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

The present study is a multicenter, upfront randomized, open label, phase II trial in patients with relapsed or refractory (r/r) *FLT3*-ITD (FMS-like tyrosine kinase-3 internal tandem duplication) acute myeloid leukemia (AML). The primary endpoint was 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 have been published elsewhere.[4] In brief, all patients received salvage therapy with Q-HAM consisting of 40 mg of quizartinib (Q) days 4-28 combined with HAM (cytarabine 3 g/m² twice daily at days 1-3, mitoxantrone 10 mg/m² at days 2 and 3). During consolidation therapy (chemotherapy as well as allogeneic hematopoietic cell transplantation [alloHCT]) patients received either HAM only in the standard-arm or continued with Q-HAM in the experimental-arm, according to upfront 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 meant that the statistical analysis could not be performed as planned.

Currently, there is no commonly accepted standard for salvage chemotherapy treatment in patients with r/r AML.[5] alloHCT offers the highest chance of cure in this clinical scenario. Hence, the objective of the salvage therapy is to reduce leukemic burden, achieve the best possible remission, and enable the patient to go forward to HCT.[6] However, a poor response to salvage therapy in affected patients often prevents them from being bridged to transplantation, and, according to previous publications, the best timing of alloHCT is after salvage chemotherapy and achievement of CR.[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 of 333 patients, quizartinib demonstrated efficacy in patients with *FLT3*-ITD (N=248), who were relapsed or refractory to second-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 arm 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 HCT, positivity for *FLT3*-ITD (defined as a ratio of mutant to wild-type alleles of at least 0.05), were aged between 18 and 75 years, and had 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 first occured: 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 NCT03989713).

The initially planned sample size was 80, but the study was terminated prematurely due to the compromised recruitment mentioned above. Out of 13 patients who were assessed for eligibility in total, 11 patients were randomized. Baseline investigations showed 3 patients (27.3%) with 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 over-represented (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 (N=1) disease.

Of the 11 patients treated, 5 achieved remission and proceeded to allo-HCT, with 2 of them completing 12 cycles of maintenance therapy with Q as per protocol; dose reduction to 20 mg was performed in one patient due to QTc prolongation at month 3 of maintenance. Two patients attained remission after salvage therapy but relapsed following allo-HCT. Five patients discontinued their treatment after salvage therapy. Of these, one had progressive disease, one achieved a partial response (PR) and was initiated on another therapy, and 3 were in stable disease (SD) and began different treatments. Details regarding the tolerability of the salvage therapy, specifically concerning Grade >3 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%), one achieved complete remission, while the other 2 achieved CRi. In contrast, of 4 patients with a positive MRD (57.1%) status, 2 achieved CR, one achieved Cri, and one achieved PR.

Four out of the 11 patients included in this study are still in CR; 3 of them have MRD negativity after four years and show no presence of a *FLT3*-ITD in peripheral blood or bone marrow. 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 2 of them had relapsed after alloHCT within the first six 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, EFS and OS at four 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%); baseline responses to previous therapies were similar. Notably, median OS was clinically relevant, being longer in the Q-HAM trial (not reached) 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, limiting further interpretation of the results. According to OS 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, 5 out of the 6 patients (83%) who achieved a CR after Q-HAM were still alive after 48 months, underlining the

Table 1. Baseline clinical characteristics of study participants.

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

AlloHCT: allogeneic hematopoietic cell transplantation; AML: acute myeloid leukemia; *CEBPA*: CCAAT / enhancer binding protein, alpha; CR: complete remission; CR1: first CR; ECOG: Eastern Cooperative Oncology Group; *FLT3*-ITD: Fms-related tyrosine kinase 3 internal tandem duplication; N: number; *NPM1*: nucleophosmin-1; *RUNX1*: Runt-related transcription factor 1. *Ten out of 11 patients received midostaurin during induction therapy.

Table 2. Grade ≥3 adverse events during Q-HAM combination therapy occurring in more than 10% of study participants.

Event	N of patients
Infection	
Febrile neutropenia	9
Sepsis	5
Lung infection	2
Hypokalemia	2
Cytopenia (anemia, thrombocytopenia, and leukopenia)	All patients

N: number.

