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All patients with AML and *FLT3*-ITD should be transplanted in first remission. Also in the era of tyrosine kinase inhibitors? - the PRO

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PRO AND CON

All patients with AML and FLT3-ITD should be transplanted in first remission. Also in the era of tyrosine kinase inhibitors? – the PRO

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Conflict of interest

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Should all patients with newly diagnosed acute myeloid leukemia (AML) and fms-like tyrosine kinase 3-internal tandem duplication (*FLT3*-ITD) in first complete remission (CR1) with an available HLA-matched donor be advised to proceed to allogeneic hematopoietic cell transplantation (alloHCT) in first remission? This important clinical question was answered before the advent of FLT3-inhibtors (FLT3i) with a clear "depends on" summarized in the European LeukemiaNet (ELN) recommendations 2010[1] and 2017[2]. In particular, the extent of mutant to wildtype ratio of *FLT3*-ITD seemed to impact the benefit-risk ratio of alloHCT performed in first CR, in that patients with an AML exhibiting a high *FLT3*-ITD ratio gained significant benefits with regard to relapse-free survival (RFS) and overall survival (OS).[3-5] In the meanwhile, FLT3i have been and are evaluated in large randomized clinical trials[6,7,8,9] with authority approval intensions. However, beyond the efficacy of the respective FLT3i, alloHCT performed during CR1 was evaluated in addition as an important confounding factor.[6,7,10] So far, the RATIFY[6] and the QuANTUM-First[7] studies are published including dedicated analyses evaluating the respective FLT3i and the interaction with alloHCT, while results from the HOVON 156/AMLSG 28-18 trial[8] and a randomized trial evaluating crenolanib vs. midostaurin (ClinicalTrials.gov identifier NCT03258931) are expected for 2026. Furthermore, non-randomized studies add important insights into the interaction between FLT3i treatment and alloHCT.[11-13]

However, before diving deeper into the exciting analyses of the afore mentioned randomized clinical studies, we first have to discuss biometric issues with regard to the impact of alloHCT on clinical survival endpoints. Whether patients proceed or not to an alloHCT after achieving CR1 upon induction therapy depends on several factors including patient related ones (such as age, presence of comorbidities, willingness of patients to perform the procedure, etc.), administrative factors (such as cost coverage of the procedure by insurance companies, access to stem cell donor programs, etc.), and disease related factors (such as *FLT3*-ITD allelic ratio, presence or absence of concurrent genetic markers e.g. *NPM1* mutations, complex karyotype, etc.), type of AML (de novo, therapy-related AML), etc.). Thus, alloHCT as a treatment procedure is not equally available for all patients. In addition, performance of the procedure is dependent on a number of covariables (known and unknown), which may interduce bias to the performance of the procedure and their impact on survival endpoints. Additionally, the timepoint when the procedure is performed vary quite widely ranging from right after first induction therapy to after

one, two or even three cycles of standard consolidation chemotherapy. This has to be addressed by the statistical methodology used, by analyzing alloHCT as a time-dependent covariable. In univariable analysis the Mantel-Byar test[14] and for graphical illustration Simon-Makuch plots[15] may be used instead of a log-rank test and Kaplan-Meier plots, whereas in multivariable models the time dependency of alloHCT is addressed by extended Cox regression models[16] such as the Andersen-Gill model.[17]

The first evaluation within a randomized setting of the interaction between FLT3i and alloHCT was available in the RATIFY study.[6] In this trial AML patients, 18 to 59 years of age with newly diagnosed *FLT3*-ITD or *FLT3*-TKD were randomized between standard 7+3 induction therapy with midostaurin or placebo starting at day 8 of induction therapy. Midostaurin or placebo were also given after each consolidation chemotherapy and in patients not proceeding to alloHCT as a single agent maintenance therapy up to 12-months.[6] The results of the RATIFY study led to the approval of midostaurin in US and Europe in 2017. AlloHCT was performed during CR1 in 28.1% of the patients in the midostaurin and in 22.7% in the placebo group. In post hoc analyses of the RATIFY trial, OSwas improved particularly in patients receiving an alloHCT in CR1 in the midostaurin arm[6,18] with estimated OS of roughly 70% after 5 years as compared to far below 60% in patients after alloHCT in CR1 in the placebo arm (FigureS3A in ref 7, Figure 1). Unfortunately, uni- and multivariable analyses including alloHCT as a time dependent covariable were not performed. Furthermore, the proportion of patients exhibiting a *FLT3*-TKD in the alloHCT group were not stated. Though it is expected that this proportion might be very small since at this time alloHCT was not recommended for these patients, we do not know this issue for sure.

