NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG

getragen von:
Deutsches Krebsforschungszentrum
Universitätsklinikum Heidelberg
Thoraxklinik-Heidelberg
Deutsche Krebshilfe

Study Title:

Quizartinib and High-dose Ara-C plus Mitoxantrone in Relapsed/Refractory AML with *FLT3*-ITD

Short Title/ Acronym: Q-HAM

Final Study Report

(acc to §42b AMG and §13(9) GCP-V)

Version Number, Date:	20230329-finalCTR Q-HAM_V1.0-upload.DOCX
Investigational product:	Quizartinib
Eudra-CT Number:	2018-002675-17
Protocol-Number:	NCT-2017-0545
ID Clinicaltrials.gov	NCT03989713

Sponsor:

Ruprecht-Karls-University of Heidelberg
Medical Faculty represented in law by
Heidelberg University Hospital and its acting
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Coordinating / Principal Investigator:

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Study Initiation and Completion Dates:

FPFV/FPI	23.9.2020
LPFV/LPI	05.07.2022
LPLV/LPO	12.9.2022
EOS	12.9.2022
DBL	20.12.2022

CONFIDENTIAL

Signatures

The present trial study report was subject to critical review and has been approved in the present version. The information contained is consistent with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (current version), the principles of ICH-GCP and all local regulatory requirements.

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of this study.

Report Version / Date: 20230329-finalCTR Q-HAM_V1.0.DOCX

Sponsor / or Designated Representatives (Reviewer)		Delegated to Coordinating Investigator
	Name	Place, Date
Principal or Coordinating Investigator (Reviewer)	Prof. Dr. Richard F. Schlenk	Heidelberg 29.03.2023
	Name, Title	Place, Date
Biostatisticians (Authors)	Lukas Baumann	Heidelberg, 29.03.2023
	Name	Place, Date

Synopsis

Name of Sponsor/Company:
Ruprecht-Karls-University of Heidelberg Medical Faculty represented in law by Universitätsklinikum Heidelberg and its acting Commercial Director Mrs. Katrin Erk
Im Neuenheimer Feld 672
D-69120 Heidelberg

Name of Finished Product:
Quizartinib

Name of Active Ingredient:
Quizartinib

Title of Study:
Quizartinib and High-dose Ara-C plus Mitoxantrone in Relapsed/Refractory AML with *FLT3*-ITD

Acronym: Q-HAM

Protocol versions:

Date	Version	Submission	Approval BfArM
06.08.2019	1.2	1st submission	13.12.2019
08.04.2020	1.4	1st subst. amendment	30.4.2020
24.08.2020	1.5	2nd subst. amendment	4.9.2020
06.04.2021	1.6	3rd subst. amendment	15.4.2021
02.11.2021	1.7	4th subst. amendment	10.11.2021

Study Center(s) and Principal Investigator(s):
A list of study centers including names of principal Investigators is given in Appendix 1.

Publication (Reference):
Jaramillo, Sonia & Le Cornet, Lucian & Kratzmann, Markus & Krisam, Johannes & Goerner, Martin & Hänel, Mathias & Röllig, Christoph & Wass, Maxi & Scholl, Sebastian & Ringhoffer, Mark & Reichart, Alexander & Steffen, Björn & Kayser, Sabine & Mikesch, J-H & Schaefer-Eckart, Kerstin & Schubert, Jörg & Geer, Thomas & Martin, Sonja & Kieser, Meinhard & Schlenk, Richard. (2021). Quizartinib and High-dose Ara-C plus Mitoxantrone in Relapsed/Refractory AML with *FLT3*-ITD. 10.21203/rs.3.rs-1117424/v1.

Studied Period (years):

Date of first enrollment (FPI):	23.09.2020
Date of last enrollment (LPI):	05.07.2022
Date notification (to BfArM & EC) of premature stop of patient recruitment:	02.08.2022
Date of last patient out (LPO):	12.09.2022

Phase of Development:
Phase II

Objectives:

Primary objectives

The primary objective of the Q-HAM trial was to evaluate whether patients with refractory/relapsed acute myeloid leukemia (r/r-AML) can benefit from receiving the oral quizartinib in terms of an improved probability for a Complete Remission (CR), Complete Remission with incomplete hematological recovery (CRi), or Complete Remission with partial recovery of peripheral blood counts (CRh).

