Quizartinib: *FLT3*-ITD or not, does it matter?

Sabine Kayser

Institute of Transfusion Medicine and Immunology, Medical Faculty Mannheim, Heidelberg University, Heidelberg; the German Red Cross Blood Service Baden-Württemberg-Hessen, Mannheim and the NCT Clinical Trial Center, National Center of Tumor Diseases, German Cancer Research Center (DKFZ), Heidelberg, Germany

Correspondence: S. Kayser
s.kayser@dkfz-heidelberg.de

Received: June 5, 2026.
Accepted: June 10, 2026.
Early view: June 18, 2026.

https://doi.org/10.3324/haematol.2026.301346

©2026 Ferrata Storti Foundation
Published under a CC BY-NC license

Up to now, two tyrosine kinase inhibitors (TKI), midostaurin and quizartinib, have been approved by the US Food and Drug Administration and the European Medicines Agency in combination with standard intensive induction and consolidation chemotherapy for the treatment of adult patients with newly diagnosed *FLT3*-mutated acute myeloid leukemia (AML).[1] Moreover, inhibition of FLT3 and other kinases through oral targeted agents could improve outcome after standard chemotherapy for adult *FLT3*-internal tandem duplication (ITD)-negative AML patients. The randomized SORAML trial showed that the addition of sorafenib to standard intensive chemotherapy including allogeneic hematopoietic stem cell transplantation (alloHCT) and maintenance monotherapy significantly improved event-free and relapse-free survival in newly diagnosed, fit AML patients, irrespective of *FLT3*-ITD mutational status.[2]

Quizartinib is a potent type II inhibitor with approximately 30% complete remissions (CR) and CR with incomplete recovery (CRi) as monotherapy for relapsed/refractory *FLT3*-ITD-negative AML.[3] In the SORAML trial, patients with an *FLT3*-ITD allelic ratio of less than 10% were considered to be *FLT3*-ITD-negative.

With this rationale, the PETHEMA group designed a randomized, double-blind, placebo-controlled phase II trial (QUIWI trial; clinicaltrials.gov identifier NCT04107727) in newly diagnosed *FLT3*-ITD-negative AML.[4] Overall, 273 patients (aged 18-70 years) were enrolled. Participants were randomized in a 2:1 fashion to receive quizartinib (orally 60 mg/daily) or placebo in combination with standard induction and consolidation chemotherapy and/or alloHCT as well as single-agent maintenance (quizartinib/placebo) until relapse, unacceptable toxicity, or discontinuation of therapy occurred.

In this issue of *Haematologica*, on behalf of the PETHEMA group, Lloret-Madrid and colleagues present a post-hoc analysis of the impact of alloHCT, modeled as a time-dependent variable, performed in first composite complete remission (CRc1) on overall survival (OS) and disease-free survival (DFS) according to treatment arm.[5]

alloHCT was performed in 32.2% (N=58/180) of the patients in the quizartinib arm and in 30.1% (N=28/93) in the placebo arm. Median time to alloHCT was 3.6 months in the quizartinib and 3.1 months in the placebo arm. Post-transplant maintenance therapy was given in 25 patients (43.1%) in the quizartinib and in 12 patients (42.9%) in the placebo arm. Exposure during maintenance was comparable between the two treatment arms, with 48% and 50% of patients receiving ≥12 cycles, respectively.

