NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG
getragen von: Deutsches Krebsforschungszentrum, Universitätsklinikum Heidelberg, Thoraxklinik-Heidelberg, Deutsche Krebshilfe

Study Title:

TEAM-Trial: Targeting Epigenetic therapy resistance in AML with Bortezomib: A multi-centre matched threshold crossing phase II approach

The trial is designed as prospective, open-label, multicenter, phase II study based on an adjusted Simon's two-stage design to gain first evidence of antitumor activity of the novel B-GA treatment regimen in comparison to matched historical controls in adult patients with r/r-AML. The primary endpoint is CR/CRi rate (response rate) as assessed after 22-56 days.

Short Title/ Acronym: TEAM

Final Study Report according to §42b AMG and §13(9) GCP-V

Version Number/ Date:	Final 1.0, March 8th 2024
Investigational Product:	Bortezomib (Velcade®), Gemtuzumab ozogamicin (Mylotarg®)
EudraCT Number:	2017-005158-12
Protocol-Number:	Version 1.1, February 22nd 2019

Sponsor:
Ruprecht-Karls-University Heidelberg
Medical Faculty
represented in law by its Commercial Director
Katrin Erk
Im Neuenheimer Feld 672
69120 Heidelberg, Germany
Phone +49 (0)6221 56 7002
Fax: +49 (0)6221 56 4888
E-mail: Kaufmaennische-Direktion@med.uni-heidelberg.de

Principal/Coordinating Investigator:
Prof. Dr. Carsten Müller-Tidow
University Hospital Heidelberg
Internal Medicine V
Hematology, Oncology and Rheumatology
Im Neuenheimer Feld 410
69120 Heidelberg
Phone: +49 6221 - 56 8001
Fax: +49 6221 - 56 33639
E-Mail: Carsten.Mueller-Tidow@med.uni-heidelberg.de

Author of Trial Report:
Lisa-Marie Lanz, M.Sc.
NCT Trial Center
Im Neuenheimer Feld 130/3
69120 Heidelberg
Phone: +49 6221/56-6085
Fax: +49 6221/56-5863
lisa-marie.lanz@nct-heidelberg.de

Initiation and Completion Dates:
First Patient in: January 22nd 2020
Last Patient in: February 1st 2023
Last Patient Last Visit: March 13th 2023
Data base lock: October 4th 2023

Signatures

The present 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.

Coordinating Investigator/ Designated Representative of Sponsor	Prof. Dr. Carsten Müller-Tidow	Place, Date
Biostatistician	Lisa-Marie Lanz, M.Sc.	Place, Date

List of abbreviations:

AE	Adverse Event
ALT	Alanine Amino Transferase, also known as SGPT
AML	Acute myeloid leukemia
AP	Alkaline Phosphatase
aPTT	activated Partial Thromboplastin Time
AST	Aspartate Amino Transferase, also known as SGOT
BGA	Bortezomib, Gemtuzumab Ozogamicin, Ara-C
BMI	Body Mass Index
CI	Confidence Interval
CR	Complete Remission
CRi	Morphological complete remission with incomplete blood count recovery
CTCAE	Common Toxicity Criteria for Adverse Events
DP	Deviation Population
EEP	Efficay-Evaluable Population
EFS	Event-free Survival
ELN	European Leukemia Net
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study
FAP	Full Analysis Population
GGT	Gamma Glutamyl Transpeptidase
INR	International Normalized Ratio
LDH	Lactatdehydrogenase
MCV	Mean Corpuscular Volume
MRD	Minimal residual disease
NT-proBNP	N-Terminales pro Brain Natriuretic Peptide
ORR	Overall Response Rate
OS	Overall Survival
PPP	Per Protocol Population
QoL	Quality of Life
RBC	Red Blood Cell
RFS	Relapse-free Survival
r/r	Refractory or Relapsed
SAE	Serious Adverse Event
SD	Standard deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase, also known as AST
SGPT	Serum Glutamic-Pyruvat Transaminase, also known as ALT
SP	Safety Population
SUSAR	Suspected unexpected serious adverse reaction

WBC	White Blood Cell

Synopsis

Name of Sponsor/Company:
Ruprecht-Karls-University Heidelberg
Medical Faculty
Im Neuenheimer Feld 672
69120 Heidelberg

Name of Investigational Medicinal Products:
Velcade®, Mylotarg®

Name of Active Ingredients:
Bortezomib, Gemtuzumab ozogamicin

Title of Study:
TEAM-Trial: Targeting Epigenetic therapy resistance in AML with Bortezomib: A multi-centre matched threshold crossing phase II approach

Short Title/ Acronym:
TEAM

Protocol versions:
Final 1.1, February 22nd 2019

Clinical trial sites and Principal Investigators:

No.	Study center	Name of Principal Investigator
01	Universitätsklinikum Heidelberg Zentrum für Innere Medizin V Hämatologie, Onkologie, Rheumatologie Im Neuenheimer Feld 410 69120 Heidelberg	Prof. Dr. med. Carsten Müller-Tidow
03	Klinikum Chemnitz gGmbH Medizinische Klinik III Flemmingstr. 2 09116 Chemnitz	PD. Dr. Mathias Hänel
04	Universitätsklinikum Dresden Medizinische Klinik und Poliklinik I Fetscherstraße 74 01307 Dresden	Prof. Dr. med. Christoph Röllig
05	Universitätsklinikum Halle Universitätsklinik und Poliklinik für Innere Medizin IV Ernst-Grube-Str. 40 06120 Halle (S.)	Dr. med. Maxi Wass, seit 01.2023: Prof. Dr. med. Christine Dierks
06	Klinikum der Universität München Medizinische Klinik und Poliklinik III Marchioninistr. 15 81377 München	Prof. Dr. med Klaus Metzler, seit 12.2022: Prof. Dr. med. Karsten Spiekermann