Secondary objectives

Secondary objectives were to assess event-free survival (EFS), relapse-free survival (RFS), overall survival (OS), cumulative incidence of relapse (CIR) and death (CID) and patient reported outcomes (PRO) according to continuation therapy strategy (preemptive continuation therapy with quizartinib vs. prophylactic quizartinib therapy).

Primary Endpoint

The primary endpoint of the trial was composite remission, defined as experiencing a CR/CRh/CRi after salvage therapy.

Secondary Endpoints

Secondary endpoints were OS, EFS, RFS, CIR, and CID. Since the trial was prematurely terminated not all objectives of the trial were addressed. Overall only 11 patients were randomized and only 2 patients received consolidation therapy.

Methodology:

The Q-HAM study was designed as a multicenter, randomized phase II trial. Patients were upfront randomized in a 1:1 ratio either to a measurable-residual disease triggered (MRD-triggered) treatment arm or to the prophylactic arm. All patients were planned to receive quizartinib in combination with high-dose cytarabine and mitoxantrone (HAM) during salvage therapy (ST). During consolidation therapy (CT) patients of both treatment arms should be treated with up to 2 cycles of HAM and, according to up-front randomization, should receive either prophylactic quizartinib therapy in addition (irrespective of MRD results) or preemptive continuation therapy with quizartinib was only to be started after patients becoming MRD-positive (i.e. switch from MRD-triggered arm to prophylactic arm). Following to CT a maintenance phase with either only observation (M/O) for patients still in the MRD-triggered arm (switch from MRD-triggered to prophylactic arm after occurrence of MRD-positivity as above) or quizartinib as single agent in the prophylactic arm was planned. Allogeneic hematopoietic cell transplantation (allo-HCT) was allowed at any time after ST. Efficacy was planned to be assessed in terms of the odds ratio for the primary endpoint composite remission by comparison of trial patients (receiving quizartinib) versus matched historical controls (not receiving quizartinib).

After the inclusion of 13 patients (11 randomized), patient recruitment was stopped prematurely (see above). The unexpectedly slow recruitment rate until July 2022 made it obvious that the planned sample size was unachievable within a reasonable timeframe.

Number of Patients (planned and analyzed):

Sample size was planned to be adjusted by a recalculation after enrolling n=20 patients and was expected to range between n=20 and n=80. However, patient recruitment was stopped after the inclusion of 11 patients.

The applicable patient analysis sets are described below (see statistical methods).

Diagnosis and Main Criteria for Inclusion:

Adult *FLT3*-ITD positive patients with relapsed/refractory AML eligible for intensive therapy, age ≥18 and ≤ 75 years, ECOG performance status ≤ 2, adequate renal function, prior AML treatment discontinued for a least 10 days, effective contraception.

Investigational Product, Dose And Mode Of Administration, Batch Numbers:

- Quizartinib (INN), Drug Code AC220, ATC Code L01EX11, 20 mg (film-coated tablets containing 17.7 mg of quizartinib), manufacturer/importer Daiichi Sankyo Europe GmbH, Batch Number: 9119XA-01

Planned Duration of Treatment:

Maximum planned overall duration of treatment per patient was approximately 16 months, consisting of a 3-week salvage therapy cycle (plus recovery of ≤3 weeks if needed), two 4-week consolidation therapy cycles (plus recovery of ≤2 weeks if needed) and up to twelve 4-week maintenance therapy cycles.

Reference Therapy, Dose and Mode of Administration, Batch Numbers:

None

Criteria for Evaluation:

Due to the premature study termination, study endpoints were not evaluable as planned per protocol.

Efficacy:

Primary endpoint

Primary endpoint is composite remission, defined as CR/CRh/CRi after salvage therapy based on the following definitions:

- CR: bone marrow blasts < 5%, absence of peripheral blasts, absence of extramedullary involvement, neutrophils ≥1.0 x 10^9/l, platelet count ≥ 100 x 10^9/l.
- CRi: all CR criteria met, but allowing for neutrophils < 1.0 x 10^9/l or platelet count < 100 x 10^9/l. CRi should only include patients not meeting the definition of CRh.
- CRh: neutrophils ≥ 0.5 x 10^9 /l and platelet count ≥ 50 x 10^9/l, otherwise all CR criteria met.