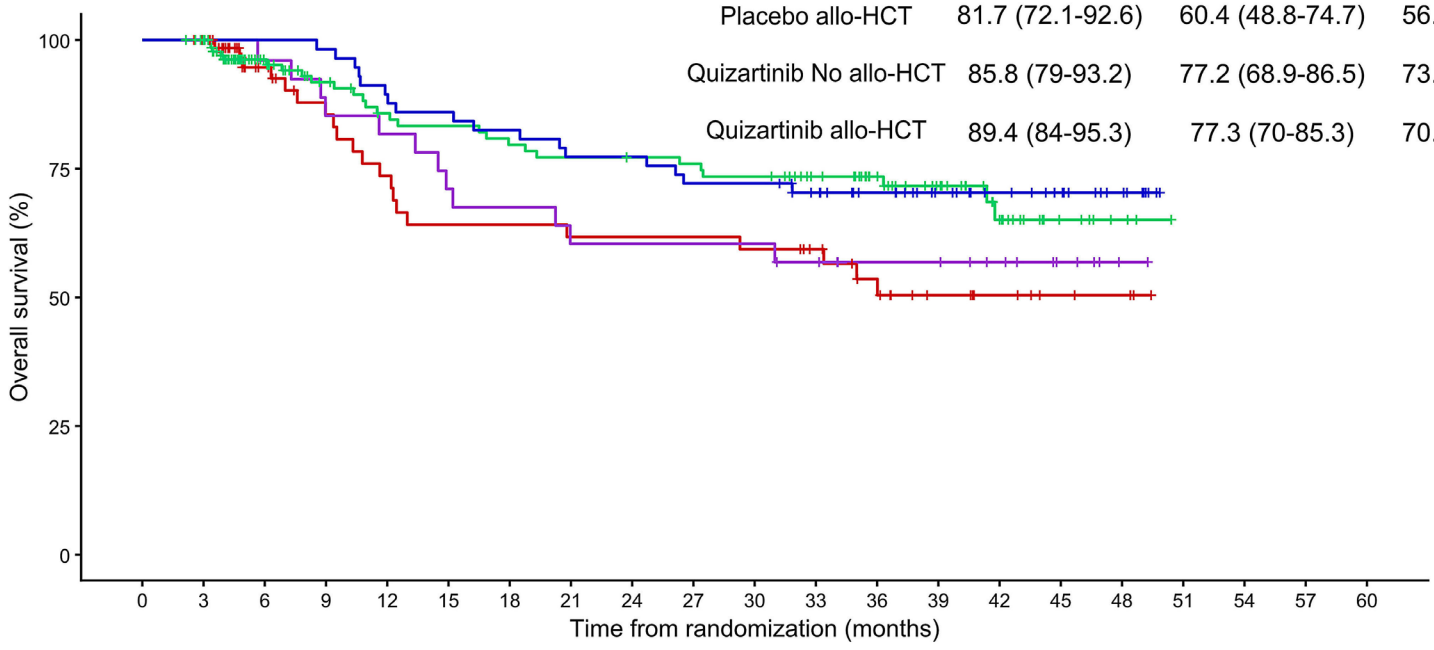
Quizartinib improved OS and DFS compared with placebo regardless of alloHCT status (Figure 1). In Cox models, with alloHCT as a time-dependent co-variate, quizartinib remained associated with improved OS (hazard ratio [HR] 0.59, 95%CI: 0.28-1.25; *P*=0.008) and DFS (HR 0.67, 95%CI: 0.48-0.95; *P*=0.03), whereas alloHCT was not significantly associated with OS (HR 0.91, 95%CI: 0.62-1.33; *P*=0.62) and showed a numerical DFS benefit (HR 0.73, 95%CI: 0.52-1.03; *P*=0.08). Multivariable analyses confirmed quizartinib as an independent favorable factor for OS (HR 0.56, 95%CI: 0.31-0.99; *P*=0.046) and DFS (HR 0.60, 95%CI: 0.38-0.97; *P*=0.04). No additional safety signals were observed. In patients with newly diagnosed *FLT3*-ITD-negative AML achieving CRc1, quizartinib improved OS and DFS in the overall population. Notably, the clinical benefit of quizartinib was observed regardless of alloHCT and appeared more evident in patients who did not proceed to transplant. However, patients proceeding to alloHCT were significantly younger and more frequently classified as adverse genetic risk, suggesting at least some bias.

