TITLE

Double- blind, placebo controlled, randomized, multicenter, phase II study to assess the efficacy of the high affinity CXCR4 inhibitor Motixafortide in addition to consolidation therapy in AML in first remission.

RUN TITLE

CXCR4 inhibition in AML consolidation therapy

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WORD COUNT MANUSCRIPT: 4000

WORD COUNT ABSTRACT: 200

REFERENCES: 27

FIGURES COUNT: 4

TABLES COUNT: 3

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KEY POINTS

The addition of motixafortide to intensive consolidation therapy did not improve relapse free survival. Motixafortide added toxicity to standard consolidation therapy.

SUMMARY

Leukemia–stroma interactions such as CXCR4-CXCL12 are attractive therapy targets in AML. The high-affinity CXCR4 antagonist motixafortide (BL-8040) affects migration, retention, and survival of myeloid blasts in the bone marrow niche. The aim of this clinical trial was to evaluate the efficacy and safety of motixafortide in combination with standard consolidation therapy in acute myeloid leukemia (AML) in first complete remission (CR/CRi/CRp). Adult patients with 1st CR not scheduled for alloSCT were 1:1 randomized. Patients received age adjusted consolidation therapy plus motixafortide/placebo on days 1-5. Primary end point was relapse free survival at 18 months. Overall, 128 patients were randomized (63 placebo; 65 motixafortide). Baseline characteristics were balanced between treatment arms. Median follow-up

time was 25.4 months. Relapse Free Survival was similar with 10.3 months [95%CI 8.0-12.0] for the motixafortide arm and 11.5 months [95%CI 8.6-24.1] for the placebo arm. Overall survival (OS) did not differ between treatment arms. Intention to treat (ITT) analyses revealed no relevant difference between placebo and motixafortide. Adverse events (but no SAEs) occurred more frequently in the motixafortide arm. The addition of motixafortide to intensive consolidation therapy was feasible, but increased toxicity and did not affect RFS or OS.

The clinical trial is registered at EudraCT number: 2014-002702-21

Keywords Acute myeloid leukemia, motixafortide, CXCR4, consolidation therapy.

BACKGROUND

The CXC chemokine receptor 4 (CXCR4) and its ligand CXCL12 (SDF-1) are expressed and secreted by bone marrow (BM) stromal cells, healthy CD34-positive hematopoietic stem and progenitor cells (HSPCs). They are also expressed by AML blasts. CXCR4 plays an essential role in migration, homing, differentiation, proliferation, and retention of myeloid blasts in the BM niche [1].

Motixafortide (BL-8040, BKT-140, 4F-benzoyl-TN14003) is a novel and highly selective CXC chemokine receptor 4 (CXCR4) antagonist, which binds with high affinity to CXCR4 and inhibits its functions [2]. Previous studies showed that in mice, motixafortide as a single agent induced a rapid, dose-dependent, and transient mobilization of white blood cells (WBC), including monocytes, B-cells, T-cells, and stem cells, from bone marrow (BM) to peripheral blood [3]. Motixafortide was recently approved by the FDA in combination with G-CSF for the mobilization of peripheral blood stem cells in multiple myeloma [4].

In vitro studies in leukemia and multiple myeloma cells demonstrated that motixafortide induces phosphatidylserine externalization, decreases mitochondrial membrane potential, activates caspases, induces sub-G1 arrest, and causes DNA double-stranded breaks [5].

More recent *in vitro* experiments showed that motixafortide increased apoptosis by upregulating miR-15a/miR-16-1 with downregulation of *BCL-2*, *MCL-1*, and *cyclin-D1* [6]. Studies in AML cells indicated that motixafortide blocked leukemic cell proliferation through the inhibition of ERK and AKT [7,8]. In the murine model efficient mobilization of AML cells to the circulation as well as induction of apoptosis in the spleen was already observed after one exposure to motixafortide [6]. Motixafortide decreased the adhesion of leukemic cells to stromal cells, which promoted their death by inducing

apoptosis. These *in vivo* and *in vitro* experiments suggest that the addition of motixafortide to standard chemotherapy could increase leukemic cell death [9,10].

An open-label safety and efficacy phase 2a study evaluated the efficacy of motixafortide in combination with high dose cytarabine (HiDAC) in patients with relapsed and refractory AML [11]. Forty-two patients received treatment with motixafortide for two days, followed by a combination of motixafortide with HiDAC for five days. Six escalating motixafortide dose levels were investigated (0.5, 0.75, 1.0, 1.25, 1.5, and 2.0 mg/kg), and 1.5 mg/kg was selected based on clinical response as the dose for the expansion phase (n = 23). No maximal tolerated dose was reached. Clinical responses were observed with motixafortide doses ≥1.0 mg/kg. Nine of 23 patients (39%) achieved a complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) in the 1.5 mg/kg dose level group. Median overall survival in this group of patients was 10.8 months and 21.8 months for responding patients, respectively. Paired BM samples available from 13 patients were evaluated for expression of CXCR4 on AML blasts at baseline and measurement of CXCR4 occupancy on AML blasts after two consecutive days of treatment with motixafortide. A decrease in the percentage of AML blasts with unoccupied CXCR4 was observed in most patients. Overall, the authors concluded that two days of motixafortide therapy triggered the mobilization of blasts into peripheral blood with significantly higher mean fold-changes in responders versus non-responders. OS of responding patients was 21.8 months compared to 7 months in non-respondents.

