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

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Currently, two TKIs (midostaurin, quizartinib) are approved by FDA and EMA in combination with standard intensive induction and consolidation chemotherapy for the treatment of adult patients with newly diagnosed adult *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*-ITD negative AML patients. The randomized SORAML trial showed that the addition of sorafenib to standard intensive chemotherapy including allogeneic hematopoietic stem cell transplantation (allo-HCT) and maintenance monotherapy improved significantly event-free and relapse-free survival (RFS) in newly diagnosed fit AML patients, irrespective of *FLT3*-ITD mutational status.[2]

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

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

In this issue of *Haematologica*, Pilar Lloret-Madrid and colleagues on behalf of the PETHEMA group present in a post-hoc analysis the impact of allo-HCT, modeled as

a time-dependent variable, performed in first composite complete remission (CRc1) on OS and disease-free survival (DFS) according to treatment arm.[5]

Allo-HCT 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 allo-HCT 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 treatment arms, with 48% and 50% of patients receiving ≥12 cycles, respectively.

Quizartinib improved OS and DFS compared with placebo regardless of allo-HCT status (Figure 1). In Cox models with allo-HCT as a time-dependent covariate, quizartinib remained associated with improved OS (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 allo-HCT 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 allo-HCT, and appeared more evident in patients who did not proceed to transplant. However, patients proceeding to allo-HCT were significantly younger and more frequently classified as adverse genetic risk, pointing to 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 allo-HCT in CR1 in the quizartinib arm of the study with a hazard ratio of 0.29 (95%-CI 0.17-0.51) translating into a risk reduction with respect to death of 70.1%.[6]

Regarding the impact of quizartinib on MRD, in the QUIWI trial OS and DFS were analyzed according to MRD status post-induction, stratified by allo-HCT status within each treatment arm. MRD was assessed by standardized RT-qPCR techniques (*NPM1*-mutated and CBF 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 ELN-2017 risk category within each treatment arm. MRD negativity rates were numerically higher in the quizartinib arm across favorable (34.1% vs 27.3%) and intermediate-risk groups (78.8% vs 60.0%), 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 allo-HCT in CRc1, the HR comparing quizartinib versus placebo was 0.23 (95%-CI 0.07–0.69), and among those who did not undergo allo-HCT, the HR was 0.59 (95%-CI 0.24–1.44). The treatment effect did not differ according to allo-HCT status (p for interaction = 0.34). Thus, among patients who remained MRD positive after induction, quizartinib was associated with more favorable OS as compared to placebo, regardless of subsequent allo-HCT, with no evidence that transplant status modified the treatment effect. These findings suggest that quizartinib may provide clinical benefit in MRD-positive patients independently of allo-HCT.[4] Furthermore,

these data also suggest that post-induction MRD may be a driver for allo-HCT decision 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 allo-HCT were nearly superimposable, and survival in quizartinib-treated patients without allo-HCT was similar to that of placebo-treated patients who underwent allo-HCT, suggesting a limited additional contribution of allo-HCT to long-term outcomes in this biologically favorable population.

In other words, maintenance with quizartinib may avoid allo-HCT, at least in MRD-negative patients. However, confirmation of this finding in larger studies is warranted.

Currently, published evidence specifically addressing the interaction between allo-HCT in CRc1 and FLT3 inhibitors in *FLT3*-ITD wild-type AML remains scarce. The QUIWI trial represents one of the first randomized studies to explore this setting, although in a post-hoc analysis in only a small cohort of the trial population.

However, the trial does not answer the question on 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 small number of patients 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 and might hopefully be answered in the ongoing global, randomized, double-blind, placebo-controlled phase III QuANTUM-Wild trial (NCT06578247).

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Figure 1: Time-dependent Simon-Makuch plots of OS and DFS according to allo-HCT in patients who achieved CRc1 by the end of induction per IRC.

