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ORIGINAL ARTICLE

Phase II clinical trial of pazopanib in patients with acute myeloid leukemia (AML), relapsed or refractory or at initial diagnosis without an intensive treatment option (PazoAML)

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Abstract

We evaluated pazopanib (800 mg orally QD) in patients not eligible for intensive treatment with relapsed/refractory AML or at initial diagnosis. Patients receiving pazopanib for ≥ 14 days were analyzed for safety, tolerability, and efficacy. Co-primary endpoints were cumulative response rate and reduction of bone marrow microvessel density. Twenty patients (median age 76 years, range 52–86) were treated. Fifteen had relapsed/refractory and five had newly diagnosed AML. Median ECOG performance status was 1 (range 1–3). Four patients had adverse, 15 intermediate, and 1 patient favorable cytogenetic/molecular risk (ELN 2010 criteria). The safety profile of pazopanib was as reported. The most common adverse events of any grade were gastrointestinal. Two patients achieved PR (blast reduction > 50%), 14 stable disease (SD), and 4 progressive disease. Median PFS was 65 days (95% CI 29–105). After the end of the study, 1 CRi and 1 CRp occurred on demethylating agents, and 1 CR upon alloSCT. In these patients, SD and improved general condition on pazopanib allowed therapy escalation. Median OS for the overall study population was 191 days (95% CI 87–435) and 1-year survival was 35%. There was no significant change in microvessel density. Clinical trial information: NCT01361334.

Keywords Pazopanib · Acute myeloid leukemia · AML · Phase II study

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Introduction

Long-term disease-free survival (DFS) of patients with acute myeloid leukemia (AML) remains unsatisfactory. Although considerable progress has been made in improving the rate of complete remission (CR) in patients with AML with intensive chemotherapy, the majority of CR patients relapse within 1 to 2 years after start of therapy [1, 2]. Efforts are being undertaken to define those patients who benefit from allogeneic stem cell transplantation (alloSCT) to decrease the incidence of relapse, but this treatment cannot be administered to every patient. In addition, a significant fraction of patients does not reach a CR since their disease is refractory to induction chemotherapy. A third group of patients does not tolerate intensive induction chemotherapy, and standard palliative treatment consists of subcutaneous administration of hypomethylating agents, low-dose cytarabine, and supportive care.

At the time of design of this study, 5-year overall survival of all patients with AML was still low at 20–45% with intensive chemotherapy and 31–52% after allogeneic SCT [1, 2]. In addition, morbidity of both chemotherapy and alloSCT substantially compromised treatment results. So-called "targeted therapy" for cancer had just been introduced to the treatment of patients with AML. Individual patients harboring the Flt3-ITD mutation experienced durable remissions with the orally administered multi-tyrosine kinase inhibitor (TKI) sorafenib [3]. However, AML relapsed in most of these patients, and the majority of patients with AML lack this specific abnormality. Nevertheless, the results indicated that targeted therapies can be beneficial, and the TKI toxicity profiles differ substantially from the ones of conventional chemotherapy and SCT. At the time of the study, no approved TKI was available for patients with AML, the FLT3 inhibitor midostaurin was approved for FLT3-ITD-positive AML in combination with chemotherapy after a positive phase III trial much later [4].

Blasts from 60 to 70% of patients with AML express KIT [5, 6], the receptor for stem cell factor (SCF). SCF promotes growth of hematopoietic progenitors and acts as a survival factor for AML blasts [5]. Furthermore, several groups including ours had gathered evidence for the involvement of proangiogenic growth factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) signaling in the bone marrow (BM) stroma of AML patients [7–11]. The microvessel density (MVD) in the BM is significantly increased in AML, and it was already shown that pharmacological inhibition of proangiogenic (including VEGF) signaling is effective to reduce angiogenesis in AML and lead to relevant clinical responses including CR [12–15]. In addition, expression of platelet-derived growth factor receptor (PDGFR)-alpha was reported in approx. 45% of AML blasts and PDGFR-beta in over 90% [16]. Finally, bFGFR, PDGFR, and VEGFR triple TK inhibition was shown to be able to induce growth inhibition and apoptosis of AML blasts [17].