The majority of AML patients treated with intensive chemotherapy achieve a CR after induction therapy [12]. Nonetheless, AML eventually relapses in the majority of patients especially those of older age. Targeting the microenvironment appears as a promising approach to increase lasting remissions.

Here, we present the results of the BLAST trial, a randomized double-blind, placebo controlled, multicenter, phase-II study, to assess the efficacy and safety of motixafortide added to consolidation treatment in patients with AML in first complete remission after intensive induction therapy.

PATIENTS AND METHODS

Twenty-nine sites in Germany recruited patients into the trial sponsored by Martin-Luther-University Halle-Wittenberg. The protocol was approved by the relevant Ethics committees and by BfArM and is registered at www.clinicaltrials.gov (NCT 02502968). The study was conducted in accordance with the Declaration of Helsinki and good clinical practice.

Patient Selection

Patients aged 18 years or older with AML in CR/CRi after a maximum number of two cycles of induction chemotherapy were included. Main exclusion criteria were: acute promyelocytic leukemia (APL), or renal, liver, cardiac ~~or~~ pulmonary dysfunction

Randomization and Therapy

Randomization of eligible patients was performed after informed consent. A stratified randomization according to subject age (< or ≥60 years), cytogenetics/molecular risk (high or low/intermediate) and CR status (CR or CRi / CRi/CRp) before consolidation therapy was performed. Consolidation therapy consisted of cytarabine twice daily administered on days 1, 3 and 5 with 3g/m² in patients <60 years of age and 1g/m² in patients ≥60 years of age. Patients <60 years were scheduled to receive three consolidation cycles, and patients >=60 years two cycles. Motixafortide (1.25 mg/kg) or placebo were administered subcutaneously on days 1 to 5 of each consolidation

cycle before the first cytarabine infusion. A minimum interval of 3 hours between motixafortide / placebo injection and start of the cytarabine infusion was required. The therapy cycles were applied at an interval of 43 to 50 days from the previous cycle after confirming CR/CRi/CRp status with a bone marrow evaluation.

Sample size calculation and statistical analysis

The calculated sample size was 202 patients based on the assumption of 60% RFS after 18 months in the experimental arm and of 40% in the control arm. An alpha level of 5% (two sided) and a power of 80% were used.

The primary endpoint RFS was evaluated by a confirmative Cox regression analysis with treatment group, age<60 and ≥60, cytogenetic/molecular risk (high or low/intermediate) and CR status at time of randomization (CR or CRi/CRp) as covariates using the intention to treat population. Time to event was displayed by Kaplan-Meier curves stratified by treatment group Hazard ratios were presented together with two-sided 95% confidence intervals (CI). The significance level alpha was 0.037 for the main analysis since the planned alpha of 0.05 had to be adjusted for multiplicity due to the interim/futility analysis. Secondary endpoints were OS, RFS at 6, 9, 12 and 18 months after randomization, time to relapse (TTR), relapse at 6, 9, 12 and 18 months after randomization, and therapy-related toxicity including their correlation with the study drug.

Secondary endpoints were analysed in an exploratory manner; thus, the given p-values were not corrected for multiple testing and need to be interpreted accordingly. The toxicity, safety, and tolerability of motixafortide in combination with high dose cytarabine was reported descriptively.

RESULTS

Accrual of patients

Between November 2015 and November 2019, 134 patients were recruited at 29 trial sites in Germany. The last patient finished the study treatment on January 31, 2020 and the follow-up period in April 2021. Considering the results of the interim analysis, the DMC did not recommend continuation of the study and recruitment was stopped by the sponsor on 02.12.2019. Nonetheless, patient follow-up continued and was completed as scheduled. Overall, 128 patients were randomized: 63 to the placebo-arm and 65 to the motixafortide arm. In the motixafortide trial arm, two patients were excluded after randomization: one due to informed consent withdrawal, and one due to investigator decision. In both cases therapy was not administered. According to the stratification criteria in the motixafortide and placebo arm, 26 patients in each arm were under the age of 60 and had a low or intermediate risk according to ELN criteria. Thirty-one patients ≥60 years with low or intermediate risk and CR at time of randomization were randomized to motixafortide and 32 to placebo. Table 1 shows the distribution of clinical parameters by up-front treatment assignment. Few patients belonged to the ELN high risk AML group. The trial is summarized in the flow diagram in Figure 1.

