original reports

Sorafenib Maintenance After Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia With *FLT3*–Internal Tandem Duplication Mutation (SORMAIN)

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abstract

PURPOSE Despite undergoing allogeneic hematopoietic stem cell transplantation (HCT), patients with acute myeloid leukemia (AML) with internal tandem duplication mutation in the *FMS*-like tyrosine kinase 3 gene (*FLT3*-ITD) have a poor prognosis, frequently relapse, and die as a result of AML. It is currently unknown whether a maintenance therapy using FLT3 inhibitors, such as the multitargeted tyrosine kinase inhibitor sorafenib, improves outcome after HCT.

PATIENTS AND METHODS In a randomized, placebo-controlled, double-blind phase II trial (SORMAIN; German Clinical Trials Register: DRKS00000591), 83 adult patients with *FLT3*-ITD–positive AML in complete hematologic remission after HCT were randomly assigned to receive for 24 months either the multitargeted and FLT3-kinase inhibitor sorafenib (n = 43) or placebo (n = 40 placebo). Relapse-free survival (RFS) was the primary endpoint of this trial. Relapse was defined as relapse or death, whatever occurred first.

RESULTS With a median follow-up of 41.8 months, the hazard ratio (HR) for relapse or death in the sorafenib group versus placebo group was 0.39 (95% CI, 0.18 to 0.85; log-rank $P = .013$). The 24-month RFS probability was 53.3% (95% CI, 0.36 to 0.68) with placebo versus 85.0% (95% CI, 0.70 to 0.93) with sorafenib (HR, 0.256; 95% CI, 0.10 to 0.65; log-rank $P = .002$). Exploratory data show that patients with undetectable minimal residual disease (MRD) before HCT and those with detectable MRD after HCT derive the strongest benefit from sorafenib.

CONCLUSION Sorafenib maintenance therapy reduces the risk of relapse and death after HCT for *FLT3*-ITD–positive AML.

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INTRODUCTION

Acute myeloid leukemia (AML) is a clonal stem cell cancer. Prognosis with AML varies substantially depending on cytogenetics, mutation status, age, and comorbidities.[1-3] FMS-like tyrosine kinase 3 (FLT3) is a receptor tyrosine kinase, which is expressed in hematopoietic precursor cells, regulating stem cell growth and differentiation.[4] Approximately 20% of patients with AML harbor *FLT3*–internal tandem duplication mutations (*FLT3*-ITD), which are usually located within the juxtamembrane part of the receptor.[5] The gene product of *FLT3*-ITD is a constitutively activated tyrosine kinase, which drives stem cell proliferation[6,7] and causes transformation in cooperation with co-occurring mutations.[8] Patients with AML harboring an *FLT3*-ITD mutation have consistently been shown to have a particularly high risk of relapse and death, despite undergoing hematopoietic stem cell transplantation (HCT).[2,9-14] Because *FLT3*-ITD causes oncogenic addiction,[15] it emerged as a bona fide target for therapeutic intervention in *FLT3*-ITD–positive AML.[16,17] In front-line therapy of *FLT3*-mutated AML, a combination of chemotherapy and midostaurin, a multitargeted tyrosine kinase inhibitor (TKI), improves overall survival (OS).[18] Other TKIs, such as quizartinib and gilteritinib, which are more specific and potent FLT3 inhibitors than midostaurin,[19] improve OS in patients with relapsed or refractory (r/r) *FLT3*-mutated AML.[20,21]

ASSOCIATED CONTENT

Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

The SORMAIN trial addressed whether a maintenance therapy using the multitargeted tyrosine kinase inhibitor sorafenib can improve outcome after allogeneic hematopoietic stem cell transplantation in high risk *FLT3*-ITD–positive AML.

Knowledge Generated

SORMAIN provides evidence that an inhibition of FLT3 and potentially additional kinases through sorafenib significantly reduces the risk of relapse and death after allogeneic hematopoietic stem cell transplantation for *FLT3*-ITD–positive AML. Molecularly detectable minimal residual disease (MRD) level prior and post-transplantation could be important predictors of relapse risk.

