

Allogeneic stem cell transplantation for AML patients with RUNX1 mutation in first complete remission: a study on behalf of the ALWP of the EBMT

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ORAL ABSTRACT - SESSION A - ACUTE AND CHRONIC LEUKEMIA

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Clinical Outcomes and Characteristics of Patients (pts) with *FLT3*–Internal Tandem Duplication (*FLT3*-ITD)–Mutated Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML) Undergoing Hematopoietic Stem Cell Transplant (HSCT) after Quizartinib (Q) or Salvage Chemotherapy (SC) in the Quantum-R Trial

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Introduction: In QuANTUM-R, the once-daily, oral, highly potent and selective *FLT3* inhibitor Q improved clinical benefit vs SC (median overall survival [mOS], 6.2 vs 4.7 mo [HR, 0.76 (95% CI, 0.58–0.98); $P=.02$]) in R/R *FLT3*-ITD AML (NCT02039726). Before randomization, 25% (Q) and 23% (SC) of pts had 1 prior HSCT.

Objective: To describe post hoc analyses in pts who underwent subsequent HSCT during QuANTUM-R.

Methods: Pts with *FLT3*-ITD R/R AML received Q (60 mg [30-mg lead-in]) or SC. Pts in the Q arm could resume Q 30–100 d after HSCT. Decisions to proceed to HSCT and resume Q after HSCT were made per investigator discretion/institutional policy.

Results: Of 367 randomized pts, 85 in the Q arm underwent any subsequent HSCT (allogeneic HSCT [allo-HSCT], 84 [6 with and 78 w/o additional AML therapy]; autologous HSCT, 1), and 19 in the SC arm underwent any HSCT (5 with and 14 w/o additional AML therapy).

Q+SC pooled data showed a longer mOS (95% CI) in 104 pts with any HSCT vs 263 w/o (12.2 [10.0–24.1] vs 4.4 [4.1–4.9] mo; $P<.0001$; Fig 1); 1-year OS rates were 50% vs 13%. Among pts preselected for low-intensity therapy, 13/57 in the Q arm and 0/29 in the SC arm underwent any HSCT. Q+SC pooled data also showed a longer mOS (95% CI) in pts with a composite complete remission (CRc) as last recorded response before allo-HSCT vs pts w/o CRc (20.1 [11.7–NA] vs 8.8 [7.0–11.4] mo). Regardless of treatment, mOS was longer with any HSCT vs w/o (Q, 11.9 [10.2–25.1] vs 4.5 [4.1–5.4] mo; SC, 12.7 [6.1–NA] vs 4.0 [2.7–5.0] mo); respective 1-year OS rates were 50% vs 13% and 51% vs 12%.

In the Q arm, mOS (95% CI) was longer in pts with a best response of CRc who resumed Q after allo-HSCT (27.1 [18.2–NA] mo) vs pts not resuming Q (5.4 [4.7–11.4] mo; Fig 2). In 48 pts (62%) in the Q arm resuming Q after allo-HSCT, median time from allo-HSCT to Q resumption was 65 d (range, 30–106 d). Four pts (5%) in the Q arm died < 30 d after allo-HSCT. As of 2/22/2018, 46/78 pts in the Q arm (59%) and 9/14 pts in the SC arm (64%) with allo-HSCT w/o additional AML therapy died, mostly due to AML progression (Q, 31 [40%]; SC, 7 [50%]). The

frequency of treatment-emergent adverse events (TEAEs) and TEAEs of interest was similar in pts resuming Q after allo-HSCT and in the overall Q population.

Conclusion: Independent of HSCT, Q improved survival vs SC in pts with *FLT3*-ITD R/R AML in QuANTUM-R. Q+SC pooled analyses showed longer survival in pts with HSCT vs pts w/o and in pts with CRc before allo-HSCT. Survival in transplanted pts was similar in both arms, indicating that HSCT-eligible pts received transplants appropriately, and the higher HSCT rate in the Q arm was beneficial. In pts preselected for low-intensity SC at study entry, 13 were able to undergo HSCT after Q treatment. Q resumption after HSCT was associated with better survival outcomes and was tolerable. These data illustrate the value of using Q to target the *FLT3*-ITD mutation as a part of the overall treatment sequence in pts with *FLT3*-ITD R/R AML.

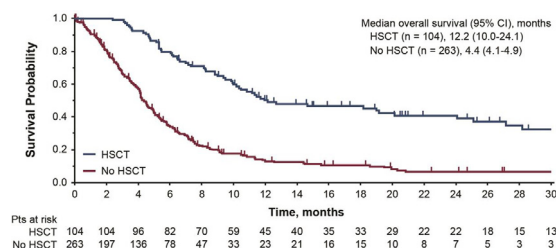


Figure 1. Kaplan-Meier Plot of OS in Pts with or without Any HSCT Regardless of Treatment Arm.

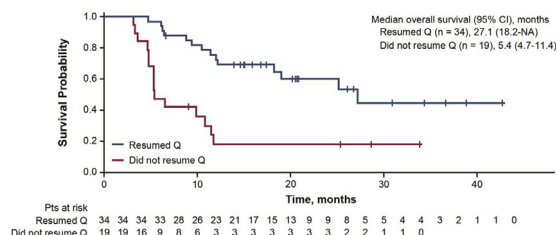


Figure 2. Kaplan-Meier Plot of OS in Pts Who Achieved a Best Overall Response of CRc with Q Who Underwent Allo-HSCT with or without Q Resumption.