No.	Study center	Name of Principal Investigator
07	Klinikum rechts der Isar Klinik und Poliklinik für Innere Medizin III Ismaninger Str. 22 81675 München	Prof. Dr. med. Katharina Götze
08	Universitätsklinikum Münster Medizinische Klinik A Albert-Schweitzer-Campus 1 48149 Münster	Prof. Dr. med. Christoph Schliemann
09	Klinikum Nord Medizinische Klinik 5 Prof.-Ernst-Nathan-Str. 1 90419 Nürnberg	Dr. med. Kerstin Schäfer-Eckart
10	Robert-Bosch-Krankenhaus GmbH ZIM 2 Auerbachstraße 110 70376 Stuttgart	Prof. Dr. med. Walter Erich Aulitzky, seit 12.2022: Dr. med. Martin Kaufmann
11	Universitätsklinikum Frankfurt/Main Medizinische Klinik II, Hämatologie und Onkologie Theodor-Stern-Kai 7 60590 Frankfurt/Main	Dr. med. Björn Steffen
12	Universitätsklinikum Erlangen Medizinische Klinik 5 Hämatologie und Internistische Onkologie Ulmenweg 18 91054 Erlangen	Prof. Dr. med. Stefan Krause

Patients were included in all listed trial centers.

Publication (reference):

Lanz LM, Edelmann D, Benner A, Schäkel U, Klose C, Labrenz J, Müller-Tidow C, Schlenk RF *Adjusting for heterogeneity in phase II trials by using a modified Simon's two stage design spiced up with historical controls.* 66. Jahrestagung der Deutschen Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie e. V. (GMDS), 12. Jahreskongress der Technologie- und Methodenplattform für die vernetzte medizinische Forschung e. V. (TMF). 2021 September; DOI: 10.3205/21gmds082

Studied period (years):

Date of first enrollment: January 22nd 2020

Date of last enrollment: February 1st 2023

Date of last completed: March 13th 2023

Phase of development:

II

Objectives:

The *primary Objective* of the trial is to assess the efficacy of B-GA treatment regimen in r/r AML patients using an extension of Simon's Optimal Two-Stage Design.

Secondary Objectives:

Secondary objectives of the trial include the safety, feasibility and efficacy of the novel treatment regimen, as well as the assessment of quality of life.

Methodology:

This trial was planned as a prospective, open label, multi-center phase II study based on an adjusted Simon's two-stage design to gain first evidence of antitumor activity of the novel B-GA treatment regimen in comparison to matched historical controls in adult patients with r/r-AML. The primary endpoint is CR/CRi rate (response rate) as assessed after 22-56 days.

For the design of the trial, an adjusted Simon's two-stage design using historical controls is used. Baseline information collected for each patient in the trial is used to recalculate sample size and critical boundaries for the interim and final analysis. Two models were fitted from historical controls:

	Variable	**Parameter**
Disease status: refractory	Intercept	1.4923
	Age	-0.0359
	FLT3-ITD	-0.2251
	Cyto_high	-0.5146
Disease status: relapsed	Intercept	-0.4760
	Age	-0.0003
	FLT3-ITD	-0.6040
	Cyto_high	-0.5690
	Corebinding-factor AML (cyto_low)	0.7828
	CEBPAdm	0.7440

It was assumed that the new drug results in an average 20% higher response rate. The assumed average response rates were: $\overline{p}_0 = 0.3$ and $\overline{p}_1 = 0.5$ for relapsed and refractory patients.

Number of patients (planned and analyzed):

Number of patients planned: 46

Number of patients analyzed: 51

Diagnosis and main criteria for inclusion:

- Patients with confirmed diagnosis of AML according to WHO-2016 (except acute promyelocytic leukemia) either de novo AML, AML after preceding myelodysplastic or myeloproliferative syndrome (MDS/MPD), and therapy related AML (t-AML) after previous cytotoxic therapy or radiation are eligible either refractory (A) to first line chemotherapy or in first relapse (B), also after stem cell transplantation. FLT3-ITD status, cytogenetics (refractory and relapsed patients), in addition status of core-binding-factor as well as double mutant CEBPA in relapsed patients must be available.

  A) Refractory to induction therapy is defined as no CR, CRi, (according to standard criteria) after 2 intensive induction cycles of at least 7 days of cytarabine 100-200 mg/m² continuously or an equivalent regimen with cytarabine with total dose not less than 700 mg/m² per cycle and 3 days of an anthracycline/antrachinone (e.g. daunorubicin, idarubicin).

  B) Relapsed after first line therapy is defined as relapsed AML after CR or CRi (according to standard criteria) after at least one intensive induction and consolidation (including intensive chemotherapy and/or hematopoietic cell transplantation) therapy.

Investigational product, dose and mode of administration, batch number (Bortezomib):

Drug Code: 63020-0049

ATC Code: L01XX32

Pharmaceutical formulation: Freeze-dried powder

Route of administration: Subcutaneous, intravenous

Storage conditions: <30°C protected from light

Manufacturer/Importer: Janssen-Cilag GmbH

Marketing Authorization number: EMEA/H/C/000539

Dose: 1.3 mg/m^2

Batch numbers: TEAM/202003, /202013, /202031, /202103, /202150, /202214, /202241

Investigational product, dose and mode of administration, batch number (Gemtuzmab ozogamicin):

Drug Code: 00008-4510

ATC Code: L01XC05

Pharmaceutical formulation: Freeze-dried powder

Route of administration: intravenous

Storage conditions: refrigerated at 2°C to 8°C, protected from light

Manufacturer/Importer: Pfizer Pharma GmbH

Marketing Authorization number: EMEA/H/C/004204

Dose: 3 mg/m^2

Batch numbers: commodity

Reference therapy, dose and mode of administration, batch number:

Not applicable.

Duration of treatment:

4 days

Criteria for evaluation:

Efficacy:

The *primary efficacy endpoint* was response defined as complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) according to ELN 2017 criteria after B-GA treatment.