Relevance

A 2-year sorafenib maintenance therapy should be considered as a new treatment standard for *FLT3*-ITD–positive AML patients in complete remission after allogeneic hematopoietic stem cell transplantation.

Sorafenib is a multitargeted TKI that also potently inhibits FLT3. It has been approved for the treatment of advanced hepatocellular and renal cell cancer.[22,23] In combination with upfront chemotherapy, sorafenib improves progression-free survival in younger patients, but not in elderly patients with AML irrespective of the *FLT3* mutation status.[24,25] In patients with r/r *FLT3*-ITD–positive AML, sorafenib monotherapy is also efficacious.[26,27] However, as with single-agent quizartinib and gilteritinib,[15,20,21] sorafenib monotherapy is a palliative therapy in r/r AML and its efficacy limited by the emergence of TKI resistance.[28] In contrast, when sorafenib is given to patients with *FLT3*-ITD–mutated AML relapsing after HCT, the outcome can be profoundly different, as evidenced by unprecedented long-term remissions in selected patients.[28,29] This led us to hypothesize about a curative antileukemic synergism between sorafenib and allo-immunity after HCT. Considering that approximately half of the patients with *FLT3*-ITD–positive AML experience relapse after HCT and eventually die as a result of AML,[2,9-11] relapse prevention after HCT represents an unmet medical need. To address the hypothesis that sorafenib can inhibit *FLT3*-ITD–positive AML recurrence after HCT,[30-33] we conducted a multicenter randomized, double-blind, placebo-controlled trial (SORMAIN), comparing sorafenib versus placebo as prophylactic treatment after HCT.

PATIENTS AND METHODS

Patients

Adults with *FLT3*-ITD–positive AML were eligible for SORMAIN if they were in complete hematologic remission (CHR) at enrollment after HCT from a 9/10 or 10/10 HLA-matched unrelated or sibling donor. HCT could be performed as part of the consolidation therapy upfront or in the context of r/r AML. Conditioning therapy for HCT could be given with or without prior achievement of a complete remission using either a dose-reduced or a myeloablative protocol.

FLT3-ITD ratio assessment or quantitative polymerase chain reaction detection of nucleophosmin 1 mutational status (*NPM1*^{mut}) mRNA from diagnostic samples and in case of relapse or end of study was measured centrally at the Munich Leukemia Laboratory in Munich, Germany, or the Laboratory for Molecular Diagnostics at the University Hospital Dresden in Dresden, Germany. Treatment with FLT3-targeting agents was allowed before study enrollment (excluding sorafenib) and for the treatment of relapse after study entry (all TKIs, including sorafenib; see complete inclusion/exclusion criteria available online in the Data Supplement).

Study Design and Treatment

This phase II study (German Clinical Trials Register: DRKS00000591) was conducted at 15 centers in Germany and Austria. The SORMAIN trial was sponsored by the Philipps University Marburg and supported in part by Bayer HealthCare (Leverkusen, Germany). It was approved by the institutional ethics committee of the Philipps University Marburg and at each participating center. The trial was conducted in accordance with all applicable laws. All patients gave written informed consent at the time of enrollment. All investigators had access to all data and have confirmed its accuracy as well as complete adherence to the study protocol (Data Supplement).

Eligible patients were randomly assigned by the Coordinating Center for Clinical Trials Marburg in a 1:1 ratio to receive either sorafenib or matched placebo, using randomization lists with permuted blocks of randomly varying size. Treatment started in CHR between day +60 to latest day +100 after HCT. The dose of study medication was escalated from 2 tablets (equivalent to 2 × 200 mg sorafenib) per day for 2 weeks (dose level 1), to 3 tablets per day for 4 weeks (dose level 2), up to the full dose of 2 × 2 tablets per day (dose level 3) thereafter. The full dose was equivalent to 800 mg. Treatment was administered continuously for 24 months or until occurrence of relapse or intolerable

