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Multicenter upfront randomized phase II trial of quizartinib and high-dose cytarabine plus mitoxantrone in relapsed/refractory acute myeloid leukemia with FMS-like tyrosine kinase 3 internal tandem duplication

by Sonia Jaramillo, Johannes Krisam, Lucian Le Cornet, Markus Kratzmann, Lukas Baumann, Sabine Kayser, Christoph Schliemann, Martin Kaufmann, Meinhard Kieser, Uwe Platzbecker, Carsten Müller-Tidow and Richard F. Schlenk

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Letter to the editor

TITLE

Multicenter upfront randomized phase II trial of quizartinib and high-dose cytarabine plus mitoxantrone in relapsed/refractory acute myeloid leukemia with FMS-like tyrosine kinase 3 internal tandem duplication

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Running title: Quizartinib and chemotherapy in relapsed/refractory AML

Contribution:

RFS developed the concept and designed the study. SJ provided study materials. All authors collected and assembled data, analyzed and interpreted data, wrote the manuscript, and gave their final approval of the manuscript.

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Data-sharing statement

Questions regarding data sharing should be addressed to the corresponding author.

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The present study is a multicenter, upfront randomized, open label, phase II trial, in patients with relapsed or refractory *FLT3*-ITD (FMS-like tyrosine kinase-3 internal tandem duplication) acute myeloid leukemia (AML) with the primary endpoint response, defined as achievement of complete remission (CR), complete remission with incomplete hematologic recovery (CRi), or complete remission with partial recovery of peripheral blood counts (CRh). Efficacy was planned to be assessed by comparison to historical controls based on the matched threshold crossing approach (1-3). Study methods are published elsewhere (4). In brief, all patients received salvage therapy with Q-HAM consisting of quizartinib ("Q", 40mg days 4-28) combined with "HAM" (cytarabine 3g/m² twice daily at days one to three, mitoxantrone 10mg/m² at days two and three). During consolidation therapy (chemotherapy as well as allo-HCT) patients received either HAM only in the standard-arm or, continued with Q-HAM in the experimental-arm, according to up front randomization. During a 12-month maintenance therapy, standard arm patients received no further treatment and patients in the experimental arm continued with Q-monotherapy.

The approval of gilteritinib as monotherapy in patients with r/r AML hampered recruitment considerably which is why the study was closed on the 5th of August 2022 after enrolling 11 evaluable patients. This small sample size did not enable statistical analysis as planned.

Currently, there is no commonly accepted standard for salvage chemotherapy treatment in patients with relapse or refractory disease AML (r/r AML) (5). Allogeneic hematopoietic cell transplantation offers the highest chance of cure in this clinical circumstance. Hence, the objective of the salvage therapy is to reduce leukemic burden, achieve best possible remission, and perform a hemopoietic stem-cell transplantation (6). However, a poor response to salvage therapy in affected patients often prevents them from being bridged to hemopoietic stem-cell

transplantation, and according to previous publications, the best timing of allogeneic hematopoietic cell transplantation is after salvage chemotherapy and CR being achieved (7, 8). The oral second-generation bis-aryl urea inhibitor quizartinib is a very selective FLT3 inhibitor with a high capacity for sustained FLT3 inhibition and an acceptable toxicity profile (9). In a phase II study (n=333), quizartinib demonstrated efficacy in patients with *FLT3*-ITDs (n=248), who were relapsed or refractory to 2nd-line, salvage chemotherapy, or had relapsed after allo-HCT (10). The randomized QUANTUM-R study in relapsed (with a duration of first CR of 6 months or less) or refractory AML compared single-agent quizartinib (n=245) to investigator's choice (n=122)(11). In this setting, single-agent quizartinib improved overall survival (OS) significantly (HR 0.76, 95% CI 0.58-0.98; stratified log-rank test, 1-sided P=0.0177). Median OS was 27 weeks (95% CI 23.1-31.3) and 20.4 weeks (95% CI 17.3-23.7) for patients treated with quizartinib and investigator's choice, respectively. After one year, the estimated OS probability was 27% for the quizartinib and 20% for investigator's choice. Although quizartinib was superior compared to investigator's choice, results may even improve when quizartinib is combined with intensive chemotherapy.