Calculation of ORR:

“Nominator: all evaluable patients with established response; denominator: all evaluable patients enrolled in the study”.

Secondary efficacy endpoints:

Event-free survival (EFS)

EFS was defined as the time of entry into the study to the date of primary refractory disease, or relapse from CR, or CRi, or death from any cause, whichever comes first. Patients not known to have any of these events are censored on the date they were last examined.

Relapse-free survival (RFS)

RFS was defined only for patients achieving CR, or CRi; defined as the time from achieving a remission until the date of relapse or death from any cause, whichever comes first. Patients not known to have relapsed or died at last follow-up are censored on the date they were last examined.

Overall survival (OS)

OS was defined as the time from entry into the trial or from the date of diagnosis (e.g., for correlative science studies) to the date of death from any cause. Patients not known to have died at last follow-up are censored on the date they were last known to be alive.

Minimal Residual Disease (MRD)

Assessment and grading of MRD is performed by flow cytometry.

Safety:

(Secondary) Safety endpoints:

The endpoints include all AEs, their severity, SAEs, the relation of AEs to the study treatment, dose modifications for toxicity and discontinuation of study treatment during the trial phase.

Other endpoints:

Quality-of-Life (QoL)

QoL is assessed using the extended EORTC questionnaires (QLQ-C30) at baseline and at the EOS visit.

Statistical methods:

Statistical analysis:

Analysis of the primary endpoint:

The primary endpoint of the study, the ***CR/CRi rate (ORR)***, is evaluated according to the adjusted Simon's two-stage design (introduced by Edelmann, Habermehl, Schlenk, Benner).

At the time of final analysis, if the number of measured responses from both stages exceeds *r''*, the null hypothesis H_0 is rejected. Else, H_0 is accepted.

In addition, descriptive statistics and patient data listing are used for the presentation of all response data. An unbiased estimate and exact 95% CI is computed for the response rate. Further exploratory efficacy analyses may be performed if deemed of clinical relevance. The primary analysis is based on the Safety Population (all treated patients); a sensitivity analysis is performed using the Per Protocol Population (patients without major protocol deviations), the Deviation Population (patients with major protocol deviations) and the efficacy evaluable set (patients with information on response). The descriptive comparison of the results of the Per Protocol Population and the Deviation Population shall be performed in terms of observed response rate and confidence intervals.

Analysis of the secondary endpoints:

Time-to-event endpoints

Standard methods for right-censored data are used for analyzing ***EFS, RFS and OS*** according to international standards recommended by the European Leukemia Net (ELN) guidelines. This includes Kaplan-Meier estimates (Kaplan, 1958) of the survival curves, Greenwood's formula (Greenwood, 1926) for estimating the standard error of event rates. Median survival times (months) and the time rates (%) are presented with their corresponding two-sided 95% confidence intervals.

Additional exploratory analyses may be carried out, using Cox proportional hazards regression to examine the influence of covariates on EFS, RFS and OS if deemed clinically relevant. The influence of potentially important prognostic factors on survival time are investigated using the Cox Proportional Hazards Model.

Descriptive statistics

The categorical variables are summarized descriptively for each visit by presenting the absolute and relative frequencies (percentages). Percentages for categorical variables are based on all non-missing values (=100%). Percentages are rounded to one decimal place and there may be occasions where the total of the percentages does not equal 100% exactly.

Continuous variables are summarized descriptively by visit. Number of observations (n, nmiss), mean, standard deviation, median, minimum and maximum will be presented. This includes changes (differences) from the baseline assessment, where appropriate.

The secondary endpoint **MRD** is analyzed descriptively.

Safety endpoints

Adverse Events

Summary tables with the number of patients observed with AEs (all causalities and drug related) and corresponding percentages are presented. AEs are grouped by body system and the preferred term is used.

In addition the most common AEs (all causalities and drug related) are reported. Most common AEs: those AEs occurring in at least 10% of the treated patients).

The analysis of the time to the first occurrence of a (first) SAE (days since start of study treatment) is carried out with the Kaplan-Meier estimator. The hazard rate, indicating the risk to experience a (first) SAE over time, is estimated with the life table method for selected time intervals.

Laboratory data are summarized by presenting summary statistics of raw data by visit and change from baseline values (means, medians, standard deviations, ranges). For selected laboratory parameters the incidence rates are summarized along with two-sided -Clopper-Pearson 95% confidence intervals if appropriate.

Quality of Life

QoL data is scored according to the algorithm described in the EORTC QLQ-C30 scoring manual. All scales and single items are scored on categorical scales and linearly transformed to 0-100 scales where:

- A high score for a symptom scale or item represents a high level of symptoms or problems.
- A high score for a functional scale represents a high or healthy level of functioning.
- A high score for the global health status/QoL represents high QoL

The QoL subscales and single item sub-scores are summarized by the mean and median and plotted by time. The change from baseline for all domains are examined.

Study populations:

A total of 51 patients were included and treated in 11 trial sites. 46 of these patients are in the Per Protocol Population, 5 patients are accordingly in the Deviation Population.

For details on discontinuations and demographics of patients, see the following tables:

Discontinuations from Study:

		Safety Population N (%)	Per Protocol Population N (%)	Deviation Population N (%)
Status at End of Study	Regular EOS day 56	11 (21.6)	10 (21.7)	1 (20.0)
	Start of new therapy line	36 (70.6)	32 (69.6)	4 (80.0)
	Premature termination	4 (7.8)	4 (8.7)	0
Reason(s) for premature end of study *	Death	4 (100)	4 (100)	0

* Documentation of multiple reasons were possible.