Pazopanib is an orally bioavailable, adenosine triphosphate (ATP)-competitive tyrosine kinase inhibitor (TKI) of VEGFR (-1, -2, and -3), platelet-derived growth factor receptor (PDGFR) -α, -β, and KIT [18]. Pazopanib has been approved for the treatment of renal cancer and soft tissue sarcomas. In an in vitro cell line screen of pazopanib-induced cytotoxicity, pazopanib induced significant cytotoxicity (IC50 below 1 μM) in 7 out of 282 cell lines tested, and out of these 7 cell lines, 2 cell lines were myeloid leukemia cell lines (GDM-1 and CML-T1) (unpublished observations, Glaxo Smith Kline 2010). GDM-1 cells showed an IC50 in the range of 10 nM. In addition, our own data demonstrated that pazopanib robustly inhibits growth and STAT5 phosphorylation in FIP1L1-PDGFRA transformed 32D myeloid cells, at doses of 100 nM (S.K., unpublished data).

Thus, we conducted a phase II study to explore the efficacy and safety of pazopanib in patients with relapsed or refractory AML or patients with AML at diagnosis, when intensive treatment was not possible.

Methods

Study design and patients

This was an investigator-initiated, open-label, uncontrolled, two-center (Muenster and Aachen) phase II clinical trial within the European Study Alliance Leukemia (SAL) with patients with AML (except AML M3), either relapsed/refractory, or at diagnosis, when further intensive therapy was not considered possible. The study was approved by the Ethics Committee of RWTH Aachen University and the Ethical Board of the Physicians Chamber of Westfalia-Lippe and the University of Muenster (2011-149-f-A) and by the German Federal Drug Authorities (BfArM). Essentially, patients diagnosed with either de novo or refractory AML not suitable for intensive therapy at the time of diagnosis were eligible for screening for participation in this trial. Importantly, life expectancy had to be at least 4 weeks. (For detailed inclusion and exclusion criteria, see Clinical trial information: NCT01361334 and Online Resource (Study Protocol).) After providing written informed consent, eligible patients received pazopanib starting on day 1 of the study orally once daily at a dose of 800 mg for up to 1 year. Extension beyond this time point was possible in responding patients. Peripheral blood (PB) and BM assessments for safety and efficacy were carried out as is standard for phase II trials in AML. Treatment was continued until one of the following occurred: disease progression (includes death due to disease progression), completion of scheduled treatment of 12 months, any adverse

events (AE, including death not due to disease progression) which in the opinion of the Coordinating Investigator made the continuation of the study participation undesirable or placed the patient at an intolerable risk, protocol deviation (as determined by the Coordinating Investigator), termination of the study, patient being lost to follow-up (Investigator discretion, reason to be specified), or decision by patient. During the study and during extended treatment until 30 days after the last administration of study drug, adverse events were documented (Online Resource, Study Protocol). Moreover, information on the remission status was recorded from data from PB and BM examinations. Information recorded after termination of treatment with pazopanib were limited to AML status, survival status, and AEs that have not resolved at the time of the last study visit/last administration of pazopanib or emerged within 30 days after termination of pazopanib treatment.

Primary study objectives were to analyze the cumulative response rate of all patients with AML within up to 1 year of pazopanib treatment and to assess the reduction of BM microvessel density (MVD) prior to treatment and on day 28 of pazopanib treatment. Complete remission (CR) was defined as platelet count > 100,000/μl, granulocyte count of > 1000/μl, bone marrow (BM) blasts < 5%, absence of Auer rods, no evidence of persisting leukemia by flow cytometry (at a sensitivity of 5%), absence of extramedullary leukemia, and transfusion-independent stable hemoglobin value. Complete remission with incomplete recovery of platelets (CRp) had to fulfill all of the above but platelet count remained below 100,000/μl. Complete remission with incomplete recovery of granulocytes (CRi) had to fulfill all of the above but granulocyte count remained below 1000/μl. Partial remission (PR) was defined as reduction by ≥ 50% of elevated blast counts in PB and BM vs baseline. Stable Disease (SD) was defined as reduction by ≤ 50% of blast counts in PB and BM vs baseline, or stable percentage of blasts in PB or BM. Progressive disease (PD) was defined as rising percentage of blasts in PB or BM.