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Allogeneic Stem Cell Transplantation for AML Patients with *RUNX1* Mutation in First Complete Remission: A Study on Behalf of the ALWP of the EBMT

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Introduction: Acute myeloid leukemia bearing a *RUNX1* gene mutation (*RUNX1*+ AML) has been proposed as a provisional entity in the 2016 WHO classification. Clinically, it has been associated with inferior response rates and outcome after conventional chemotherapy. Accordingly, *RUNX1*+ AML is allocated in the unfavorable prognostic category of the 2017 European Leukemia Net classification. Following allogeneic stem cell transplantation (alloSCT), *RUNX1* was an unfavorable factor in one study in MDS/secondary AML, while data in *de novo* AML are scarce.

Objectives: Here, we present a retrospective study by the EBMT Acute Leukemia Working Party, aiming to elucidate the prognostic value of *RUNX1* mutation in patients undergoing alloSCT for AML in first complete remission (CR1).

Methods: Adults undergoing alloSCT for AML in CR1 from matched related or unrelated donors between 2013 and 2018 with complete information on conventional cytogenetics and *RUNX1* mutational status were selected from the EBMT registry. Variables of interest were overall and leukemia-free survival (OS/LFS), GvHD/relapse free survival (GRFS), cumulative relapse incidence (RI), non-relapse mortality (NRM) and GvHD. Log rank test, Gray test and Cox regression models were used.

Results: 128 *RUNX*+ and 388 *RUNX*- patients were identified, >80% of both subgroups presenting as *de novo* AML. As expected, *RUNX1*+ patients rarely had co-mutations in *NPM1* (6% vs. 26%, $p=10^{-3}$), and showed a positive correlation with *ASXL1* mutations (50% vs. 16%, $p=10^{-4}$). Cytogenetic categories and other mutations (*FLT3*-ITD, *CEBPA*) were equally distributed between the two groups, as were age, donor and graft type, CMV, conditioning and T cell depletion (TCD). Median follow-up was 16.4 (*RUNX*+) and 19.8 (*RUNX*-) months. 2y OS/LFS of the entire cohort were 64% [59-69]/57% [52-62], with no difference between *RUNX1*+ and *RUNX1*- patients either in univariate or multivariate analysis (2y OS: 67.9% [57.3-78.5] vs. 63.1% [57.4-68.7] $p=0.15$; 2y LFS: 57.6% [46.4-68.7] vs. 57% [51.4-62.6], $p=0.38$), figure 1). *RUNX1* mutation neither had any impact among patients with normal karyotype (figure 2). Similarly, no other outcome parameter was influenced by *RUNX1* mutational status. Instead, multivariate analysis revealed age and donor type as risk factors for OS, LFS and NRM. Poor cytogenetic was associated with higher RI and inferior LFS/GRFS, in vivo TCD with a lower rate of aGvHD II-IV, cGvHD, and better GRFS. Among patients with available information, *FLT3*-ITD was an independent risk factor for relapse, LFS and GRFS. *RUNX1* did not modify the role of *FLT3*-ITD.

Conclusion: Within the limits of a retrospective registry analysis, we could not find a negative influence of *RUNX1* mutation on outcome after allogeneic SCT in CR1. Hence, transplantation in CR1 might overcome the unfavorable prognostic value of

RUNX1 mutation and can be recommended as consolidation treatment in this entity.

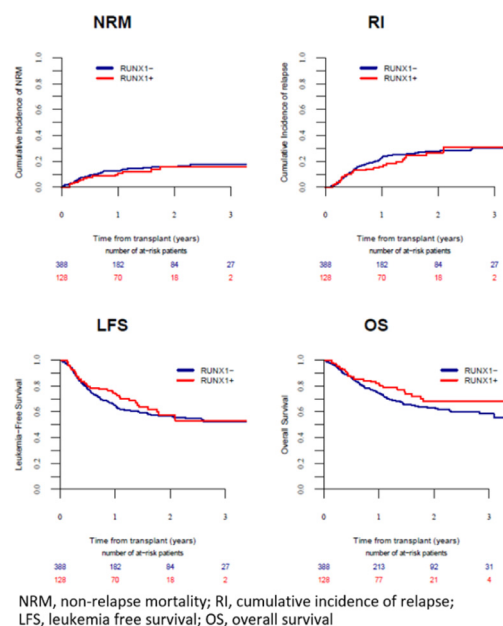


Figure 1. Outcome of patients with AML transplanted in first complete remission as of presence or absence of a *RUNX1* mutation; Entke cohort (n=5151).

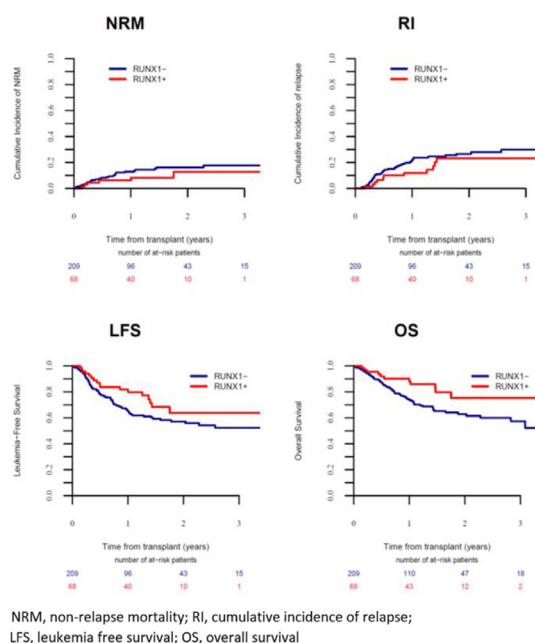


Figure 2. Outcome of patients with AML transplanted in first complete remission as of presence or absence of a *RUNX1* mutation; Patients with normal karyotype (n=277).

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Outcomes in Patients with Acute Myeloid Leukemia with Myelodysplasia-Related Changes (AML-MRC) Who Achieved Remission with CPX-351 Versus 7+3: Phase 3 Exploratory Analysis

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