Demographics Safety Population/Full Analysis Population:

	All Patients	Male	Female
Sex, n (%)			
Male	36 (70.6)	36 (100)	0
Female	15 (29.4)	0	15 (100)
Age continuous (years), Mean (SD)	58.2 (11.77)	57.2 (12.74)	60.6 (8.96)
BMI (kg/m^2), Mean (SD)	26.3 (5.20)	27.8 (4.97)	22.8 (4.04)
Body Surface Area (m^2), Mean (SD)	2.0 (0.29)	2.1 (0.24)	1.7 (0.13)
Height (cm), Mean (SD)	174.9 (9.71)	179.2 (7.83)	164.8 (5.24)
Weight (kg), Mean (SD)	81.6 (21.99)	89.8 (20.33)	61.9 (10.24)
Age categorical (years), n (%)			
18-59	22 (43.1)	17 (47.2)	5 (33.3)
60-69	22 (43.1)	13 (36.1)	9 (60.0)
≥70	7 (13.7)	6 (16.7)	1 (6.7)
Childbearing Potential, n(%)			
Missing childbearing potential	36	36	0
no	11 (73.3)	0	11 (73.3)
yes	4 (26.7)	0	4 (26.7)
Ethnic Group, n(%)			
Caucasian/white	51 (100)	36 (100)	15 (100)

Demographics Per Protocol Population:

	All Patients	Male	Female
Sex, n (%)			
Male	32 (69.6)	32 (100)	0
Female	14 (30.4)	0	14 (100)
Age continuous (years), Mean (SD)	58.0 (11.80)	56.9 (12.73)	60.5 (9.29)
BMI (kg/m^2), Mean (SD)	26.2 (5.17)	27.5 (5.08)	23.1 (4.07)
Body Surface Area (m^2), Mean (SD)	2.0 (0.28)	2.1 (0.24)	1.7 (0.13)

	All Patients	Male	Female
Height (cm), Mean (SD)	174.8 (9.78)	179.2 (7.76)	164.6 (5.40)
Weight (kg), Mean (SD)	80.8 (21.66)	88.9 (20.42)	62.5 (10.38)
Age categorical (years), n (%)			
18-59	20 (43.5)	15 (46.9)	5 (35.7)
60-69	20 (43.5)	12 (37.5)	8 (57.1)
≥70	6 (13.0)	5 (15.6)	1 (7.1)
Childbearing Potential, n(%)			
Missing childbearing potential	32	32	0
no	10 (71.4)	0	10 (71.4)
yes	4 (28.6)	0	4 (28.6)
Ethnic Group, n(%)			
Caucasian/white	46 (100)	32 (100)	14 (100)

Demographics Deviation Population:

	All Patients	Male	Female
Sex, n (%)			
Male	4 (80.0)	4 (100)	0
Female	1 (20.0)	0	1 (100)
Age continuous (years), Mean (SD)	60.0 (12.63)	59.5 (14.53)	62 (.)
BMI (kg/m^2), Mean (SD)	28.0 (5.73)	30.1 (3.57)	19.4 (.)
Body Surface Area (m^2), Mean (SD)	2.0 (0.35)	2.2 (0.28)	1.6 (.)
Height (cm), Mean (SD)	176.6 (9.91)	179.0 (9.63)	167.0 (.)
Weight (kg), Mean (SD)	88.9 (26.40)	97.6 (20.57)	54.0 (.)
Age categorical (years), n (%)			
18-59	2 (40.0)	2 (50.0)	0
60-69	2 (40.0)	1 (25.0)	1 (100)
≥70	1 (20.0)	1 (25.0)	0
Childbearing Potential, n(%)			
Missing childbearing potential	4	4	0
no	1 (100)	0	1 (100)
yes	0	0	0
Ethnic Group, n(%)			
Caucasian/white	5 (100)	4(100)	1 (100)

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

The primary objective of the trial is to assess the efficacy of B-GA treatment regimen in r/r AML patients using an extension of Simon's Optimal Two-Stage Design.

Primary endpoint therefore is the overall response rate (ORR) defined as the rate of patients with complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) according to ELN 2017 criteria after B-GA treatment.

Secondary endpoints include minimal residual disease (MRD), event-free survival (EFS), relapse-free survival (RFS) and overall survival (OS).

Primary endpoint: ORR:
In the following table binary response information and response-status are shown for the Safety Population/Full Analysis Population (SP/FAP), the Efficacy Evaluable Population (EEP) the Per Protocol Population (PPP) and the Deviation Population (DP):

		Full Analysis Population N(%)	**Efficacy Evaluable Population N(%)**	**Per Protocol Population N(%)**	**Deviation Population N(%)**
Response (y/n)	Missing	2	0	2	0
	Yes	17 (34.7)	17 (34.7)	16 (36.4)	1 (20.0)
	No	32 (65.3)	32 (65.3)	28 (63.6)	4 (80.0)
Response-Status	Missing	2	0	2	0
	Complete remission (CR)	10 (20.4)	10 (20.4)	10 (22.7)	0
	Complete remission with incomplete hematologic recovery (CRi)	7 (14.3)	7 (14.3)	6 (13.6)	1 (20.0)
	No CR/CRi	32 (65.3)	32 (65.3)	28 (63.6)	4 (80.0)

For the primary analysis the FAP used. Overall, 33.3% (17/51) of these patients were assessed as responders (95%-Clopper-Pearson CI of all patients including patients with missing response-status: [20.76%, 47.92%]).

As a sensitivity analysis, the same calculations were performed on the Efficacy Evaluable Population, the Per Protocol Population and the Deviation Population. In the Efficacy Evaluable Population 34.7% (17/49) patients were assessed as responders (95%-Clopper-Pearson CI: [21.67%, 49.64%]). In the Per Protocol Population 34.8% (16/46) patients were assessed as responders (95%-Clopper-Pearson CI of all patients including patients with missing response status: [21.35%, 50.25%]. In the Deviation Population 20.0% (1/5) patients were assessed as responders (95%-Clopper-Pearson CI: [0.51%, 71.64%]. The Per Protocol Population shows a higher response rate than the Deviation Population, but the confidence interval of the Deviation Population overlaps the confidence interval of the Per Protocol Population completely due to the small sample size, thus no significant difference in response rates can be detected.