Main secondary study objectives were to assess the safety and tolerability of pazopanib for patients with AML, to assess relapse-free survival (RFS), overall survival (OS), and duration of response.

Study drug

The study drug, pazopanib (GW786034, GlaxoSmithKline [GSK]), an orally bioavailable, adenosine triphosphate (ATP)-competitive tyrosine kinase inhibitor (TKI), was kindly provided by GSK. At the beginning of this study, pazopanib was approved for use in patients with renal cancer upon the results of a phase III trial [19].

MVD assessment

MVD assessment was performed by two independent investigators as described by our group before [11].

Statistical analysis

Baseline disease characteristics and demographic data of all patients were summarized descriptively, using medians and ranges for continuous variables and absolute and relative frequencies for categorical variables. All patients who received pazopanib over 14 days or longer were included in the analysis of safety, tolerability, and efficacy. OS was measured from the first day of treatment until death of any cause, and PFS was measured from the first day of treatment until death of any cause or progression of disease. OS und PFS were estimated using the Kaplan-Meier method. The Wilcoxon matched-pair signed rank test was used to compare levels of MVD in individual patients at diagnosis and day 28. Two-sided p values lower than 0.05 were considered to indicate significant differences. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient population

This study was designed to recruit patients until 20 subjects received at least 14 daily doses of pazopanib to ensure validity of the primary endpoints. Primary study objectives were to analyze the cumulative response rate (CR, CRp, CRi, and PR combined) of all patients with AML within up to 1 year of pazopanib treatment and to assess the reduction of BM microvessel density (MVD) prior to treatment and on day 28 of pazopanib treatment in patients with AML. Date of first patient enrollment was February 1, 2012, last patient visit was on March 3, 2017, and data base closure was April 24, 2017. Consort diagram of the study is depicted in Fig. 1. Twenty-five patients were enrolled, but 5 patients dropped out during the first 14 days (Fig. 1). Reasons for dropping out early were overwhelming leukemia with hyperleukocytosis requiring immediate other cytoreductive therapies in three cases, and withdrawn consent in two cases. Table 1 summarizes the clinicopathological characteristics of the 20 evaluable patients enrolled between 2012 and 2015. Patients had a median age of 76 (range 52–86) years. The majority ($n = 15$, 75%) had relapsed ($n = 7$) or refractory ($n = 8$) AML; five patients (25%) were enrolled with newly diagnosed AML. Median ECOG performance status was 1 (range 1–3). According to ELN 2010 criteria, 4 patients (20%) had adverse risk, 15 (75%) had intermediate risk, and 1 patient (5%) had favorable cytogenetic/molecular risk.