Consolidation Therapy

Figure 1 shows details regarding patient disposition throughout the trial. A first course of consolidation therapy was administered in 126 patients. Sixty-three patients of the 65 initially randomized patients received study therapy in the motixafortide arm and 63 in the placebo arm. The proportion of patients receiving three therapy courses in patients younger than 60 years was higher in the placebo arm than in the motixafortide arm [26/27 (96%)] and [17/28 (61%)], respectively, p=0.002). In line, the proportion of patients 60 years old or older than 60 years receiving two cycles of consolidation

therapy appeared higher in the placebo arm compared to the motixafortide arm [31/36 (86%) and 24/35 (69%)], respectively, p=0.233). Forty-four of the 128 initially randomized patients (25/65 in the motixafortide group and 19/63 in the placebo group) did not reach the regular end of the study for the following reasons: death (32/44) and withdrawal of informed consent (6/44) loss to follow up (5/44), investigator discretion (1/44). Treatment discontinuation in the motixafortide arm occurred in 24 patients, some of them with several reasons for discontinuation (as listed in Figure 1). Hence, treatment was discontinued in 29 patients in total in both arms. Time to blood cell reconstitution after consolidation therapy did not differ between treatment arms (data not shown).

Adverse Events

Treatment discontinuation due to AE or SAE occurred more frequently in the moxifortide group compared to placebo group (12 and 2 patients, respectively). Follow-up after the last cycle of consolidation was more frequent in patients in the placebo group (59 and 39 patients, respectively). One related SAE, dermal necrosis, was assessed as unexpected (SUSAR) during the study. Skin necrosis was known to be related to the study drug, but the severity of the skin reaction was unexpected. Non-regular end of study and non-regular end of therapy due to adverse events were higher in motixafortide than in placebo arm. Also, more patients went off study due to personal reasons in the motixafortide arm. Overall, non-regular end of study was observed in 25 of 63 patients in the motixafortide and 19 of 63 patients in the placebo arm. Non-regular end of therapy due to AE was seen in 13/63 patients in the motixafortide and 2/63 in the placebo arm.

Overall, a higher number of AEs were documented in the motixafortide versus the placebo arm (739 versus 576, respectively). Grade 3 and 4 adverse events were recorded in 40 (63%) and 42 (67%) (p=0.85) of patients treated with motixafortide and placebo, respectively. The most frequent subgroup of AE grade 3 and 4 were infections, present in 32% of the patients in both therapy arms and administration site conditions present in 21% of the patients treated with motixafortide and in 14% of patients treated with placebo. Overall, no relevant differences regarding grade 3-5 AE rates were observed between both treatment groups. Of note, only infections resulting in prolonged hospitalization were defined as serious according to protocol. Regarding the motixafortide arm, 33 SAEs were reported in 17 of 63 patients, comparable to the placebo arm where 34 SAEs were reported in 23 of 63 patients as shown in Table 2. Grade 5 SAEs in both treatment arms were closely related to disease relapse in both treatment arms. Two patients who underwent allogeneic stem transplantation died due to refractory GVHD. None of the grade 5 SAEs, in both arms appeared related to study drug.

S**urvival Analysis**

Data were locked as of April 8th, 2022. For the intention to treat analysis, the median follow-up time was 25.5 months (range: 0.1 - 70.4) for patients in the motixafortide arm and 24.9 months (range: 0.4, - 61.0) for patients in the placebo arm. Median RFS was 10.3 months (95% CI= (8.0 - 12.0)) for the motixafortide arm and 11.5 months (95% CI= (8.6 - 24.1)) for the placebo arm. Kaplan-Meier plots did not show differences between treatment arms for RFS (two-sided p=0.98 by log-rank test) (Figure 2). The confirmative Cox regression analysis yielded a HR estimate of 1.00 [95% CI= (0.65 - 1.55) adjusted for age (≥60 or <60 years), cytogenetic/molecular risk (high or low/intermediate) and CR status at time of randomization (CR or Cri/CRp), Table 3).

The 18-month RFS rates were 33% (95% CI= (21%, 47%)) and 41% (95% CI= (29%, 54%)) for the motixafortide and placebo arms, respectively. Median OS was not reached. In the OS Cox model adjusted for age (≥60 or <60 years), cytogenetic/molecular risk (high or low/intermediate) and CR status at time of randomization (CR or CRi/CRp), no significant differences were observed between treatment arms (HR= 1.08 with 95% CI= (0.58, 2.00)).

In patients ≤ 60 years of age, there was a trend to longer RFS in the placebo treatment arm (Figure 3). No such difference was observed in patients > 60 years. Similarly, no differences in OS were observed between treatment arms (Figure 3).