Secondary endpoints

- OS defined as the time from randomization to time of death from any cause. Patients without the event censored on the last date of follow-up.
- EFS defined as the time from randomization until failure to obtain CR/CRi/CRh after Q-HAM salvage therapy, relapse from CR/CRh/CRi (bone marrow blasts ≥ 5%/ reappearance of peripheral blasts/ extramedullary disease/ re-occurrence of MRD as assessed by multiparameter flow cytometry) or death from any cause, whatever occurs first. Patients without event censored at the last date of follow-up.
- RFS defined as the time from achievement of CR/CRh/CRi after salvage therapy to time of recurrence of the disease (bone marrow blasts ≥ 5%/ reappearance of peripheral blasts/ extramedullary disease/ re-occurrence of MRD as assessed by multiparameter flow cytometry) or death from any cause, whatever occurs first. Patients without event censored at the last date of follow-up.
- CIR defined as time from achievement of a CR/CRh/CRi after salvage therapy to time of recurrence of the disease where death from any cause is a competing event.
- CID defined as the time from achievement of a CR/CRh/CRi after salvage therapy to death from any cause whereby recurrence of the disease is a competing event.

Safety:

The safety evaluation is primarily based on adverse event data. Laboratory data were evaluable to only a limited extent.

Statistical methods:

Due to unexpectedly slow recruitment, the trial was prematurely terminated after randomization of 11 patients and prior to the interim analysis that was scheduled to occur after randomization of 20 patients. Only a fraction of the initially planned analysis was conducted and analyses are of purely descriptive nature. No historical controls were matched against the study patients for the analysis of the primary endpoint. PROs were not evaluated. With respect to study endpoints see above (Criteria for Evaluation).

Analysis Sets:

- The full analysis population (FAP) includes all randomized patients with treatment groups assigned in accordance with the randomization scheme, who received at least one day of quizartinib treatment.
- The safety population encompasses all enrolled patients who received at least one dose of quizartinib. Regarding consolidation therapy, patients were analyzed according to the treatment they actually received. No treatment switch occurred before end of treatment, therefore the safety population is identical to the FAP.

Missing Data:

For patients with incomplete follow-up, time to last follow-up date was used as the censoring time in the analysis of time-to-event data. Otherwise, no imputation of missing data was conducted.

Descriptive Methods:

Disposition of patients (numbers of patients randomized per group, assessed for eligibility excluded from analysis sets etc.) is presented via a CONSORT flow diagram (Appendix 2). Continuous variables are described using number of observations, mean, standard deviation, median, Q1, Q3, minimum and maximum. For categorical variables, absolute and relative frequencies are given with missing values being reported as a separate category. Percentages for categorical variables are based on all non-missing values in the respective groups. Time-to-event endpoints are described by Kaplan-Maier estimates (including the numbers at risk for different time points), median survival time (or other quantiles if median survival time could not be calculated), number of events and number of censorings.

Analysis of efficacy endpoints:

The primary endpoint composite remission was analyzed by providing the absolute and relative frequency of all FAP patients experiencing a composite remission. Additionally, a 95% Wilson-type confidence interval for the composite remission rate was calculated.

Descriptive methods for time-to-event endpoints as described above were used to analyze EFS, RFS and OS. No group comparisons were done for secondary endpoints and no cumulative incidences of relapse and death were computed, since no meaningful results were expectable.

Analysis of safety endpoints:

AEs during salvage therapy were summarized by number and percentage of patients experiencing any AE or SAE, and by counts of each individual type of AE, and by determination of the maximum individual toxicity grades. Most common AEs were also determined. Laboratory data were summarized at the end of salvage therapy.

AEs before and after salvage therapy are displayed as listings.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Due to the small number of patients randomized and finally treated (n=11), no robust analyses concerning efficacy were possible. Based on descriptive analysis for the primary endpoint CR/CRi/CRh 6 out of 11 patients responded (54.5%; 95%-CI, 0.28-0.79) and 5 of them proceeded to an allo-HCT that was performed in remission. Two patients who underwent allo-HCT relapsed subsequently. At the time of data base closure 4 patients in total were still in remission. Based on the short follow-up, analyses of the endpoints relapse-free survival and overall survival were not expected to render robust results and not evaluated here.

SAFETY RESULTS:

With respect to the ST, the number of patients experiencing at least one or more adverse events was overall 100% (11/11). The number of patients experiencing one or more serious adverse events was overall 73% (8/11). Most common AE was febrile neutropenia (9/11).

AEs observed after ST were in the expected range.

Overall, the spectrum and frequency of AEs as well as SAEs were in the expected range.

CONCLUSION:

Due to the premature termination of the trial after only n=11 being randomized, no conclusion could be drawn. However, the efficacy and toxicity observed in the trial mirrored the response rates observed with single agent quizartinib in the QuANTUM-R trial.