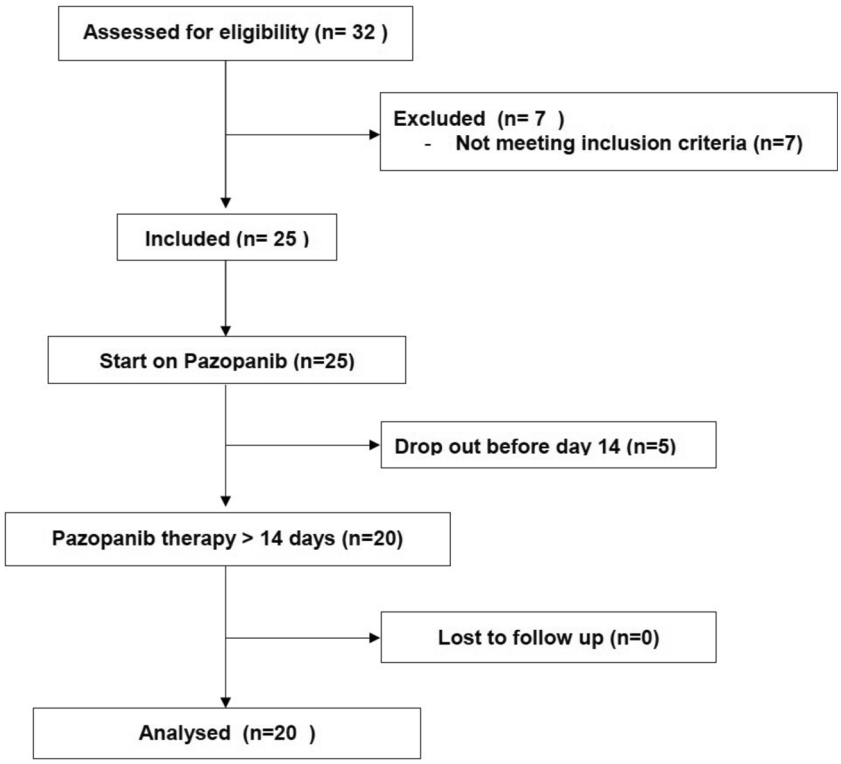

Fig. 1 Consort diagram of PazoAML phase II study

Safety and tolerability

Overall, the safety profile of pazopanib was similar to that reported in previous studies [18, 19]. The most common AEs (CTCAE version 4.0) of any grade related to pazopanib as assessed by the investigators were gastrointestinal AEs, including nausea ($n = 8$), diarrhea ($n = 6$), decreased appetite ($n = 5$), and vomiting ($n = 3$) (Table 2). Also, fatigue occurred in a quarter of patients ($n = 5$). Grade 3 adverse events attributed to pazopanib occurred in the form of nausea ($n = 2$), fatigue ($n = 3$), hypertension ($n = 1$), blood bilirubin increased ($n = 1$), and no grade 4 or higher AEs were attributed to pazopanib.

A total of 24 SAEs (encoded with 14 MedDRA codes) were reported in 12 patients during and 30 days after cessation of pazopanib treatment. However, all were typical for AML and were thus considered unrelated to pazopanib. All were single events except neutropenic fever, which was reported 3 times in 3 patients, and pyrexia, which occurred in 3 patients, pneumonia, and worsening of general condition (Table 3). Two patients died due to neutropenic fever and pneumonia within 2 weeks after pazopanib was stopped because of progressive disease after 3 months of therapy. One patient died of respiratory insufficiency while having infection with *Clostridium difficile* 3 months after start of pazopanib. At this time point, a stable blast count but no recovery of granulocytes was recorded. One patient died due to progression of AML 2 weeks after pazopanib was stopped. Another patient was diagnosed with gastric cancer after 17 days of therapy with pazopanib within the trial and therefore excluded. This patient died 2 weeks later due to gastric cancer and persisting leukemia.

Antileukemic activity

Best response while on therapy was partial remission (PR) reached by 2 out of 20 treated patients (10%) as defined by reduction more than 50% of elevated blast counts in PB and BM vs baseline. The first patient achieving this was diagnosed in February 2015 at age of 75 years with AML FAB M0 after a history of myelodysplastic syndrome of 10 years without specific treatment. Cytogenetics revealed trisomy 7 and deletion of 20q, no molecular alterations were found, resulting in intermediate risk according to ELN 2010 criteria. Initial white blood count was 72,000/μl with 80% blasts, platelets of 50,000/μl, and anemia of Hb 8.7 g/dl. After 5 days of cytoreductive therapy with hydroxyurea, hyperleukocytosis disappeared while thrombocytopenia, anemia, and high blast percentage persisted. Pazopanib was started and after 6 weeks of therapy, this patient showed good platelet recovery (149,000/μl) and normal white blood count (3.950/μl) without blasts and a persisting anemia (Hb 9.7 g/dl). Bone marrow cytology showed recovering hematopoiesis with persisting dysplasia and a blast count of 20%. Another 4 weeks later, this patient had progressive disease with rising blast count, thrombocytopenia, and hyperleukocytosis and