In comparison, in *post hoc* analyses of the phase III QuANTUM-First trial in patients with newly diagnosed *FLT3*-ITD AML using appropriate biometric methods, OS was improved particularly in patients receiving an alloHCT in CR1 in the quizartinib arm of the study with a hazard ratio of 0.29 (95%CI: 0.17-0.51), reducing the risk of death by 70.1%.[6]

Regarding the impact of quizartinib on MRD, in the QUIWI trial, OS and DFS were analyzed according to measurable residual disease (MRD) status post-induction, stratified by alloHCT status within each treatment arm. MRD was assessed by standardized RT-qPCR techniques (*NPM1*-mu-

A

Group	1-year	2-year	3-year	4-year
Placebo No allo-HCT	73.6 (61.7-87.8)	61.7 (48.8-78)	53.6 (40.3-71.2)	50.4 (37-68.6)
Placebo allo-HCT	81.7 (72.1-92.6)	60.4 (48.8-74.7)	56.8 (45.2-71.4)	56.8 (45.2-71.4)
Quizartinib No allo-HCT	85.8 (79-93.2)	77.2 (68.9-86.5)	73.5 (64.7-83.4)	65.1 (53.8-78.7)
Quizartinib allo-HCT	89.4 (84-95.3)	77.3 (70-85.3)	70.3 (62.4-79.2)	70.3 (62.4-79.2)