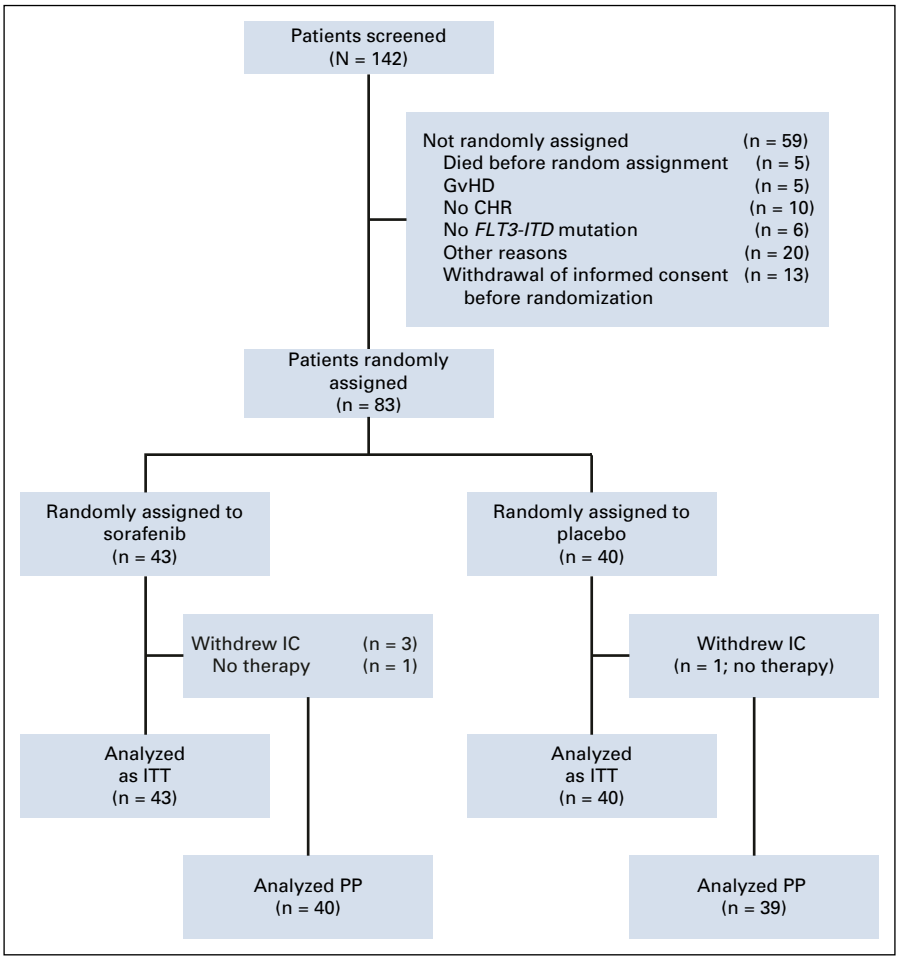

FIG 1. Patient disposition. Of 142 screened patients, 59 were not randomly assigned to treatment: 21 of 142 patients (14.7%) did not meet the inclusion/exclusion criteria, including 6 FMS-like tyrosine kinase 3–internal tandem duplication (*FLT3*-ITD) mutation-negative patients (4.2%). Five of 142 patients (3.5%) died before random assignment, 13 of 142 patients (9.1%) failed screening by withdrawal of consent before randomization, and 20 of 142 patients (14%) failed screening because of other reasons. CHR, complete hematologic remission; GvHD, graft versus host disease; IC, informed consent; ITT, intention to treat; PP, per protocol; RFS, relapse-free survival.

toxicity. Treatment after relapse could be performed according to the established standards at the centers.