Table 1 Patient demographics and baseline disease characteristics

Patients	$n = 20$
Median (range) age, years	76 (52–86)
Male/female, *n*	15/5
ECOG performance status, *n*	
0	1
1	14
2	4
3	1
Disease status, *n*	
De novo	12
Secondary	8
Untreated	5
Relapsed	7
Refractory	8
Median (range) initial PB and BM values	
Hemoglobin, g/dl	9.5 (3.7–13.3)
Platelets, 10^3/μl	34 (7–172)
White blood cell count (WBC), 10^3/μl	2.9 (0.3–16.5)
Blast count PB, %	3 (0–76)
Blast count BM, %	40 (10–90)
FAB classification, *n*	
M0/M1/M2	13
M4/M5	4
M7	1
Unclassified	2
ELN risk, *n*	
Favorable	1
Intermediate	15
Adverse	4
Median (range) previous lines of therapy, *n*	1 (0–1)

was taken off study. Subsequent antileukemic therapy with hydroxyrurea was able to control the disease for another year before patient died due to progressive disease. The 2nd patient achieving a PR on pazopanib was 73 years old when he was diagnosed with AML (FAB M2) with myelodysplasia-related changes. At diagnosis, he was pancytopenic with a BM blast percentage of 40%. There were no cytogenetic or molecular abnormalities detected resulting in intermediate risk according to ELN 2010 criteria. After 4 weeks of therapy, blast count in the BM decreased to 15% and stayed below 20% for 12 months. However, platelet counts did not recover above 60,000/μl. After 12 months of therapy with pazopanib, the patient showed rising BM blast count and was taken of study. Demethylating therapy with 5-azacytidine was initiated and was able to control the disease for another year before the patient died due to progressive disease. Stable disease (SD) was reported in additional 14 patients, and 4 patients experienced progressive disease (PD). Median progression-free survival (PFS) was 65 days (95% CI 29–105) (Fig. 2). In one patient with relapsed AML who had SD for 3 months on therapy with pazopanib, the general condition improved significantly. Thus, the patient was evaluated and underwent alloSCT resulting in CR lasting for 2 years. Unfortunately, he died 2 years later due to chronic graft versus host disease and infectious complications. Another patient achieved a complete remission with incomplete hematological recovery (CRi) and 1 patient a complete remission with incomplete platelet recovery (CRp), both beyond the study period on subsequent therapies such as demethylating agents. All patients died due to progressive disease or opportunistic infections at the time of OS evaluation. Median OS of the treated study cohort was 191 days (95% CI 87–435) and 1-year survival was 35% (Fig. 3).

Microvessel density

Mean MVD in the BM obtained from 17 patients at baseline was 22/ hPF (hPF, high-power field; range 8–44/ hPF) and decreased to 17/ hPF (range 5–76/ hPF) at day 28. This decrease, however, was not statistically significant ($p = 0.677$, Wilcoxon test). Data are depicted

Table 2 Frequency of adverse events possibly related to pazopanib (MedDRA v19.0)

MedDRA preferred term	*n*	Max. CTCAE grade
Nausea	8	3
Diarrhea	6	1
Fatigue	5	3
Decreased appetite	5	2
Vomiting	3	2
Dizziness	2	1
Asthenia	2	2
Alanine aminotransferase increased	2	1
Abdominal pain	1	2
Hypertension	1	3
Abdominal pain upper	1	2
Rash	1	1
Abdominal distension	1	1
Blood bilirubin increased	1	3
Constipation	1	1
Mucosal inflammation	1	2
Oral candidiasis	1	2
Alopecia	1	1
Aspartate aminotransferase increased	1	1
Dysgeusia	1	1
Hyperbilirubinemia	1	1

Table 3 SAEs reported in the study (MedDRA codes for overall 24 cases in 12 patients, MedDRA v19.0)