Patients were included in our Q-HAM study if they had AML according to the 2016 WHO classification, relapse or refractory disease also after autologous or allogeneic hematopoietic cell transplantation, positivity for *FLT3*-ITD defined as a ratio of mutant to wild-type alleles of at least 0.05, age between 18 and 75 years, and Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2. The primary endpoint of the study was achievement of CR, CRi or CRh after salvage therapy with HAM in combination with quizartinib following the definition as recommended by the European LeukemiaNet (12). Secondary survival endpoints were OS and event free survival (EFS), defined as time from randomization until one of the following events occurs first, failure to obtain CR, CRi, CRh after Q-HAM therapy, relapse from CR/CRi/CRh, or death from any cause. Measurable residual disease-negativity was defined as

the absence of leukemic cells assessed by flow cytometry with a sensitivity of 10^{-4}-10^{5}. Q-HAM was approved by the competent authority BfArM in Germany and the ethical review board of the University of Heidelberg (EudraCT Number: 2018-002675-17; ClinicalTrials.gov ID NCT03989713).

The initially planned sample size was 80, but the study was terminated prematurely due to the above-mentioned hampered recruitment. Out of 13 patients who were assessed for eligibility in total, 11 patients were randomized. Baseline investigations showed 3 patients (27.3%) having an aberrant karyotype; 7 patients (77.8%) received additional therapy beyond the induction with daunorubicin (DA), and 5 patients had undergone allo-HCT before study inclusion. Overall, patients had a median age of 42 years and had either ECOG 0 (n=5) or ECOG 1 (n=6) at inclusion. Men were slightly overrepresented (7 vs 4). Baseline and disease characteristics are further detailed in Table 1. Five patients were allocated to the experimental arm and 6 to the standard arm respectively.

All 11 randomized patients received salvage therapy with Q-HAM and 6 out of 11 patients responded (CR/CRi/CRh) (54.5%; 95% CI, 0.28-0.79) with 5 of the responders proceeding to allo-HCT in remission. Of the remaining 5 patients without CR/CRi/CRh, one achieved partial remission and 4 failed to respond achieving either stable (n=3) or progressive disease (n=1).

Of the 11 patients treated, 5 achieved remission and proceeded to allo-HCT, with two of them completing 12 cycles of maintenance therapy with Q as per protocol; dose reduction to 20mg was performed in one patient due to QTc prolongation at month 3 of maintenance. Two patients attained remission after ST but relapsed following allo-HCT. Five patients discontinued their treatment after ST. Of these, one had progressive disease, one achieved a partial response (PR) and was initiated on another therapy, and three were in stable disease (SD) and began different treatments. Details regarding the tolerability of the salvage therapy, specifically

concerning Grade 3 and above treatment-emergent adverse events during salvage therapy, are outlined in Table 2.

Measurable residual disease (MRD) status after salvage therapy was assessable in 7 of 11 patients. Of 3 patients with negative MRD-status (42.9%), 1 achieved complete remission, the 2 others achieved complete remission with incomplete hematologic recovery. In contrast, of 4 patients with a positive MRD (57.1%) status, 2 achieved complete remission, 1 achieved complete remission with incomplete hematologic recovery and 1 partial remission.

Four out of the 11 patients included in this study are still in CR and 3 of them have MRD negativity after 4 years and show no presence of a *FLT3*-ITD in peripheral blood (PB) or bone marrow (BM). Interestingly, 3 of these 4 patients had an aberrant karyotype, and one had a concomitant *NPM1* mutation. Furthermore, 3 out of these 4 patients were refractory to induction therapy, all except one were pre-exposed to midostaurin, and two of them had relapsed after allogeneic stem cell transplantation within the first 6 months of their conditioning regimen indicating very aggressive AML before treatment in the Q-HAM study. After a median follow-up of 53.6 months, event-free and overall survival at 4 years were 36.4% (95% CI, 16.6-79.5) and 70% (95% CI, 46.7-100%), respectively (Figure 1).