CXCR4 expression

CXCR4 expression on bone marrow CD34+ cells was analyzed in 34 of 63 patients in the motixafortide arm and was expressed by CD34+ cells in 13 patients. In the placebo arm, CXCR4 was analyzed in 41 of 63 patients and was expressed by CD34+ cells in 12 patients (Table 1).

Regarding RFS, in the subgroup of patients with CXCR4 expression (n=25) no differences were observed between motixafortide and placebo (HR= 0.95, 95% CI [0.31,2.87]). The same applied for the OS endpoint, where the subgroup of patients with CXCR4 expression showed no relevant differences according to treatment arm (HR= 2.50, 95% CI [0.45,13.8]).

DISCUSSION

According to the literature, after intensive induction therapy, 60% to 80% of younger (≤60 years) and 40% to 60% of older (>60 years) patients with AML achieve a complete remission [14]. However, despite intensive consolidation therapy with high dose cytarabine or alloSCT approximately 50% of younger and 80% of older patients relapse

and many finally succumb to their disease [20]. Thus, an improvement of consolidation efficacy is required to improve patient survival. Cytarabine-based regimens are regularly used in patients achieving complete hematological remission after intensive induction therapy [21].

In preclinical and clinical studies, these regimens have limited efficacy due to intrinsic or acquired resistance mechanisms such as impaired uptake of the chemotherapy into the blast population, increased deamination as well as stromal retention and pro-survival signaling of the leukemia stem cells [22]. Inhibition of leukemia cell interactions with the microenvironment are thus attractive for novel therapy approaches. The chemokine receptor CXCR4 plays an essential role in the retention and survival of AML blasts within the bone marrow microenvironment. Hence, CXCR4 contributes to AML relapse. Thus, its inhibition could counteract several of the resistance mechanisms in AML.

The Blast study was performed to provide information of the combination of motixafortide and intensive consolidation after achieving a first remission hypothesizing that the motixafortide–induced mobilization of blasts would increase the efficacy of chemotherapy and prolong RFS.

By design of our study, RFS as an early endpoint was analyzed in an interim/ futility analysis 18 months following the first dose of the last patient among the first 50% of the population planned to be recruited. Altogether, the trial showed that among patients 18 years or older who had AML and a first CR or CRi after induction therapy, the addition of motixafortide to high dose cytarabine did not decrease the risk of relapse nor death. The assumption of a 60% RFS after 18 months in the experimental arm was not reached. The lack of benefit might result from the substantially higher rate of early discontinuation of therapy in the motixafortide arm compared to the placebo arm 39% vs. 4% in patients younger than 60 years and 31% vs. 14% in patients 60 years and

older. A putative reason for this difference is the increased toxicity caused by the combination of motixafortide with high dose cytarabine which led to frequent discontinuation. Also, more frequent study termination due to patient choice might reflect side effects. We also note that study recruitment was much slower than anticipated most likely due to increased use of allogeneic stem cell transplantation as consolidation therapy in AML. Also, the number of patients with high risk disease by cytogenetics or molecular genetics was very low. Both phenomena preclude analyses of moxifortide efficacy in high-risk AML subtypes.

Preclinical and clinical studies have demonstrated that blockage of CXCR4 resulted in enhanced antileukemic effects of chemotherapy, reduces leukemic burden, and prolongs overall survival (OS) [11]. In a phase II clinical study treating relapsed or refractory AML with motixafortide and high dose cytarabine, the composite CR (CR/CRi) rate was 39% and the median OS 10.8 months, whereas salvage therapies in similar conditions in previous studies with cytarabine as single agent resulted in CR achievement of 19% and median OS of 6 months [23,24]. In the same study, blast mobilization was evident in approximately 60% of patients who received treatment with motixafortide, with the greatest degree of blast mobilization observed in responders, who had both increase in peripheral blood blasts from baseline after motixafortide treatment and reduction in bone marrow blasts compared with non-responders [11]. In contrary to this hypothesis data from our current trial showed no improved efficacy in PFS and OS. But, these results may be affected by a higher rate of treatment discontinuation compared to placebo and compared to available data of AE-related discontinuation in other HD-AraC trials.

The association between CXCR4 expression and responses to inhibitors of CXCR4 and its ligand CXCL12 has been described *in vivo* and *in vitro* with AML cells in

previous publications [26]. Although some AML cells did not express CXCR4 on their surface, all tested AML cells expressed internal CXCR4 and CXCL12. Culture of AML cells with CXCL12 led to their survival, whereas the addition of neutralizing anti-CXCR4 or anti-CXCL12 antibodies, or plerixafor significantly decreased it. In addition, pretreatment of human AML cells with anti-CXCR4 antibodies blocked their homing into the bone marrow and spleen of transplanted NOD/SCID/B2m(null) mice. Further, weekly administration of an anti-human CXCR4 antibody to mice previously engrafted with primary AML cells also decreased human AML cells in the bone marrow, blood, and spleen. These observations suggest that CXCR4 plays an important role in AML proliferation. However, treatment of patients with high-risk AML with the CXCR4 antagonist plerixafor in combination with chemotherapy or hematopoietic cell transplantation did not result in improved relapse and survival endpoints compared to controls after a limited follow-up [27].