MedDRA preferred term	*n*	Max. CTCAE grade
SAE	24	
Pyrexia	3	2
General physical health deterioration	3	3
Pneumonia	3	5
Febrile neutropenia	1	2
Alanine aminotransferase increased	1	2
Diarrhea	1	4
Hyperglycemia	1	3
Laryngeal stenosis	1	2
Pleural effusion	1	3
Pneumonitis	1	5
Malignant neoplasm progression	1	3
Atrial fibrillation	1	3
Cellulitis	1	3
Acute myocardial infarction	1	5
Acute abdomen	1	3
Intestinal adenocarcinoma	1	5
Subcutaneous abscess	1	3
Deep vein thrombosis	1	3

in Fig. 4. In addition, a single case analysis of MVD development during therapy with pazopanib in order to detect, e.g., decrease in responders or stable disease patients versus increase in non-responders, did not show any correlation with clinical response to the drug (details not shown).

Discussion

To our knowledge, this is the first trial of pazopanib therapy in AML. However, at the initiation of the trial, pazopanib already was approved for renal cell carcinoma and soft tissue sarcoma. As all phase III studies in these entities revealed only limited toxicities for pazopanib, we opted for a phase II trial without the need for a phase I trial. The starting dose for pazopanib as well as dose modifications were determined as in the previous phase III trials in other entities and the prescribing information. So, this single-arm phase II trial was the first to investigate the safety and efficacy of the angiokinase inhibitor pazopanib in patients with newly diagnosed, relapsed or refractory AML. At study entry, none of the patients was amenable to intensive therapy. Overall, the toxicity profile of pazopanib observed in this study was consistent with the phase III trial of pazopanib as single agent in patients with renal cancer [19]. Gastrointestinal toxicities were the main pazopanib-related AEs reported. In the study reported here, a disease control rate of 80% (including PR and SD) has been observed in a cohort in which two-thirds of patients had relapsed or refractory AML, thus representing a population particularly difficult to treat. However, the duration of response or disease stabilization for most patients was rather short, with a median PFS of 65 days, and only in one patient treated with pazopanib beyond month 3. Best responses were two PR; in one patient, this lasted only for 1 month, but he achieved

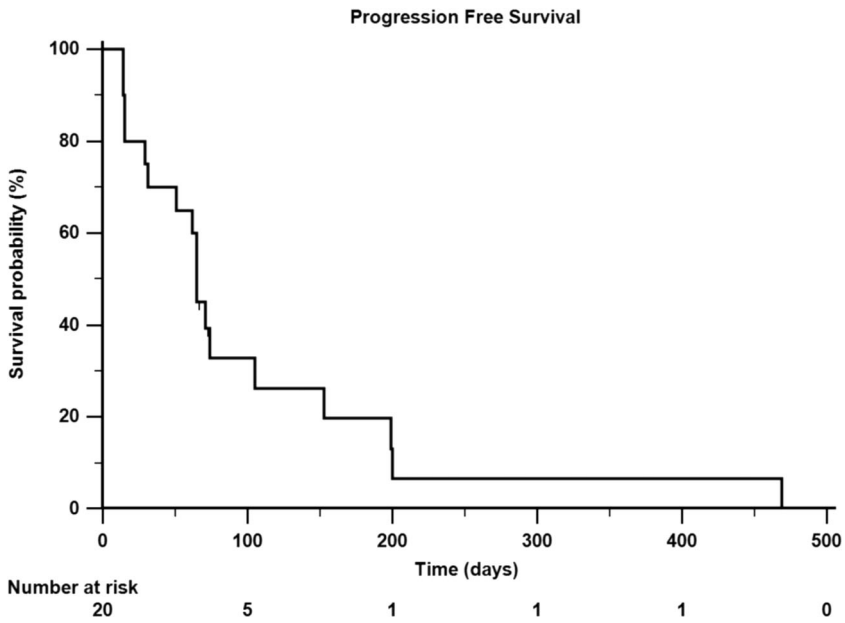

Fig. 2 Kaplan-Meier curve for progression-free survival (PFS). Median PFS of treated patients was 65 days (95% CI 29–105)