Compared to the Q-group in QUANTUM-R, the Q-HAM trial population was slightly younger (median age 42 vs. 55 years), had a better ECOG status (100% vs. 89% with ECOG 0-1), and included a higher proportion of men (63% vs. 46%), with baseline responses to previous therapies being similar. Notably, median overall survival was clinically relevantly longer in the Q-HAM trial with not reached as compared to 6.2 months (95% CI 5.3-7.2) in the Q-group. The meaningfulness of this comparison is however compromised by the considerable difference in the sample sizes (n=245 vs. n=11) and the premature termination of the Q-HAM study. Furthermore, the planned crossover in the maintenance phase and the intended assessment of

efficacy through comparison to historical controls based on the matched threshold-crossing approach were also not conducted making further interpretations of the results more limited. According to overall survival data from a follow-up study of QUANTUM-R, the survival rate at 36 months for patients who achieved a CR before allo-HCT was 40% (13). In contrast, in the Q-HAM trial five out of the six patients (83%) who achieved a CR after Q-HAM were still alive after 48 months underlining the high antileukemic potential of the combination Q plus HAM. The toxicity observed in the Q-HAM patients was similar in terms of infection complications, such as febrile neutropenia and sepsis, to published data on salvage therapy with HAM. However, the influence of quizartinib on the safety profile, particularly regarding QTc prolongation and electrolyte disturbances, has to be carefully monitored.

Despite the limitations caused by the very small sample size, the survival data and stable remission observed in these few patients with aggressive disease characteristics were encouraging.

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Table 1: Clinical Characteristics of the Participants at Baseline

Parameter	Number of Patients
ECOG performance status	
Grade 0	n = 5
Grade 1	n = 6
Prior exposure to other toxic agents	n = 2
Disease status:	
Refractory after induction therapy	n= 3
Relapse after first line therapy	n= 8
Mutational status:	
FLT3-ITD	n= 11
Median allelic ratio: 0.3 (range 0.2-0.5)	
NPM1-mut	n = 3
CEBPA-mut biallelic	n = 1
RUNX1-mut	n = 1
Karyotype:	
Normal	n = 8
Abnormal	n = 3
Previous AML therapy*:	
Relapse after first line therapy:	
Allogeneic HCT (in CR1)	n = 5
High dose cytarabine consolidation	n = 3
Refractory to induction therapy:	
Standard 7+3 induction (2 cycles)	n = 3

Abbreviations: CEBPA, CCAAT/enhancer binding protein, alpha; CR, complete remission; ECOG, Eastern Cooperative Oncology Group; FLT3-ITD, Fms-related tyrosine kinase 3 internal tandem duplication; HCT, hematopoietic cell transplantation; NPM1, nucleophosmin-1; RUNX1, Runt-related transcription factor 1.
*Ten out of eleven patients received midostaurin during induction therapy.

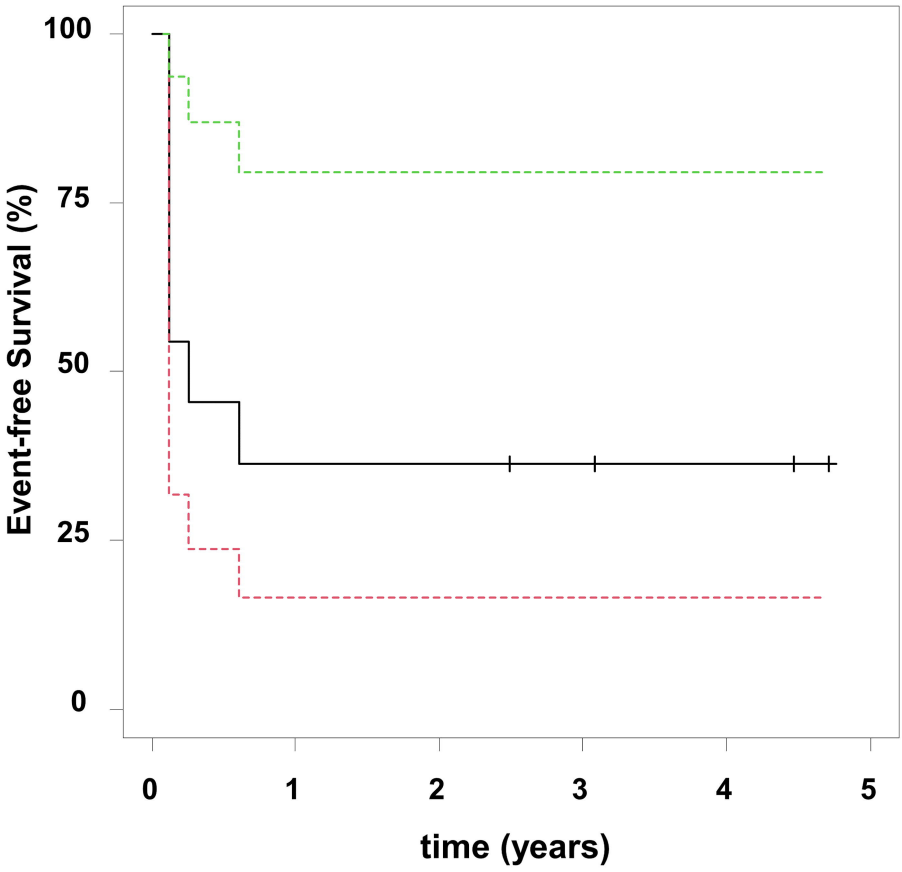
Table 2: Grade ≥ 3 Adverse Events during Q-HAM Occurring in More than 10% of patients