Secondary endpoint: EFS
The secondary endpoint EFS is analyzed using the FAP. The number of patients with an event is 41. Median event-free survival is 1.1 months. For more information see the following table:

	FAP
Number of Patients	51
Number of Patients with the Event (%)	41 (80.4)
25 Percent Point Estimate* (95% CI)	0.9 (0.8, 1.0)
Median* (95% CI)	1.1 (1.0, 1.4)

	FAP
75 Percent Point Estimate* (95% CI)	4.8 (1.4, .)
6-month event-free rate** (95% CI)	0.175 (0.080, 0.299)
12-month event-free rate** (95% CI)	0.175 (0.080, 0.299)
18-month event-free rate** (95% CI)	0.117 (0.031, 0.264)
24-month event-free rate** (95% CI)	0.117 (0.031, 0.264)

*corresponding to time to event in months
**Kaplan-Meier estimates for the respective time points are displayed

Secondary endpoint: RFS
The secondary endpoint RFS is analyzed using the FAP. This endpoint is only defined for patients achieving remission. The number of patients with remission in the trial is 17. The number of patients with the event until database lock is 7. Median relapse-free survival is 10.8 months. For more information see the following table:

	FAP
Number of Patients	17
Number of Patient with the Event (%)	7 (41.2)
25 Percent Point Estimate* (95% CI)	3.6 (3.0, 10.8)
Median* (95% CI)	10.8 (3.5, .)
75 Percent Point Estimate* (95% CI)	. (10.8, .)
6-month event free rate** (95% CI)	0.542 (0.250, 0.762)
12-month event-free rate** (95% CI)	0.361 (0.076, 0.668)
18-month event-free rate** (95% CI)	0.361 (0.076, 0.668)
24-month event-free rate** (95% CI)	0.361 (0.076, 0.668)

*corresponding to time to relapse in months
**Kaplan-Meier estimates for the respective time points are displayed

Secondary endpoint: OS
The secondary endpoint OS is analyzed using the FAP. The following tables show the results for time to death starting at trial entry (first table) and the results for time to death starting at first diagnosis (second table). The number of patients with the event until database lock is 21. Median overall survival is 14.5 months (starting at trial entry) and 28.1 months (starting from first diagnosis). For more information see the following tables:

OS (time to death starting at trial entry)

	FAP
Number of Patients	51
Number of Patient with the Event (%)	21 (41.2)
25 Percent Point Estimate* (95% CI)	6.5 (3.6, 9.8)
Median* (95% CI)	14.5 (8.3, .)
75 Percent Point Estimate* (95% CI)	. (., .)
6-month event free rate** (95% CI)	0.808 (0.663, 0.896)

	FAP
12-month event-free rate** (95% CI)	0.599 (0.431, 0.731)
18-month event-free rate** (95% CI)	0.456 (0.284, 0.613)
24-month event-free rate** (95% CI)	0.456 (0.284, 0.613)
30-month event-free rate** (95% CI)	0.456 (0.284, 0.613)

*corresponding to time to death in months
**Kaplan-Meier estimates for the respective time points are displayed

OS (time to death starting at first diagnosis)

	FAP
Number of Patients	51
Number of Patient with the Event (%)	21 (41.2)
25 Percent Point Estimate* (95% CI)	18.0 (11.4, 23.8)
Median* (95% CI)	28.1 (21.8, .)
75 Percent Point Estimate* (95% CI)	. (40.6, .)
12-month event free rate** (95% CI)	0.872 (0.738, 0.941)
24-month event free rate** (95% CI)	0.597 (0.430, 0.729)
36-month event free rate** (95% CI)	0.491 (0.318, 0.642)
48-month event free rate** (95% CI)	0.429 (0.246, 0.601)
60-month event free rate** (95% CI)	0.429 (0.246, 0.601)
72-month event free rate** (95% CI)	0.429 (0.246, 0.601)
84-month event free rate** (95% CI)	0.429 (0.246, 0.601)
96-month event free rate** (95% CI)	0.429 (0.246, 0.601)
108-month event free rate** (95% CI)	0.429 (0.246, 0.601)

*corresponding to time to death in months
**Kaplan-Meier estimates for the respective time points are displayed

Secondary endpoint: MRD

Minimal residual disease was assessed at screening and at V15 (EOS). The results are shown in the following table:

		FAP N(%)
Screening	Missing status	2
	+	49 (100)
V15	Missing status	4
	+	33 (70.2)
	+/-	2 (4.3)
	-	12 (25.5)
MRD change	+ to +	33 (64.7)
	+ to +/-	2 (3.9)

		FAP N(%)
	+ to -	12 (23.5)
	+ to Missing	2 (3.9)
	Missing to Missing	2 (3.9)

SAFETY RESULTS:

For the Safety Set the total drug exposure for all patients was 201 days.

All patients experienced at least one (all causality) AE (total number of AEs=408) that occurred after first treatment and prior to EOS. AEs occurring more than once were only counted once per patient if they were assigned to the same preferred term. The most frequent AEs in terms of system organ class were “General disorder and administration site conditions” and “Gastrointestinal disorders”. AEs with causality assessed as related to at least one study drug or with missing information on relatedness were considered as treatment related. 45 (88.2%) patients experienced at least one treatment related AE (total number of treatment-related AEs=128). The most frequent treatment related AEs in terms of system organ class were “General disorder and administration site conditions” and “Gastrointestinal disorders”. 9 SAEs occurred in overall 7 (13.7%) patients. Most of these SAEs were reported in the system organ class “Infections and infestations”.

Overall two SUSARs in two patients occurred (Cardiac failure (recovered/resolved) and a fatal pneumonia).