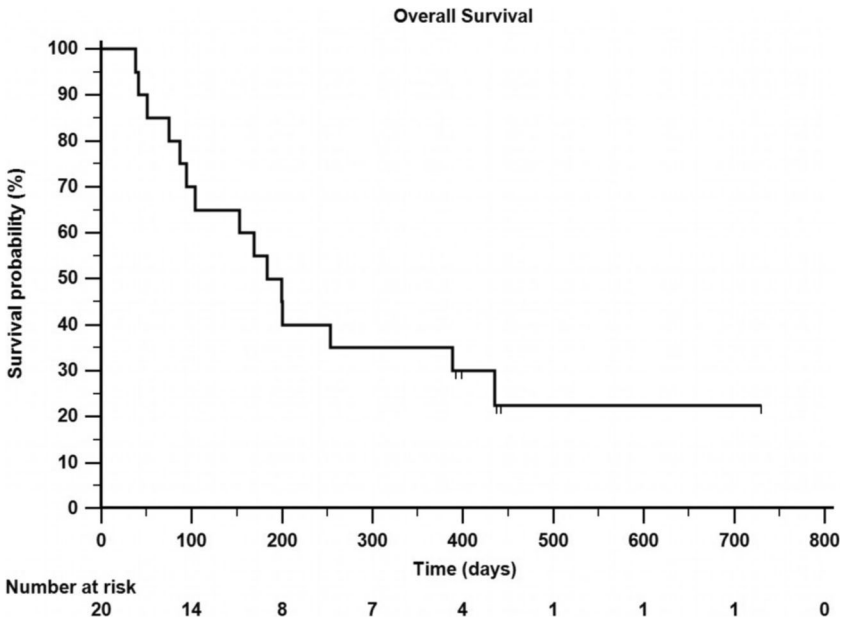

Fig. 3 Kaplan-Meier curve for overall survival (OS). Median OS was 191 days (95% CI 87–435), and 1-year OS was 35%

disease stabilization and survival for another year on subsequent hydroxyurea monotherapy. The only patient treated for more than 3 months showed a rather indolent course of AML and was further controlled by 5-azacytidine for another year. Altogether, the 1-year OS rate of 35% observed in the study cohort is a promising preliminary finding but is most probably due to later off-study therapies and optimized supportive care than due to pazopanib. However, beneficial effects of consecutive therapies including those of pazopanib are not excluded.

Given that the majority of patients entered the study in a relapsed or refractory situation, the overall results are at least comparable with other agents such as low-dose cytarabine (LDAC) or other tyrosine kinase inhibitors such as nintedanib [20]. Of note, traditionally it was assumed that improvement of outcome in AML required induction of complete remission, but recent data on hypomethylating agents suggested that prolongation of overall survival may be achieved in AML patients also without complete remission [21, 22]. These