Event	**Number of Patients**
Infection:	
Febrile neutropenia	n = 9
Sepsis	n = 5
Lung infection	n = 2
Hypokalemia	n = 2
Cytopenia (anemia, thrombocytopenia, and leukopenia)	All patients

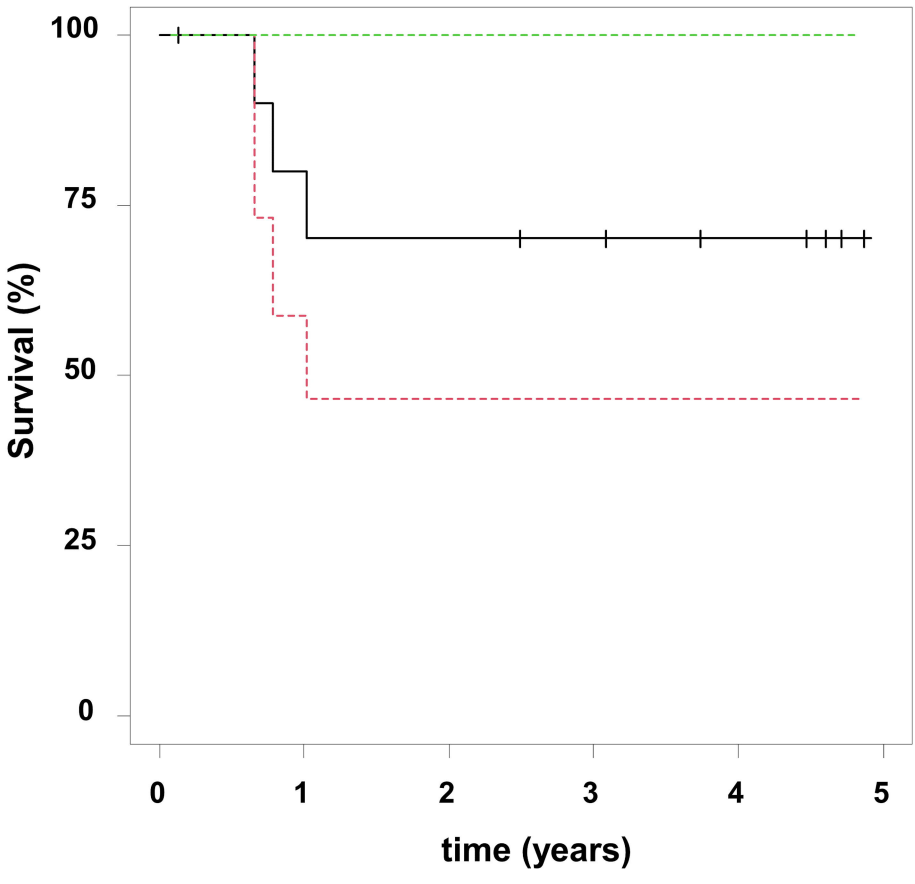
Figure legend:

Figure 1 Survival analysis. (A) Event-free survival (solid black line, 95%-Confidence interval dotted green line [upper] and red line [lower]), (B) Overall survival, (solid black line, 95%-Confidence interval dotted green line [upper] and red line [lower]).

A


100
75
50
25
0
Event-free Survival (%)
0
1
2
3
4
5
time (years)

B


100
75
50
25
0
Survival (%)
0
1
2
3
4
5
time (years)