While our data showed no benefit regarding therapy response or survival endpoints in patients with CXCR4 expression this conclusion is tentative due to missing data in the measurement of CXCR4 as 46% of the patients in the motixafortide arm and 35% of the patients in the placebo arm were not analyzed for CXCR4 expression.

Altogether, on an ITT basis, neither a predictive value of CXCR4 expression nor a beneficial effect of motixafortide were established. Further, we observed that the combination of motixafortide with high dose cytarabine increased therapy interruptions and adverse event rates compared to standard of care.

In conclusion, our study did not demonstrate a beneficial effect of motixafortide on clinical endpoints in patients receiving standard consolidation therapy. The combination of motixafortide with high dose cytarabine led to a higher number of therapy interruptions partly due to a higher rate of adverse events. In consequence,

the intensity of cytarabine consolidation was lower in the motixafortide arm, which may have contributed to the observed results.

ACKNOWLEDGMENTS

We are grateful to all participating patients and participating centers of the OSHO and the Study Alliance of Leukemia Study Group.

AUTHOR CONTRIBUTIONS

Sonia Jaramillo and Enise Ceran wrote the manuscript and analyzed data. Marina Scheller, Bayram Edemir and Beatrice Ludwig-Kraus acquired and analyzed flow cytometry data. Maxi Wass, Judith Schaffrath, Richard Schlenk, Simone Kowoll, Jörg Steighardt, Lutz P. Müller, Sabine Edemir, Abi Vainstein-Haras, Ella Sorani, Irit Glicko-Kabir, Shaul Kadosh, Cora Gromann, Andreas Wienke designed the study, conducted the trial, and analyzed data. Axel Nogai, Mathias Hänel, Regina Herbst, Friedrich Stölzel, Christoph Röllig, Edgar Jost, Richard Noppeney, Christian Brandts, Utz Krug, Katharina S. Götze, Sebastian Buske, Axel Florschütz, Jörg Schubert, Bernhard Opitz, Martin Mohren, Eva Eßeling, Stephan von Witzendorff, Marion Subklewe, Martin Kaufmann, Norbert Frickhofen, Christian W. Scholz, Kristin Schäfer-Eckart, Volker Kunzmann, Martin Schmidt-Hieber, Herbert Sayer, Andreas Rank, Philipp Hemmati, Frank Schüler, Claudia D. Baldus, Uwe Platzbecker, Hubert Serve, Martin Bornhäuser and Christian Junghanß recruited and treated patients and supported trial conduct. Carsten Müller-Tidow designed the study, conducted, and supervised the trial, analyzed data, and wrote the manuscript.

CONFLICT OF INTEREST DISCLOSURES

Carsten Müller Tidow: BiolineRX: Research Funding; Pfizer: Research Funding.

Ella Sorani: BiolineRX: Current Employment, Current equity holder in publicly traded company.

Irit Gliko Kabir: BiolineRX: Current Employment, Current equity holder in publicly traded company.

Abi Vainstein-Haras: BioLineRx Ltd.: Current Advisor Current equity holder in publicly traded company.

Martin Schmidt-Hieber (last 3 years):

Advisory Role or Expert Testimony: AbbVie, Amgen GmbH, Bristol Myers Squibb GmbH & Co. KG, Gilead Sciences, Glaxo Smith Kline GmbH & Co. KG, Incyte, MICE, NewConceptOncology, Pfizer Deutschland, Sanofi-Aventis Deutschland GmbH, Shionogi GmbH, Stemline Therapeutics (no personal fees)

Other Financial Relationships: financial support of educational meetings at the Carl-Thiem-Klinikum Cottbus by Celgene GmbH, Janssen-Cilag GmbH, Novartis Pharma GmbH, Pfizer Pharma GmbH, Roche Pharma AG, Takeda Pharma Vertrieb GmbH & Co. KG, Vifor Pharma Deutschland GmbH (no personal fees)

LP Müller: Advisory Role or Expert Testimony: Pfizer, Gilead, Novartis, Amgen; Honoraria / Travel grants Gilead; Financing of Scientific Research Amgen

C.W. Scholz: Payment or honoraria for lectures, presentations, speakers' bureaus, abstract writing, or educational events: Gene, GILEAD, Janssen-Cilag, Roche, Lilly, Takeda; Support for attending meetings and/or travel: Roche, Gene, Takeda

Participation on a Data Safety Monitoring Board or Advisory Board: GILEAD, Incyte, Janssen-Cilag, MSD, Miltenyi Biotec, Novartis, Roche, Takeda, all the above-mentioned activities were participation in advisory boards.