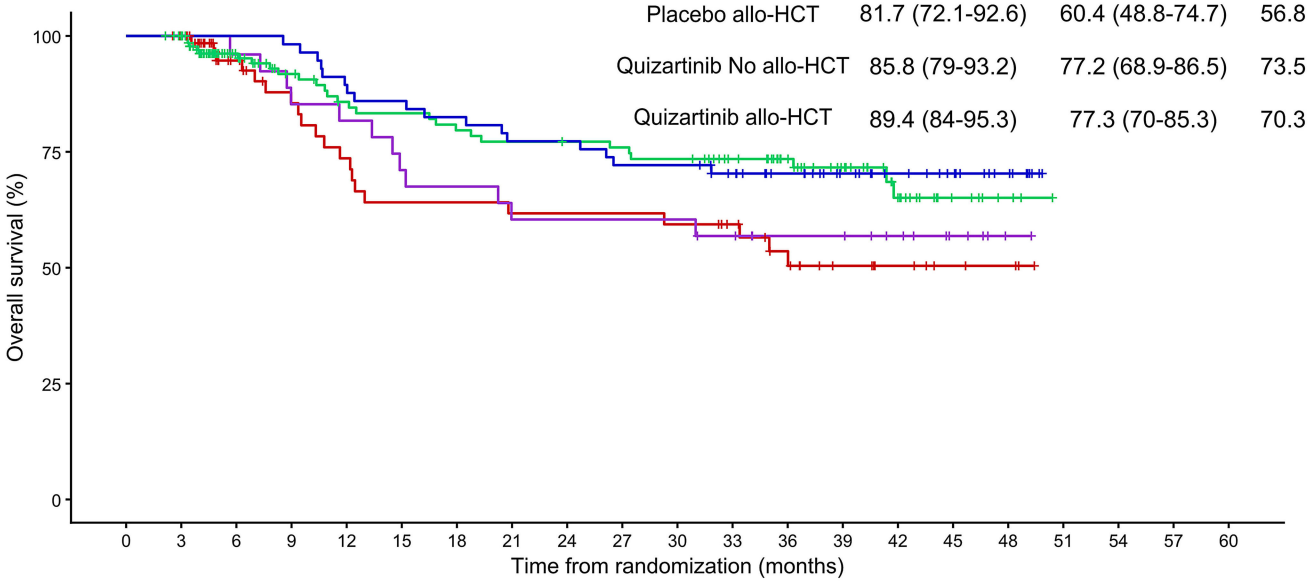
(A) Time-dependent Simon-Makuch plot of OS from randomization by allo-HCT in patients who achieved CRc1 by the end of induction per IRC.

(B) Time-dependent Simon-Makuch plot of DFS by allo-HCT in patients who achieved CRc1 by the end of induction per IRC.

Abbreviations: Allo-HCT: allogeneic hematopoietic cell transplantation; CRc1: first composite complete remission; DFS: disease-free survival; IRC: independent review committee; NE: not estimated; OS: overall survival. Figure from Lloret-Madrid et al.[5]

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)

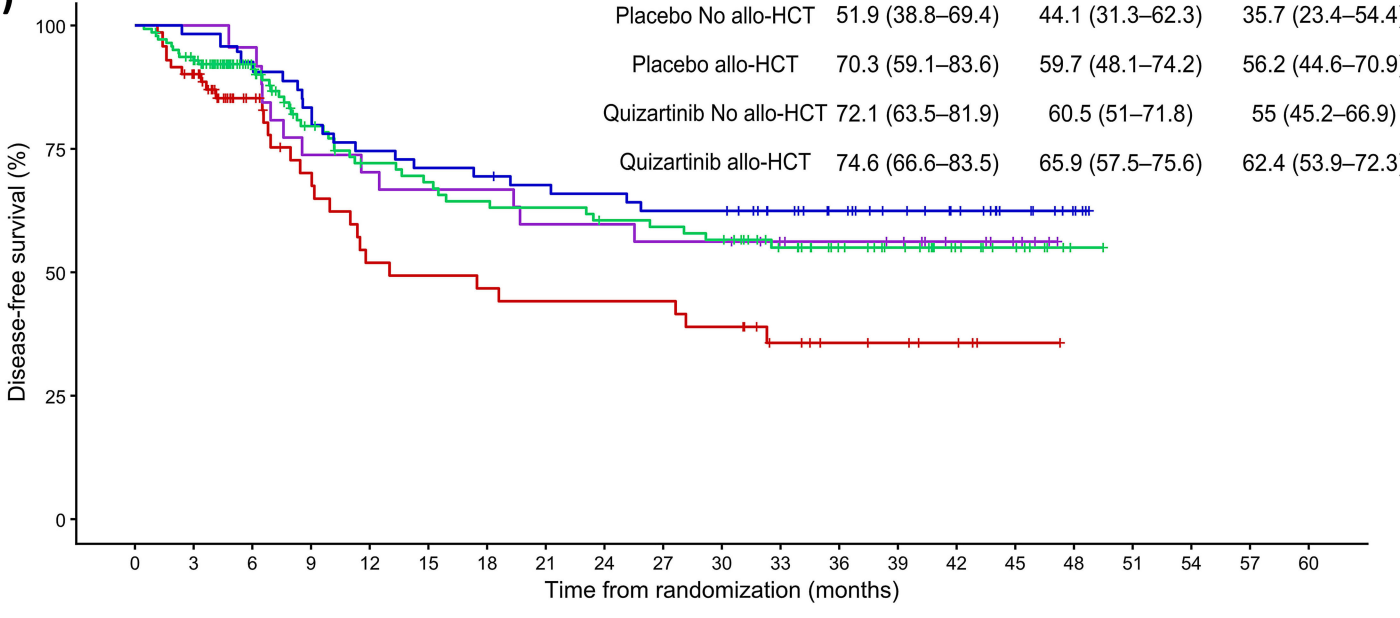


Number at risk

	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