Study Endpoints and Assessments

The primary endpoint of relapse-free survival (RFS) was calculated as time from randomization to either AML relapse or death from any cause, whatever occurred first. Relapse was defined according to revised recommendations of the International Working Group[34] as loss of CHR. Data entry lock for the primary endpoint analysis and relapse mortality analysis was July 10, 2018. The secondary endpoint included OS, calculated as time from randomization to death from any cause. Data entry lock for the OS analysis was October 31, 2018. Other secondary objectives were RFS and OS survival analyses at month 24, subgroup survival analyses by pre- and post-treatment *FLT3*-ITD ratio, and *NPM1* mutational status, as well as the assessment of graft versus host disease (GvHD) incidence and the evaluation of the safety of treatments. Acute and chronic GvHD were categorized according to the Mount Sinai Acute GVHD International Consortium and National Institutes of Health consensus criteria, respectively.[35,36]

Sample Size Calculation

Sample size calculations for the primary endpoint RFS were performed assuming a hazard ratio (HR) of 0.45 and a dropout rate of 8%, which led to 200 patients who were needed to observe 49 events after a minimum observation period of 24 months for each patient, corresponding to a power of 80% and a 2-sided alpha of 5% for the log-rank test.

Statistical Analysis

The primary efficacy analysis was performed in the intention-to-treat population. A sensitivity analysis was performed in the per-protocol population, which consisted of patients without major protocol violations. To compare event time distributions, we used Kaplan-Meier analysis. The 95% CIs of the event rates were calculated via the log-log transformation method, based on SEs computed using Greenwood's formula. RFS and OS were analyzed using a 2-sided log-rank test with a significance level of .05. The treatment effect was measured by the HR with a 95% CI, which was estimated by a Cox proportional hazard model. RFS and OS survival analyses at t = 24 months were calculated such that all survival times were censored at 24 months if still at risk. Differences in survival time distributions across treatment arms were assessed using the log-rank test. Differences in categorical and continuous characteristics were assessed between treatment arms using Fisher's exact test or the Wilcoxon rank-sum test, respectively.

TABLE 1. Demographic and Baseline Characteristics (ITT population)

Baseline Characteristics (at randomization)	All Patients (N = 83)	Placebo (n = 40)	Sorafenib (n = 43)
Age at trial entry (years)			
Median	54.0	53.59	54.17
Range	18.58-75.58	18.58-75.58	23.58-74.58
Sex			
Female	42 (50.6)	17 (42.5)	25 (58.14)
Male	41 (49.4)	23 (57.5)	18 (41.86)
ECOG performance status			
0	31 (37.4)	18 (45.0)	13 (30.23)
1	51 (61.4)	22 (55.0)	29 (67.44)
Missing	1 (1.2)	0 (0.0)	1 (2.33)
WBC counts (10^3/mL)			
Median	4.88	5.6	4.62
Range	1.88-12.75	1.98-11.22	1.88-12.75
Platelet count (10^3/mL)			
Median	142.0	141.0	143.0
Range	56.0-408.0	56.0-353.0	70.0-408.0
FLT3-ITD detectable			
Positive	7 (8.43)	3 (7.5)	4 (9.3)
Negative	68 (81.93)	33 (82.5)	35 (81.4)
Missing	8 (9.64)	4 (10.0)	4 (9.3)
NPM1 detectable	*NPM1*^{mut} patients (n = 52)	*NPM1*^{mut} patients (n = 23)	*NPM1*^{mut} patients (n = 29)
Positive	15 (28.85)	7 (30.43)	8 (27.59)
Negative	31 (59.62)	14 (60.87)	17 (58.62)
Missing	6 (11.54)	2 (8.7)	4 (13.79)

NOTE. All data are No. (%) unless otherwise indicated.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FLT3, FMS-like tyrosine kinase 3; ITD, internal tandem duplication; ITT, intention to treat; mut, mutation; NPM1, nucleophosmin 1.