CONSENT FOR PUBLICATION

The senior author signs for and accepts responsibility for releasing this material on behalf of all co-authors.

TRANSPARENCY DECLARATION

Sonia Jaramillo Segura and Carsten Müller-Tidow declare that the manuscript is an honest, accurate, and transparent account of the study being reported.

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Table 1: Patient and disease characteristics of patients

Characteristics	All patients	Motixafortide	Placebo
Age at trial entry – yr.			
Median	61.5	61	63
Range	22 – 79	22 – 79	37 – 79
Female sex – no./total no. (%)	63/126 (50)	32/63 (51)	31/63 (49)
ECOG performance status –no./total no. (%)			
0	61/126 (48)	32/63 (51)	29/63 (46)
1	61/126 (48)	28/63 (44)	33/63 (52)
2	4/126 (3)	3/63 (5)	1/63 (2)
European LeukemiaNet classification – no./total no. (%)			
Low or intermediate	122/126 (97)	60/63 (95)	62/63 (98)
High	4/126 (3)	3/63 (5)	1/63 (2)
CXCR4 expression – no./total no. (%)			
yes	25/126 (20)	13/63 (21)	12/63 (19)
N/A	51/126 (40)	29/63 (46)	22/63 (35)
Type of AML – no./total no. (%)			
De novo	115/126 (91)	59/63 (94)	56/63 (89)
s-AML	10/126 (8)	4/63 (6)	6/63 (10)
t-AML	1/126 (1)	–	1/63 (2)
Remission status at time of randomization (at screening) –no./total no. (%)			
CR	117/126 (93)	58/63 (92)	59/63 (94)
CRiCRi/CRp	9/126 (7)	5/63 (8)	4/63 (6)
Cycles of induction – no./total no. (%)			
1	73/126 (58)	38/63 (60)	35/63 (56)
2	53/126 (42)	25/63 (40)	28/63 (44)

Abbreviations: no - number of cases, s-AML - secondary acute myeloid leukemia after previous myelodysplastic syndrome or myeloproliferative neoplasm; t-AML - therapy-related acute myeloid leukemia.

Table 2: Summary of Serious Adverse Events

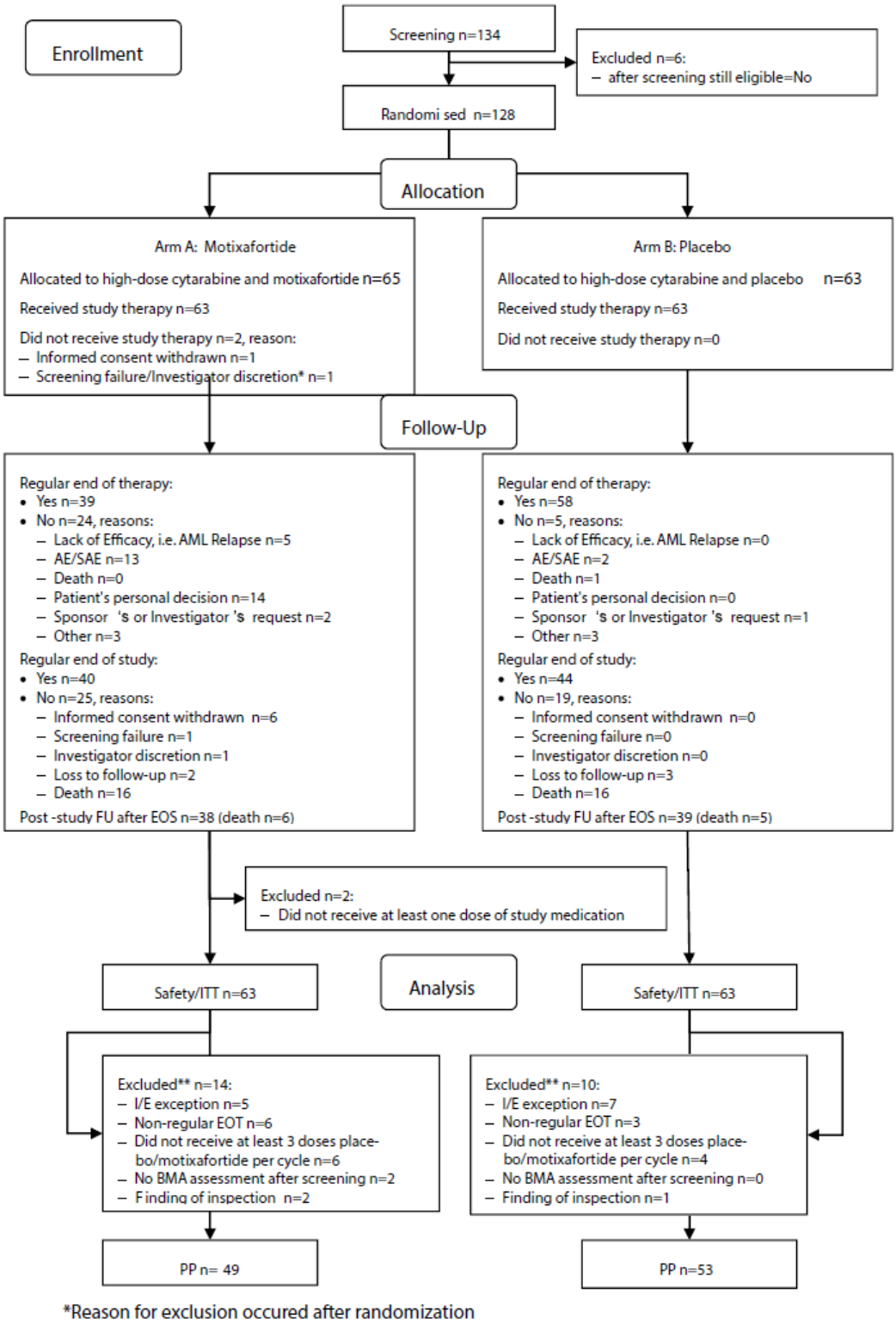
Serious Adverse Event	motixafortide n=63	Placebo n=63	Total n=126
Any SAE	33	34	67
Infections	16	16	32
Sepsis	13	8	21
Pneumonia	2	4	6
Other	1	4	5
Immune system disorders	2	-	2
Graft versus host disease	1		
Anaphylactic reaction	1		
Nervous system disorders	-	1	1
Cerebral hemorrhage		1	
Cardiac disorders	-	2	2
Cardiac failure	-	2	
Vascular disorders	2	-	2
Hematoma	2		
Respiratory, thoracic and mediastinal disorders	-	2	2
Epistaxis		1	1
Hypoxia		1	1
Gastrointestinal disorders	2	1	3
Enterocolitis	1		
Ileus paralytic	1		
Intestinal mass	-	1	
Skin and subcutaneous tissue disorders	1	-	1
Skin necrosis	1		
Renal and urinary disorders	1	-	1
Renal infarct	1		
Others	9	12	21

