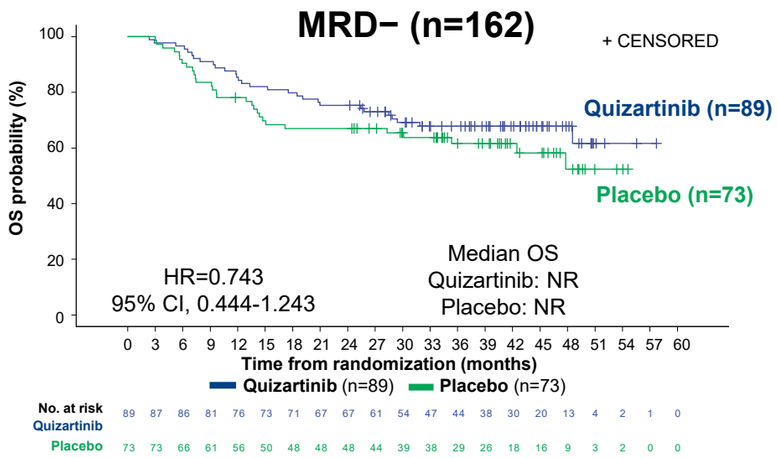
FLT3-ITD MRD Reduction Predicts Survival Across Therapy Time Points (Cutoff 10^{-4})

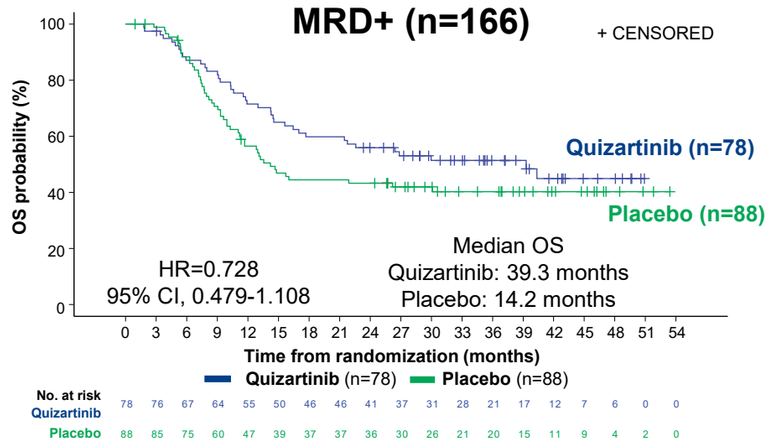
CRc After Induction
(1 or 2 cycles)



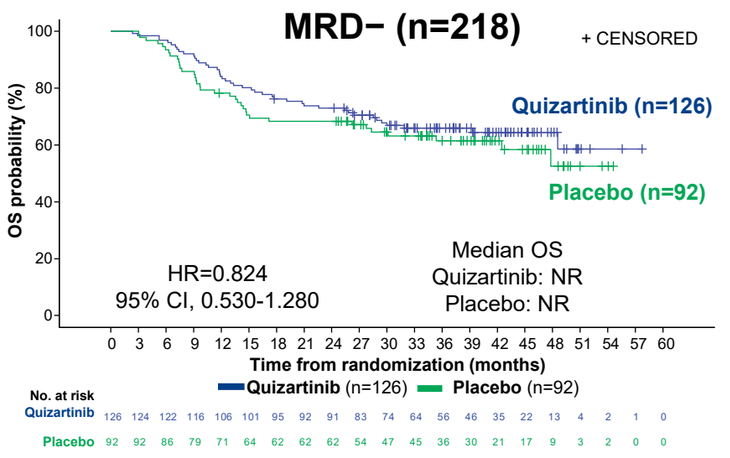


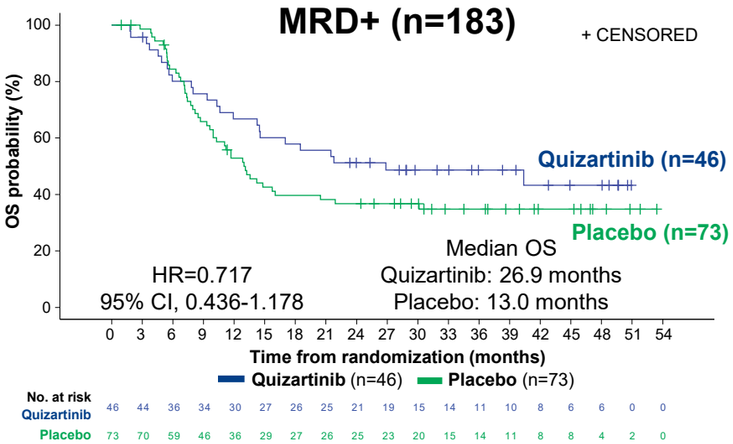
After 2 Cycles of CTx[a]
(CRc after induction × 2 cycles or
CRc after induction #1 + consolidation #1)





After Last Consolidation Cycle[b]
(up to 4 cycles)





Post hoc analysis. [a]Defined as 2 cycles of induction CTx or 1 cycle of induction CTx + 1 cycle of consolidation CTx. [b]Include samples up to end of consolidation; if there was no MRD data for the last consolidation cycle, the earlier available MRD status was used, including from induction. CRc, composite complete remission; CTx, chemotherapy; *FLT3*-ITD, FMS-like tyrosine kinase 3–internal tandem duplication; HR, hazard ratio; MRD, measurable residual disease; NR, not reached; OS, overall survival.