Substantial Amendments / Interruptions or Early Termination:

Notification of recruitment stop Aug 02, 2022, early termination of study Sep 12, 2022; recruitment goal turned out unachievable.

Version / Date of Report:

20230329-finalCTR Q-HAM_V1.0-upload.DOCX

Appendices

Appendix 1 – List of Study Centers

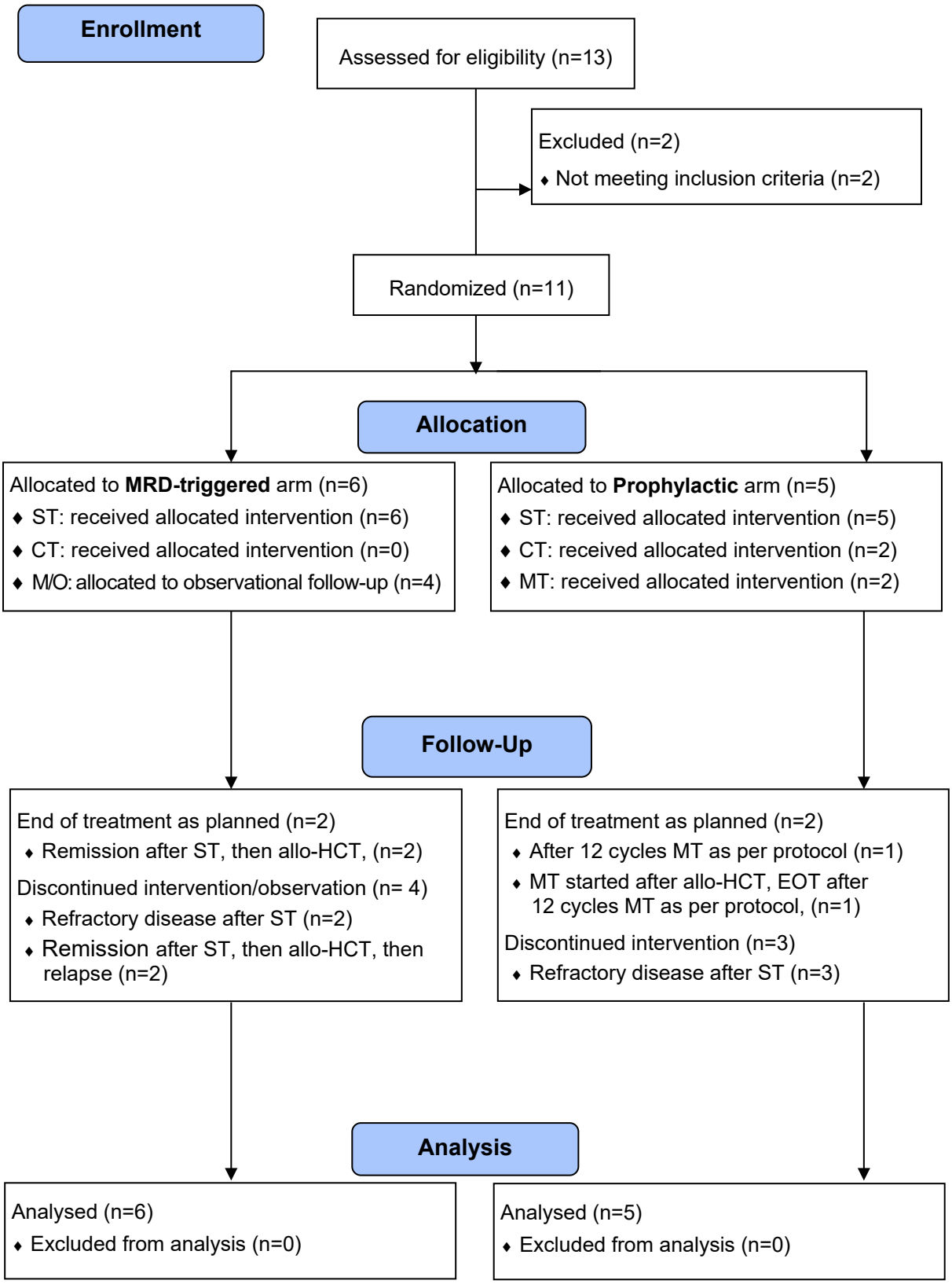
Appendix 2 -Patient Disposition (CONSORT Flow Diagram)