Table 3: Primary endpoint Relapse Free Survival Cox regression

Characteristics	HR	95% CI	p-value
motixafortide vs. Placebo	1.0	0.7 – 1.6	0.99
Age ≥ 60 yrs. vs. < 60 yrs.	1.7	1.1 – 2.6	0.03
High vs. low/intermediate cytogenetic/molecular risk	1.7	0.6 – 4.7	0.35
CRi/CRp vs. CR	0.3	0.1-0.97	0.04

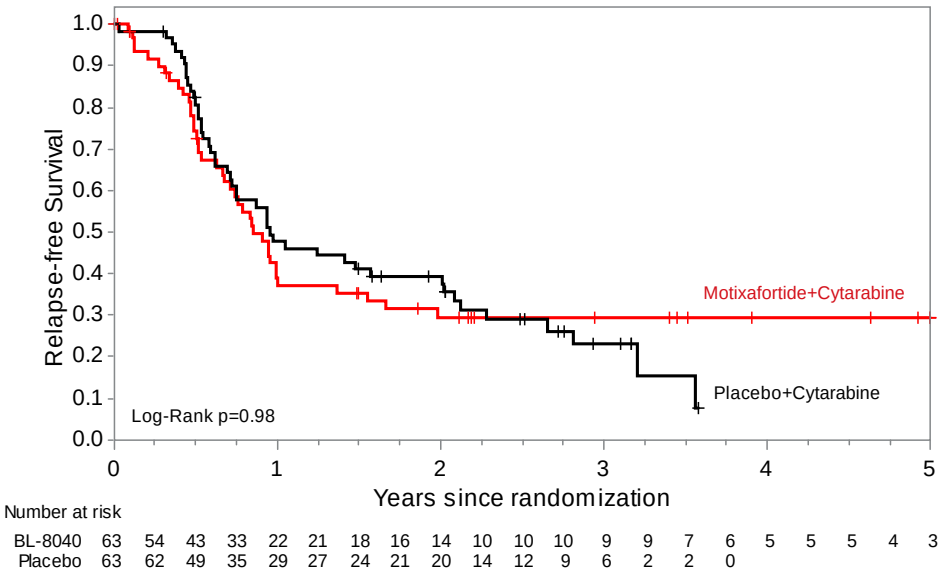
Abbreviations: complete remission (CR), CR with incomplete platelet or hematological recovery (CRi/CRp).