For detailed information see the following table:

	N (%)
Overview all AEs	
Any AE	51 (100)
Any SAE	7 (13.7)
Any Severe Adverse Event (CTCAE v5.0 grade ≥ 3 or intensity severe)	39 (76.5)
Any SUSAR	2 (3.9)
Patients discontinued study drug Bortezomib due to AEs	0
Patients discontinues study drug Gemtuzumab ozogamicin due to AEs*	3 (5.9)
Patients with dose of study drug Bortezomib reduced or temporarily discontinued due to AE	0
Patients with dose of study drug Gemtuzumab ozogamicin reduced or temporarily discontinued due to AE (on second and last dose)	2 (3.9)
Patients with AE resulting in death	4 (7.8)
Overview related AEs**	
Any AE	45 (88.2)
Any SAE	1 (2.0)
Any Severe Adverse Event (CTCAE v5.0 grade ≥ 3 or intensity severe)	21 (41.2)
Any SUSAR	1 (2.0)
Patients discontinued study drug Bortezomib due to AEs	0
Patients discontinued study drug Gemtuzumab ozogamicin due to AEs*	3 (5.9)
Patients with dose of study drug Bortezomib reduced or temporary discontinuation due to AE	0
Patients with dose of study drug Gemtuzumab ozogamicin reduced or temporary discontinuation due to AE (on second and last dose)	1 (2.0)
Patients with AE resulting in death	1 (2.0)
Overview SAEs	
Any SAE	7 (13.7)

	N (%)
Any Severe Adverse Event (CTCAE v5.0 grade ≥ 3 or intensity severe)	7 (13.7)
Any SUSAR	2 (3.9)
Patients discontinued study drug Bortezomib due to AEs	0
Patients discontinued study drug Gemtuzumab ozogamicin due to AEs*	1 (2.0)
Patients with dose of study drug Bortezomibreduced or temporary discontinuation due to AE	0
Patients with dose of study drug Gemtuzumab ozogamicin reduced or temporary discontinuation due to AE	0
Patients with AE resulting in death	4 (7.8)
AEs by System Organ Class (MedDRA 25.1), all causalities* **	
Cardiac disorders	15 (29.4)
Ear labyrinth disorders	2 (3.9)
Endocrine disorders	1 (2.0)
Eye disorders	3 (5.9)
Gastrointestinal disorders	30 (58.8)
General disorders and administration site conditions	43 (84.3)
Hepatobiliary disorders	1 (2.0)
Immune system disorders	5 (9.8)
Infections and infestations	25 (49.0)
Injury, poisoning and procedural complications	6 (11.8)
Investigations	17 (33.3)
Metabolism and nutrition disorders	27 (52.9)
Musculoskeletal and connective tissue disorders	14 (27.5)
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	2 (3.9)
Nervous system disorders	16 (31.4)
Psychiatric disorders	2 (3.9)
Renal and urinary disorders	2 (3.9)
Respiratory, thoracic and mediastinal disorders	16 (31.4)
Skin and subcutaneous tissue disorders	19 (37.3)
Vascular disorders	17 (33.3)
SAEs by System Organ Class (MedDRA 25.1), all causalities* **	
Cardiac disorders	1 (14.3)
General disorders and administration site conditions	2 (28.6)
Infections and infestations	5 (71.4)
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	1 (14.3)
SAEs by System Organ Class (MedDRA 25.1), related* **	
Infections and infestations	1 (100)

* These patients discontinued Gemtuzumab ozogamicin on day 4 (second and last dose).

** AEs were counted as treatment related if a relationship to one of the study drugs was suspected by the investigator.

*** The displayed number shows the amount of patients with one or more events in the specific system organ class. Each patient is counted only once per system organ class. The percentage is calculated using the number of all patients experiencing at least one AE of the respective type (i.e. AEs, SAEs and related SAEs).

Secondary endpoint: Time to SAE

The secondary endpoint Time to (first) SAE is analyzed using the Safety Set. The number of patients with the event until database lock is 7. For more information see the following table:

	FAP/ Safety
Number of Patients	51
Number of Patient with the Event (%)	7 (13.7)
25 Percent Point Estimate* (95% CI)	62.0 (38.0, .)
Median* (95% CI)	. (62.0, .)
75 Percent Point Estimate* (95% CI)	. (.,.)
30-day event free rate** (95% CI)	0.960 (0.851, 0.990)
60-day event free rate** (95% CI)	0.813 (0.579, 0.925)

*corresponding to time to SAE in months
**Kaplan-Meier estimates for the respective time points are displayed

Other Safety Data

Laboratory Data

In the following tables coagulation and urinalysis data for the safety set is presented. These were only tested at baseline.

Coagulation:

Parameter	N	Unit	Mean	SD	Median	Minimum	Maximum
Fibrinogen	41	mg/dl	383.7	117.1	367.0	199.0	678.0
aPTT	51	sec	29.6	6.6	29.0	20.0	56.0
INR	49		1.1	0.1	1.0	0.9	1.4

Urinalysis numeric:

Parameter	N	Unit	Mean	SD	Median	Minimum	Maximum
pH-Value	40		6.0	0.9	6.0	5.0	7.5
Glucose	6	mg/dl	45.0	100.5	5.1	0.0	250.0
Protein	3	mg/dl	30.0	0.0	30.0	30.0	30.0

Urinalysis categorical:

Parameter		N (%) (N=51)
Glucose	neg	32 (94.1)
	pos +	1 (2.9)
	pos +++	1 (2.9)
Protein	neg	32 (86.5)
	pos +	3 (8.1)
	pos ++	1 (2.7)
	pos +++	1 (2.7)

In the following tables data for clinical chemistry and hematology (absolute and relative) for the safety set are shown. Baseline information of each patient and change from baseline for each patient with at least two observations of the respective laboratory value are displayed. The last available laboratory value is used.