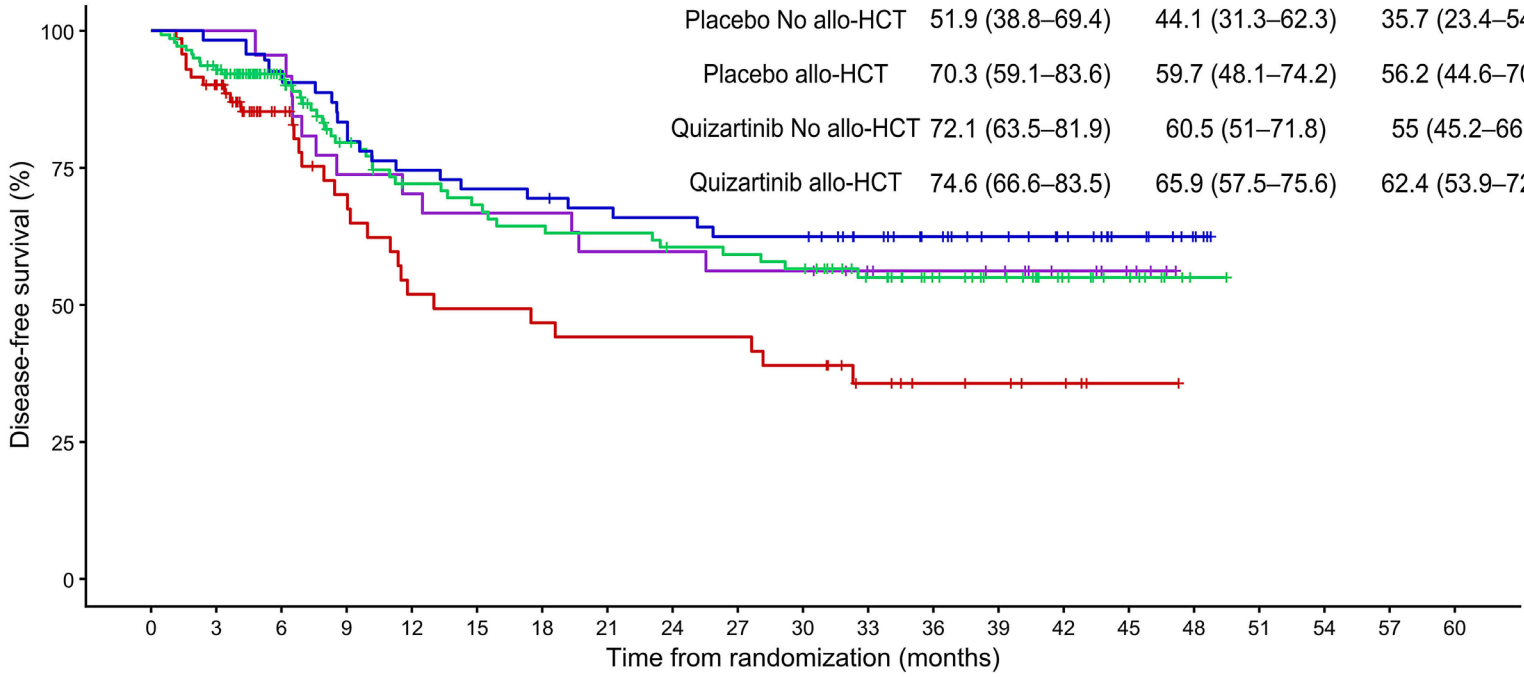


Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Placebo No allo-HCT	71	57	41	36	31	27	27	26	26	26	25	22	17	11	7	4	3	0	0	0	0
Placebo allo-HCT	0	14	26	24	23	20	19	17	17	17	17	15	12	12	9	5	1	0	0	0	0
Quizartinib No allo-HCT	142	120	87	77	70	68	65	63	62	61	59	50	41	31	18	8	3	0	0	0	0
Quizartinib allo-HCT	0	21	49	54	51	49	47	44	45	42	42	37	31	24	19	14	8	0	0	0	0

B

Group	1-year	2-year	3-year	4-year
Placebo No allo-HCT	51.9 (38.8–69.4)	44.1 (31.3–62.3)	35.7 (23.4–54.4)	35.7 (23.4–54.4)
Placebo allo-HCT	70.3 (59.1–83.6)	59.7 (48.1–74.2)	56.2 (44.6–70.9)	56.2 (44.6–70.9)
Quizartinib No allo-HCT	72.1 (63.5–81.9)	60.5 (51–71.8)	55 (45.2–66.9)	55 (45.2–66.9)
Quizartinib allo-HCT	74.6 (66.6–83.5)	65.9 (57.5–75.6)	62.4 (53.9–72.3)	62.4 (53.9–72.3)



Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Placebo No allo-HCT	71	53	34	28	23	19	19	17	17	17	15	12	8	6	4	1	1	0	0	0	0
Placebo allo-HCT	0	14	26	23	21	19	19	17	17	17	16	15	12	12	9	5	1	0	0	0	0
Quizartinib No allo-HCT	142	116	81	67	58	55	50	49	48	46	44	37	28	22	15	8	3	0	0	0	0
Quizartinib allo-HCT	0	21	47	49	44	43	41	39	39	37	37	33	27	22	18	13	8	0	0	0	0

Figure 1. Time-dependent Simon-Makuch plots of overall survival and disease-free survival. (A) Time-dependent Simon-Makuch plot of overall survival (OS) from randomization by allogeneic hematopoietic cell transplantation (alloHCT) in patients who achieved first composite complete remission (CRc1) by the end of induction as per Independent Review Committee (IRC). (B) Time-dependent Simon-Makuch plot of disease-free survival (DFS) by alloHCT in patients who achieved CRc1 by the end of induction as per IRC. NE: not estimated. Figure taken from Lloret-Madrid *et al.*[5]

tated and core-binding factor AML) in peripheral blood. In the remaining AML subtypes, MRD was evaluated in bone marrow samples using standardized multiparametric flow cytometry. MRD negativity was stratified by European LeukemiaNet (ELN)-2017 risk category within each treatment arm. MRD negativity rates were numerically higher in the quizartinib arm across favorable-risk (34.1% *vs.* 27.3%) and intermediate-risk (78.8% *vs*. 60.0%) groups and were comparable in the adverse-risk group (59.5% *vs*. 59.3%), although none of these differences reached statistical significance.