Figure 1: Consort diagram



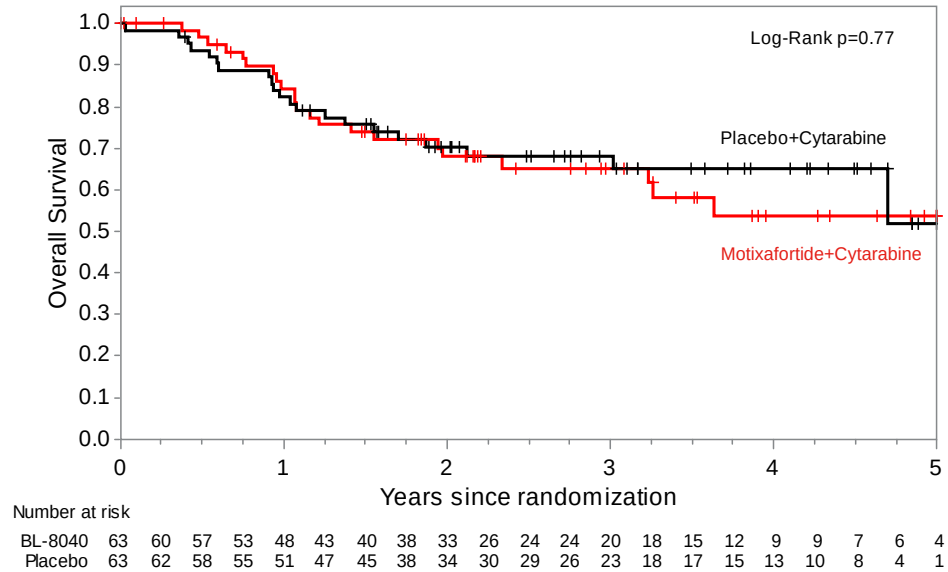
Legend: The diagram depicts the flow of the patients through the trial. Several patients had more than one reason for end of trial (EOT) or end of study (EOS)

Figure 2 Relapse free survival (RFS) Kaplan-Meier estimate



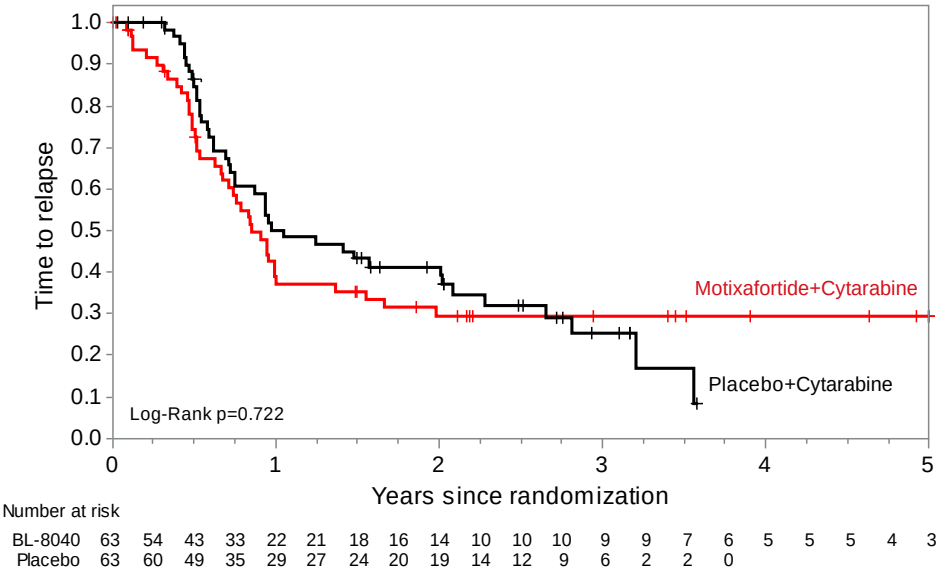
Legend: Kaplan-Meier plot (ITT, n=126) for relapse free survival in the motixafortide and placebo arm as randomized (age and cytogenetic/molecular risk and CR status at time of randomization adjusted risk hazard ratio HR= 1.0; 95% CI= (0.65, 1.55); p = 0.992). Overall, 86 events were observed (motixafortide arm, n = 40; placebo arm, n = 46).

Figure 3 Overall survival (OS), Kaplan-Meier estimate



Legend: Kaplan-Meier (ITT, n=126) plot illustrating overall survival defined according to European LeukemiaNet 2017 recommendations in the motixafortide and placebo arm as randomized (age and cytogenetic/molecular risk and CR status at time of randomization adjusted hazard ratio HR= 1.08; 95% CI= (0.58, 2.00); p = 0.80).). Overall, 43 events were observed (motixafortide arm, n = 22; placebo arm, n = 21).

Figure 4 Time to relapse (TTR), Kaplan-Meier estimate



Legend: Kaplan-Meier plot (ITT, n=126) illustrating time to relapse defined according to European LeukemiaNet 2017 recommendations in the motixafortide arm and placebo arm as randomized (age and cytogenetic/molecular risk and CR status at time of randomization adjusted hazard ratio HR= 1.10; 95% CI= (0.70, 1.71); p = 0.69). Overall, 82 events were observed (motixafortide arm, n = 40; placebo arm, n = 42).