The next evaluation within a randomized setting of the interaction between FLT3i and alloHCT was available in the QuANTUM-first study.[7] In this trial, AML patients 18 to 75 years of age with newly diagnosed *FLT3*-ITD were randomized between standard 7+3 induction therapy with qizartinib or placebo starting at day 8 of induction therapy. Quizartinib or placebo were also given after each consolidation chemotherapy and in patients proceeding or not to an alloHCTas single agent maintenance therapy for up to 36-months. The results of the QuANTUM-first study led to the approval of quizartinib in US and Europe in 2023. AlloHCT was performed during CR1 in 41% of

the patients in the quizartinib and in 32% in the placebo arm. In post hoc analyses of the Quantum-first trial using appropriated biometrical methods, OS was improved particularly in patients receiving an alloHCT in CR1 in the quizartinib arm of the study.[10] In both arms patients who achieved CR by the end of induction had a statistically significant OS benefit with alloHCT in CR1. Furthermore, an extended Cox regression analysis in patients who achieved CR by the end of induction revealed quizartinib treatment (HR=0.553, 95% CI: 0.383-0.798, P=0.0015) and alloHCT in CR1 (HR=0.527, 95% CI: 0.349-0.796, P=0.0023) as key factors predicting better OS. Although these biometrical methods cannot completely prohibit bias towards alloHCT, they very convincingly show, that both quizartinib added to standard chemotherapy and as single agent maintenance therapy as well as alloHCT performed in CR1 improve outcome in AML patients exhibiting *FLT3*-ITD, paraphrased by Jan J Cornelissen and Jurjen Versluis as “It takes two to tango”.[19] Based on the QuANTUM-first analysis, quizartinib-treated patients who achieved a CR by the end of induction and proceeded to alloHCT in CR1 had an OS advantage with a Hazard ratio of 0.292 (95% CI: 0.168-0.505) translating in a risk reduction with respect to death of 70.08% (Figure 1).[10] However, patients proceeding to alloHCT were on average 10 years younger (table 2 in ref 10) pointing at least to some bias. With regards to age and alloHCT the AMLSG 16-10 trial evaluated midostaurin in combination with intensive chemotherapy according to the 7+3 scheme followed by an early alloHCT and a 12 months midostaurin maintenance therapy in adult (18-70 years) patients with newly diagnosed AML and *FLT3*-ITD mutations.[11,12] Primary and key secondary endpoints were event-free survival (EFS) and OS. Results were compared with a historical cohort of 415 patients treated on five prior AMLSG trials as well as with patients (18-59 years) treated on the placebo arm of the Cancer and Leukemia Group B (CALGB) 10603/RATIFY trial. Overall, the trial accrued 440 patients (18-60 years, n = 312; 61-70 years, n = 128). An alloHCT from matched-related (MRD) or unrelated donors (MUD) was intended in all patients achieving CR or CR with incomplete hematological recovery (CRi) after induction therapy. Overall, n=199 (45%) patients received alloHCT in first CR/CRi, 150 (48%) and 49 (38%) patients in the younger and older cohort, respectively. Median time to alloHCT was 98 days (range, 49-202 days). Within this trial, the addition of midostaurin to intensive induction chemotherapy and alloHCT led to a significant improvement in outcome in younger and even more pronounced in older patients with *FLT3*-ITD mutated AML as

compared to historical controls.[11,12] The reduction of cumulative incidence of relapse was substantial, in particular, in patient 60 to 70 years of age proceeding to an alloHCT in CR1 compared to standard chemo-consolidation (Supplementary Figure 1 in Ref 11). Overall, multivariate analyses revealed that midostaurin treatment had a significant beneficial effect on EFS (HR, 0.55, range: 0.47-0.65; P<0.001) and OS (HR, 0.56, range: 0.47-0.58; P<0.001) in patients with *FLT3*-ITD AML. Of note, the improvement in EFS and OS was even more pronounced in older (61-70 years) as compared to younger (18-60 years) patients. In sensitivity analysis, adjusting for alloHCT in first CR/CRi as a time-dependent covariate, the treatment effect of midostaurin remained significant.

In conclusion, FLT3i treatment before and after alloHCT offers currently the highest chance of cure in AML with *FLT3*-ITD in CR1.

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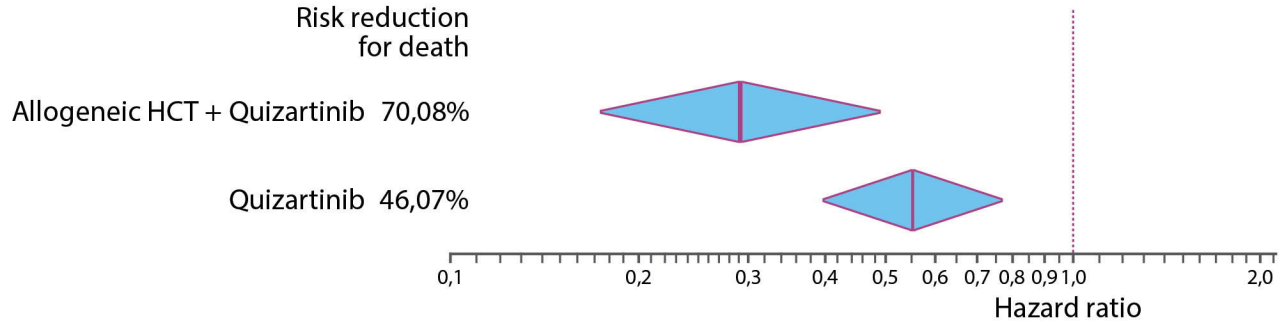
Figure 1: Hazard ratios and corresponding 95%-Confidence Intervals; QuANTUM-first, Hazard ratio of overall survival of patients achieving CR after induction therapy; RATIFY, Hazard ratio of cumulative incidence of relapse (*only patients receiving allogeneic HCT) of patients achieving CR after induction therapy.

QuANTUM-first



RATIFY