In the OS analysis, among patients with MRD positivity post-induction undergoing alloHCT in CRc1, the HR comparing quizartinib *versus* placebo was 0.23 (95%CI: 0.07-0.69), and among those who did not undergo alloHCT, the HR was 0.59 (95%CI: 0.24-1.44). There was no difference in treatment effect according to alloHCT status (*P* for interaction = 0.34). In fact, among patients who remained MRD positive after induction, quizartinib was associated with more favorable OS as compared to placebo, regardless of subsequent alloHCT; thus, there was no evidence that transplant status modified the treatment effect. These findings suggest that quizartinib may provide clinical benefit in MRD-positive patients independently of alloHCT.[4] Furthermore, these data also suggest that post-induction MRD may be a driver in the decision to proceed to alloHCT in routine practice.

In patients who were MRD-negative after induction, a favorable trend was observed in non-transplanted patients treated with quizartinib. OS curves for quizartinib-treated patients with or without alloHCT were nearly superimposable, and survival in quizartinib-treated patients without alloHCT was similar to that of placebo-treated patients who underwent alloHCT, suggesting that the additional contribution of alloHCT to long-term outcomes in this biologically favorable population remained limited. In other words, maintenance with quizartinib may allow patients to avoid alloHCT, at least in those who are MRD-negative. However, confirmation of this finding in larger studies is warranted.

Little evidence has been published so far specifically addressing the interaction between alloHCT in CRc1 and FLT3 inhibitors in *FLT3*-ITD wild-type AML. The QUIWI trial represents one of the first randomized studies to explore this setting, although this was carried out as a post-hoc analysis in only a small cohort of the trial population. However, the trial does not answer the question as to how the TKI exerts its activity. One would expect a higher rate of MRD negativity resulting in deeper remissions, which seems not to be the case (albeit the fact that only a small number of patients were included should be taken into account). Nevertheless, it seems that quizartinib may be doing more than FLT3 kinase inhibition and that the biology in so-called *FLT3*-ITD-negative AML may still leave room for FLT3-targeted pressure, at least when paired with intensive chemotherapy and maintenance.

Taken together, these findings provide a strong rationale for the ongoing global, randomized, double-blind, placebo-controlled phase III QuANTUM-Wild trial (*clinicaltrials.gov identifier: NCT06578247*) which may, hopefully, provide some answers.

Disclosures

No conflicts of interest to disclose.

References

1. Kayser S, Levis MJ. The clinical impact of the molecular landscape of acute myeloid leukemia. Haematologica. 2023;108(2):308-320.
2. Röllig C, Serve H, Noppeney R, et al. Sorafenib or placebo in patients with newly diagnosed acute myeloid leukaemia: long-term follow-up of the randomized controlled SORAML trial. Leukemia. 2021;35(9):2517-2525.
3. Cortes J, Perl AE, Döhner H, et al. Quizartinib, an FLT3 inhibitor, as monotherapy in patients with relapsed or refractory acute myeloid leukaemia: an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol. 2018;19(7):889-903.
4. Montesinos P, Rodríguez-Veiga R, Bergua JM, et al. Quizartinib for newly diagnosed FLT3-internal tandem duplication-negative AML: the randomized, double-blind, placebo-controlled, phase II QUIWI study. J Clin Oncol. 2026;44(1):42-53.
5. Lloret-Madrid P, Rodríguez-Veiga R, Bergua JM, et al. Impact of hematopoietic cell transplantation and quizartinib in patients with newly diagnosed FLT3-internal tandem duplication-negative acute myeloid leukemia: results from the QUIWI study. Haematologica. 2026;111(12):4001-4018.
6. Schlenk RF, Montesinos P, Kim HJ, et al. Impact of hematopoietic cell transplantation and quizartinib in newly diagnosed patients with acute myeloid leukemia and FMS-like tyrosine kinase 3-internal tandem duplications in the QuANTUM-First trial. Haematologica. 2025;110(9):2024-2039.