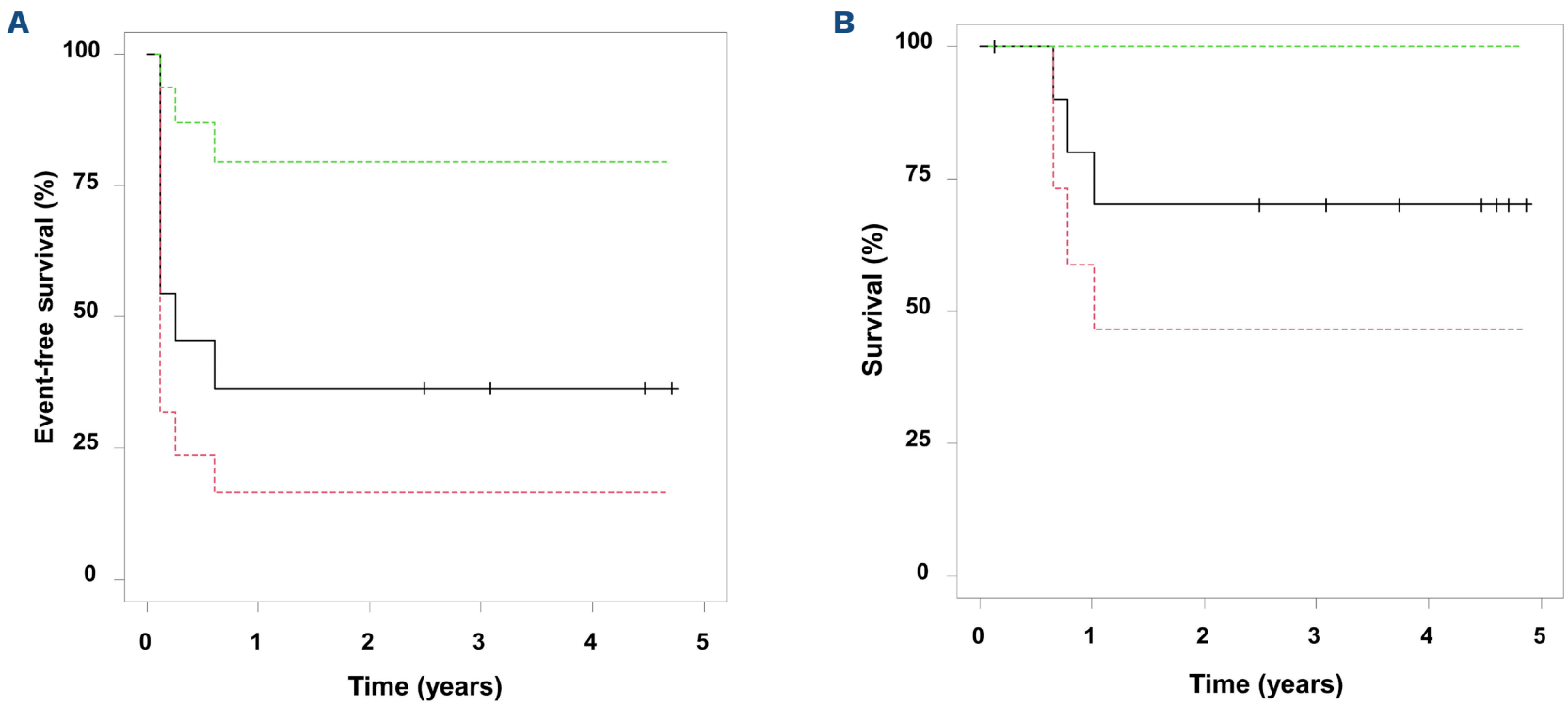

Figure 1. Survival analysis. (A) Event-free survival (solid black line), upper 95%CI (dotted green line), and lower 95%CI (red line). (B) Overall survival (solid black line), upper 95%CI (dotted green line), and lower 95%CI (red line).

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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Contributions

RFS developed the concept and designed the study; SJ provided study materials; all authors collected, assembled, analyzed and interpreted data, wrote the manuscript, and approved the final version for publication.

Data-sharing statement

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

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