Appendix 3 – Abbreviations

Appendix 1 – List of Study Centers

#	Principal Investigators	Study Centers
1	Prof. Dr. Richard F. Schlenk	Universitätsklinikum Heidelberg Innere Medizin V Im Neuenheimer Feld 410, 69120 Heidelberg
2	PD Dr. med. Martin Görner	Städtisches Klinikum Bielefeld Klinik für Hämatologie, Onkologie und Palliativmedizin Teutoburger Str. 50, 33604 Bielefeld
3	PD Dr. med. Mathias Hänel	Klinikum Chemnitz gGmbH Klinik für Innere Medizin III Bürgerstr. 2, 9113 Chemnitz
4	Prof. Dr. med. Christoph Röllig	Universitätsklinikum Carl Gustav Carus Dresden Medizinische Klinik und Poliklinik I Fetscherstr. 74, 01307 Dresden
5	Prof. Dr. Christine Dierks	Universitätsklinikum Halle (Saale) Klinik und Poliklinik für Innere Medizin 4 Ernst-Grube-Str. 40, 6120 Halle (Saale)
6	PD Dr. Sebastian Scholl	Universitätsklinikum Jena Klinik für Innere Medizin II Am Klinikum 1, 7747 Jena
7	Prof. Dr. med. Mark Ringhoffer	Städtisches Klinikum Karlsruhe Medizinische Klinik III Moltkestraße 90 Haus D D115, 76133 Karlsruhe
8	Dr. med. Jan-Henrik Mikesch	Universitätsklinikum Münster Medizinische Klinik A Albert-Schweitzer-Campus 1 Gebäude A1, 48149 Münster
9	Dr. Kerstin Schaefer-Eckart	Klinikum Nürnberg Nord Klinik für Innere Medizin V Prof.-Ernst-Nathan-Str. 1, 90419 Nürnberg
10	Prof. Dr. med. Jörg Schubert	Elblandklinikum Riesa Klinik für Innere Medizin II Weinbergstraße 8, 1589 Riesa
11	Dr. med. Alexander Reichart	Rems-Murr-Klinikum Winnenden Hämatologie, Onkologie und Palliativmedizin Am Jakobsweg 1, 71364 Winnenden
12	Dr. med Sonja Martin	Robert-Bosch-Krankenhaus Stuttgart Hämatologie, Onkologie und Palliativmedizin Auerbachstraße 110, 70376 Stuttgart
13	Dr. med. Thomas Geer	Diakoneo - Diak Klinikum Schwäbisch Hall Innere Medizin III Stammhaustr 8, 74523 Schwäbisch Hall
14	Dr. Björn Steffen	Universitätsklinikum Frankfurt Medizinische Klinik II Theodor-Stern-Kai 7, 60590 Frankfurt (Main)
15	Prof. Dr. med. Klaus Metzeler	Universitätsklinikum Leipzig Medizinische Klinik I – Hämatologie und Zelltherapie Liebigstraße 22, 04103 Leipzig

Appendix 2 – Disposition of Patients (CONSORT Flow Diagram)



Appendix 3 – Abbreviations

AE	Adverse Event
allo-HCT	Allogeneic Hematopoietic Cell Transplantation
AML	Acute Myeloid Leukemia
ATC	Anatomical Therapeutic Chemical Code
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices, Germany)
CI	Confidence Interval
CID	Cumulative Incidence of Death
CIR	Cumulative Incidence of Relapse
CR	Complete Remission
CRi	Complete Remission with incomplete hematological recovery
CRh	Complete Remission with partial recovery of peripheral blood counts
DBL	Database Lock
CT	Consolidation Therapy
EC	Ethics Commitee
EFS	Event-free Survival
ECOG PS	Eastern Cooperative Oncology Group performance status
EOS	End of Study
FAP	Full Analysis Population
FPFV	First Patient First Visit
FPI	First Patient In
HAM	High-dose Cytarabine, Mitoxantrone
INN	International Nonproprietary Name
ITT	Intention To Treat
LPFV	Last Patient First Visit
LPI	last Patient In
LPLV	Last Patient Last Visit
LPO	Last Patient Out
MRD	Measurable Residual Disease
M/O	Maintenance with observation only
MT	Maintenance Therapy
OS	Overall Survival
PRO	Patient Reported Outcome
RFS	Relapse-free Survival
r/r-AML	refractory/relapsed Acute Myeloid Leukemia
SAE	Serious Adverse Event
ST	Salvage Therapy