Clinical Chemistry:

Visit	Parameter	Unit	N	Mean	SD	Median	Minimum	Maximum
Baseline (Visit 1)	Sodium	mmol/l	51	139.0	3.0	140.0	131.0	144.0
	Potassium	mmol/l	51	4.2	0.5	4.1	3.2	5.5
	Calcium	mmol/l	51	2.3	0.1	2.3	2.0	2.5
	AP	U/l	51	97.4	48.0	87.0	13.0	326.3
	AST/SGOT	U/l	51	27.4	15.6	23.0	9.0	84.0
	ALT/SGPT	U/l	51	33.3	23.9	29.0	8.0	127.0
	GGT	U/l	51	53.7	55.3	38.0	11.0	318.6
	Creatinine	mg/dl	51	0.9	0.2	0.9	0.4	1.3
	Creatinine clearance	ml/min	48	93.7	23.9	90.0	52.0	172.6
	Total bilirubin	mg/dl	50	0.5	0.3	0.5	0.1	1.3
	Direct bilirubin	mg/dl	20	0.2	0.1	0.2	0.1	0.4
	Glucose	mmol/l	51	6.4	1.5	6.0	4.7	11.4
	LDH	U/l	50	344.3	341.4	243.5	122.0	1813.2
	Uric acid	µmol/l	49	277.6	93.9	285.6	95.2	487.9
	NT-proBNP	pmol/l	43	90.0	272.5	22.1	1.7	1588.6
Change from Baseline for patients with at least two assess-ments	Sodium	mmol/l	51	-0.4	3.3	0.0	-7.0	7.0
	Potassium	mmol/l	51	-0.1	0.5	-0.1	-1.4	1.1
	Calcium	mmol/l	51	0.0	0.2	0.0	-0.3	0.4
	AP	U/l	51	34.1	85.6	16.0	-105.0	401.0
	AST/SGOT	U/l	51	18.9	56.2	11.0	-64.0	281.0
	ALT/SGPT	U/l	51	8.5	40.0	1.0	-93.0	172.0
	GGT	U/l	51	76.1	233.7	19.0	-23.0	1607.0
	Creatinine	mg/dl	51	0.0	0.2	0.0	-0.3	0.5
	Creatinine clearance	ml/min	48	3.0	16.2	1.5	-23.2	68.5
	Total bilirubin	mg/dl	50	0.0	0.3	0.0	-0.7	0.6
	Direct bilirubin	mg/dl	20	0.0	0.1	0.0	-0.1	0.5
	Glucose	mmol/l	49	-0.3	1.6	-0.1	-5.4	4.4
	LDH	U/l	50	-20.9	328.3	46.0	-1458.0	587.0

	Parameter	Unit	N	Mean	SD	Median	Minimum	Maximum
	Uric acid	µmol/l	48	-15.8	109.6	-8.9	-249.9	269.5

Absolute Hematology:

Visit	Parameter	Unit	N	Mean	SD	Median	Minimum	Maximum
Baseline (Visit 1)	RBC	/pl	51	3.4	0.6	3.3	2.2	4.7
	MCV	fl	51	93.1	6.8	93.0	80.0	109.8
	Hemoglobin	mmol/l	51	6.7	1.3	6.6	4.9	9.7
	Hematocrit	%	51	31.1	6.0	30.7	21.0	44.0
	Platelets	/nl	51	80.8	75.3	54.0	5.0	357.0
	WBC	/nl	51	5.2	6.2	3.3	0.4	28.1
	Neutrophils	/nl	46	1.6	2.1	0.9	0.0	12.4
	Segmented Neutrophils	/nl	10	1.1	1.0	0.8	0.0	2.5
	Banded Neutrophils	/nl	10	0.0	0.0	0.0	0.0	0.1
	Myelocytes	/nl	8	0.0	0.0	0.0	0.0	0.1
	Meta-myelocytes	/nl	7	0.0	0.0	0.0	0.0	0.1
	Pro-myelocytes	/nl	8	0.0	0.0	0.0	0.0	0.0
	Blasts	/nl	7	11.4	23.9	0.0	0.0	64.0
	Eosinophils	/nl	12	0.0	0.0	0.0	0.0	0.0
	Basophils	/nl	12	0.0	0.0	0.0	0.0	0.0
	Monocytes	/nl	12	0.7	1.3	0.2	0.0	4.2
	Lympho-cytes	/nl	13	0.9	0.5	0.9	0.4	2.0
Change from Baseline for patients with at least two assess-ments	RBC	/pl	51	-0.2	0.6	-0.2	-1.7	0.9
	MCV	fl	51	-1.0	6.8	93.0	80.0	109.8
	Hemoglobin	mmol/l	51	-0.6	1.2	-0.4	-3.5	1.4
	Hematocrit	%	51	-2.4	6.1	-1.5	-15.0	9.0
	Platelets	/nl	51	42.0	97.4	17.0	-166.0	231.0
	WBC	/nl	51	-1.2	5.8	-0.2	-23.0	8.9
	Neutrophils	/nl	41	0.3	2.6	0.4	-12.3	4.3
	Segmented Neutrophils	/nl	8	0.7	0.7	0.9	-0.3	2.0
	Banded Neutrophils	/nl	8	0.0	0.0	0.0	0.0	0.1
	Myelocytes	/nl	8	0.0	0.1	0.0	0.0	0.2
	Meta-myelocytes	/nl	6	0.0	0.0	0.0	0.0	0.1

	Parameter	Unit	N	Mean	SD	Median	Minimum	Maximum
	Pro-myelocytes	/nl	6	0.0	0.0	0.0	0.0	0.0
	Blasts	/nl	7	-11.4	23.9	0.0	-64.0	0.1
	Eosinophils	/nl	11	0.0	0.1	0.0	0.0	0.3
	Basophils	/nl	11	0.0	0.1	0.0	0.0	0.2
	Monocytes	/nl	11	-0.1	1.5	0.0	-3.6	2.2
	Lympho-cytes	/nl	12	-0.2	0.4	-0.1	-0.9	0.5

Relative Hematology:

Visit	Parameter	Unit	N	Mean	SD	Median	Minimum	Maximum
Baseline (Visit 1)	Neutrophils	%	1	0.0	.	0.0	0.0	0.0
	Segmented Neutrophils	%	37	37.2	25.4	34.0	0.0	85.0
	Banded Neutrophils	%	32	1.1	2.0	0.0	0.0	8.0
	Myelocytes	%	33	0.5	1.2	0.0	0.0	5.0
	Meta-myelocytes	%	32	0.6	2.2	0.0	0.0	12.0
	Pro-myelocytes	%	32	0.1	0.4	0.0	0.0	2.0
	Blasts	%	37	24.4	28.2	16.0	0.0	98.0
	Eosinophils	%	36	1.4	1.8	0.7	0.0	7.0
	Basophils	%	36	0.3	0.6	0.0	0.0	2.0
	Monocytes	%	35	9.4	14.4	5.0	0.0	76.0
	Lympho-cytes	%	36	25.0	18.2	18.0	0.0	64.0
Change from Baseline for patients with at least two assess-ments	Neutrophils	%	1	13.0	.	13.0	13.0	13.0
	Segmented Neutrophils	%	32	3.0	26.5	-2.5	-46.0	77.0
	Banded Neutrophils	%	26	0.3	2.3	0.0	-6.0	6.0
	Myelocytes	%	27	0.0	1.3	0.0	-5.0	3.0
	Meta-myelocytes	%	27	0.1	0.7	0.0	-3.0	1.0
	Pro-myelocytes	%	26	0.0	0.3	0.0	-1.0	1.0
	Blasts	%	32	-13.8	27.7	-2.0	-98.0	33.0
	Eosinophils	%	31	0.6	4.1	0.0	-6.0	15.0
	Basophils	%	32	0.2	0.8	0.0	-2.0	2.0
	Monocytes	%	31	8.3	16.9	5.0	-23.0	62.0

	Parameter	Unit	N	Mean	SD	Median	Minimum	Maximum
	Lympho-cytes	%	31	-1.5	19.4	3.0	-42.0	39.0

OTHER ENDPOINTS

Secondary endpoint: Quality of life

The following table shows the results of the QoL scores. Missing values due to death were imputed with the values indicating the worst QoL.

Visit	Parameter	N	Mean	SD	Median	Minimum	Maximum
Baseline (V1)	Global health status / QoL	51	59.3	21.3	66.7	0.0	100.0
	Physical Functioning	51	75.6	19.9	80.0	20.0	100.0
	Role Functioning	51	58.8	33.6	66.7	0.0	100.0
	Emotional Functioning	51	62.4	27.7	58.3	0.0	100.0
	Cognitive Functioning	51	79.7	25.7	83.3	0.0	100.0
	Social Functioning	51	56.2	32.0	66.7	0.0	100.0
	Fatigue	51	39.5	24.4	33.3	0.0	100.0
	Nausea/ Vomitting	51	6.2	12.5	0.0	0.0	50.0
	Pain	51	17.6	25.7	0.0	0.0	100.0
	Dyspnoea	51	29.4	28.8	33.3	0.0	100.0
	Insomnia	51	34.6	34.6	33.3	0.0	100.0
	Appetite loss	51	16.3	25.3	0.0	0.0	100.0
	Constipation	51	7.8	18.4	0.0	0.0	66.7
	Diarhoea	51	12.4	23.1	0.0	0.0	100.0
	Financial Difficulties	51	28.8	34.7	0.0	0.0	100.0
Day 22 - Day 56 (V15)	Global health status / QoL	40	46.9	22.8	50.0	0.0	91.7
	Physical Functioning	40	64.9	27.5	70.0	0.0	100.0
	Role Functioning	38	41.2	33.5	33.3	0.0	100.0
	Emotional Functioning	40	63.1	28.7	66.7	0.0	100.0
	Cognitive Functioning	40	76.7	27.7	83.3	0.0	100.0
	Social Functioning	40	42.1	35.0	33.3	0.0	100.0
	Fatigue	40	49.4	26.5	44.4	0.0	100.0

	Parameter	N	Mean	SD	Median	Minimum	Maximum
	Nausea/ Vomitting	40	15.0	26.1	0.0	0.0	100.0
	Pain	40	27.9	33.2	16.7	0.0	100.0
	Dyspnoea	40	34.2	35.0	33.3	0.0	100.0
	Insomnia	40	35.8	31.5	33.3	0.0	100.0
	Appetite loss	40	41.7	39.8	33.3	0.0	100.0
	Constipation	40	15.0	25.0	0.0	0.0	100.0
	Diarhoea	40	15.0	30.1	0.0	0.0	100.0
	Financial Difficulties	40	34.2	35.8	33.3	0.0	100.0

CONCLUSION:

For the primary endpoint response 17 responders were documented. Using the baseline information and the adjusted Simon's two-stage design with the model calculated from historical controls, the critical value r'' is 23 (i.e. 24 responders are needed to reject the null hypothesis). With the collected information, the null hypothesis cannot be rejected.

Limitations:

- For one patient information for the variable cyto_high is missing, but in this case this information does not influence the critical value r''.
- One patient was initially misclassified as refractory. After the interim analysis this information was corrected to relapsed. Due to the high influence of this value for the design (see also section "Methodology") this information could not be included in the final analysis using the adjusted Simon's optimal two-stage design. If this information was included prior to the interim analysis, the recalculated values r_1' and n_2' would have been different, resulting in a different (smaller) number of recruited patients. To include all observed patients in the final analysis, the patient is counted as refractory (better prognosis for the patient). Thus the true critical value r'' with respect to the real disease status of the patient might be slightly below 23, thus the null hypothesis still cannot be rejected.

Overall 13.7% (7/51) patients experienced an SAE, 2.0% (1/51) experienced a treatment related SAE and 3.9% (2/51) experienced a SUSAR.

Substantial amendments / interruptions:

No substantial amendments were submitted.

Interruptions:

The trial was not interrupted.

Date of the report:

March 8th 2024