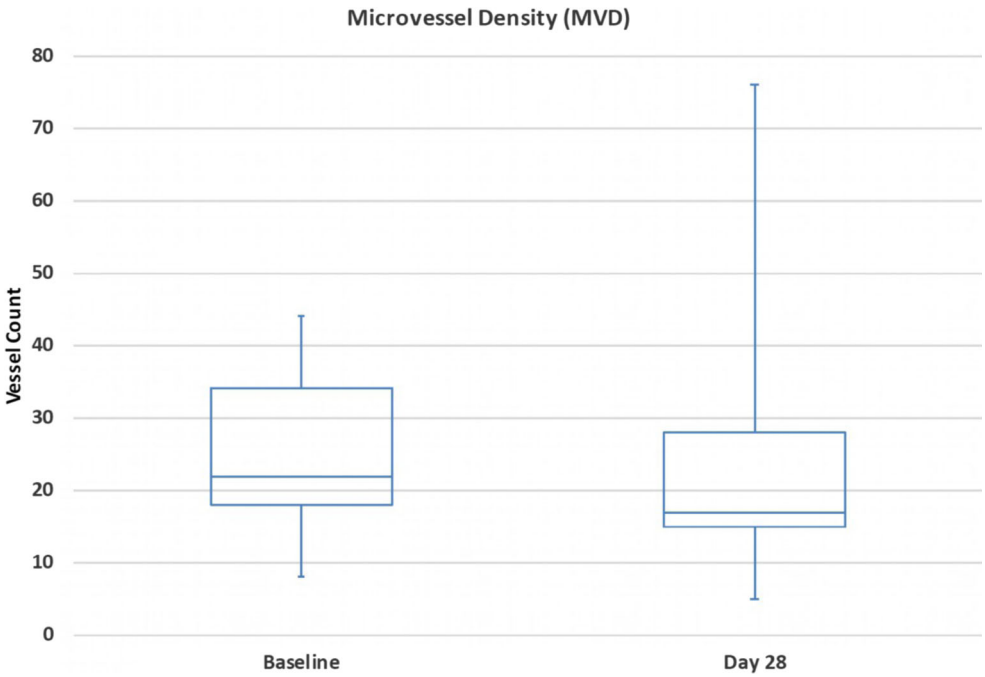

Fig. 4 Development of microvessel density in the bone marrow of the patients from baseline to day 28. No significant decrease was observed (p = 0.677, Wilcoxon test)

observations are in line with the observations in this trial. Pazopanib may predominantly work via effects onto the microenvironment in AML bone marrow. Nonetheless, the reduction of bone marrow microvessel density from baseline to day 28 was statistically not significant. Thus, the findings of disease stabilization and improvement in patients' conditions cannot mechanistically be explained by effects due to pazopanib which is supported with the clinical interpretation. Besides, this is in line with previously published data where VEGF A inhibition alone by bevacizumab was of limited clinical activity in AML [23, 24].

Conclusions

Pazopanib was found to be safe in patients with AML who were not suitable for intensive therapy. However, response data suggest limited and rather short efficacy. Thus, we conclude that the data of this trial do not warrant further trials with pazopanib in AML, at least not as monotherapy. Within the developing landscape of therapeutic maneuvers for AML, targeting alternative molecules and pathways and new combinations such as venetoclax with demethylating agents produce much higher response rates up to 67% CR or CRi [25].

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Authors' contributions T.K., S.K., C.S., and W.E.B. designed the study. T.K. and S.K. were principal investigators. E.W. and W.H. were involved in the MVD analysis. E.B., J.G., T.K., and S.K. were involved in the statistical analysis. T.K., S.K., C.S., M.C., J.-H. M., S.v.S., M.S., M.P., G.L., A.K., K.V., T.B., C.M.-T., and W.E.B. provided and treated patients. T.K., S.K., and W.E.B. wrote the manuscript. All authors revised and agreed to the manuscript.

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Compliance with ethical standards

Institutional review board or independent ethics committee approval and written informed consent from all patients for being included in the study were obtained. The study was performed in accordance with the ethical principles of the Declaration of Helsinki and in compliance with national laws.

Conflict of interest Dr. Koschmieder declares Consultancy, Honoraria, and Research Funding by Novartis. Dr. Stelljes declares Pfizer Consultancy, Honoraria and Research Funding; MSD Consultancy; JAZZ Honoraria; Amgen Honoraria; Novartis Honoraria. Dr. Lenz reports the following: Celgene Corp. Consultancy, Honoraria, Travel, Accommodations, Expenses, Research Funding and Speakers Bureau; Janssen Consultancy, Honoraria, Travel, Accommodations, Expenses, Research Funding and Speakers Bureau; Roche Consultancy, Honoraria, Travel, Accomodations, Expenses, and Research Funding; Bayer Consultancy, Honoraria, Research Funding and Speakers Bureau; Novartis Research Funding; Gilead Consultancy and Honoraria. Dr. Brümmendorf reports Pfizer Consultancy and Research Funding, Novartis Consultancy and Research Funding, Takeda Consultancy, Janssen Consultancy, and Merck Consultancy. Dr. Müller-Tidow reports Pfizer Research Funding. Dr. Berdel reports research grants by GSK and Novartis. The other authors declare that they have no conflict of interest.

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