Competing risk analysis was used to estimate the incidence of relapse and nonrelapse mortality by calculation of the cumulative incidence function (CIF) for each treatment arm. Relapse mortality was defined as death after a prior relapse. Competing risks for relapse mortality included death in the absence of relapse, whereas competing risks for nonrelapse mortality included relapse. The resulting CIFs were then compared for each event of interest between the 2 treatment arms using Gray's test. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients

Between October 2010 and May 2016, 142 patients entered screening. Overall, 83 patients (41 males, 42 females) were randomly assigned (Fig 1) and included in the primary analysis (placebo, n = 40; sorafenib, n = 43). Median age was 54 years (range, 18.58-75.58 years) for the entire study population (Table 1). Treatment arms were well balanced with regard to potential prognostic factors, for example, cytogenetic and genetic risk category,[2] time of transplantation (in first complete remission [CR1] versus outside CR1; Table 2). The median duration of therapy was 54.36 weeks (range, 1.71-128.29 weeks) for placebo and 34.57 weeks (range, 1.29-106.86 weeks) for sorafenib. The most common reasons for treatment discontinuation were adverse events in the sorafenib group (n = 9; 20.93%) and relapse in the placebo group (n = 17; 42.50%). Based on a decision of the Trial Steering Committee and the independent Data and Safety Monitoring Committee, the study recruitment was prematurely terminated on July 1, 2016, because of inadequate slow patient recruitment.

Efficacy

At the time of the RFS data entry lock (July 10, 2018), the median follow-up was 41.8 months (interquartile range, 24.1 to 42.5 months). The median RFS was not reached in the sorafenib group and was 30.9 months in the placebo group. The HR for relapse or death in the sorafenib group versus the placebo group was 0.39 (95% CI, 0.18 to 0.85;

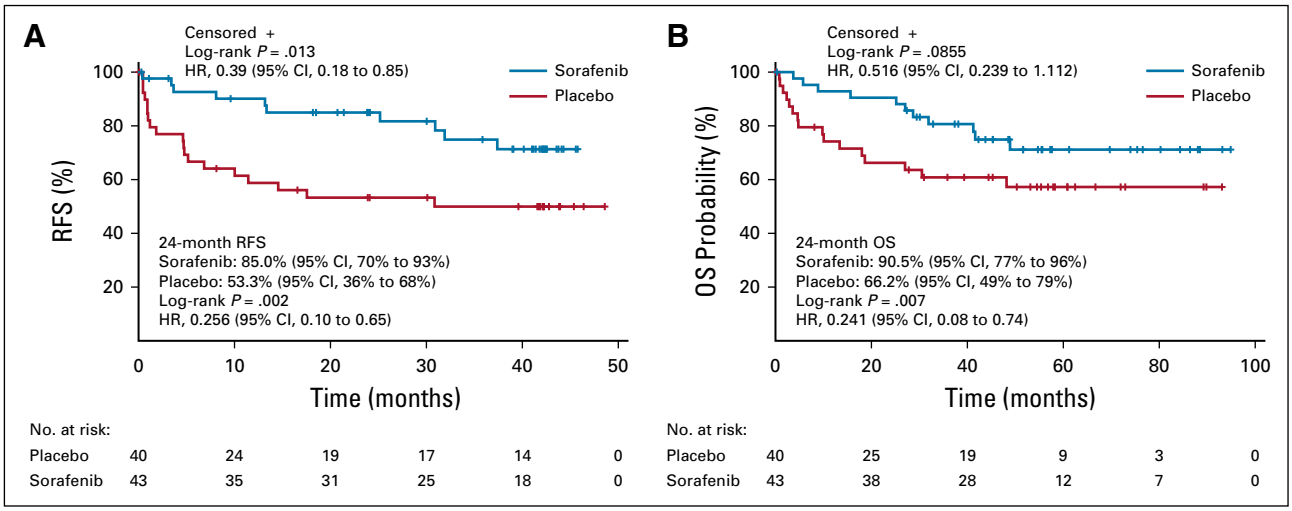

FIG 2. Relapse-free survival (RFS) and overall survival (OS) in patients positive for FMS-like tyrosine kinase 3–internal tandem duplication acute myeloid leukemia in complete remission after hematopoietic stem cell transplantation treated with sorafenib versus placebo (intention-to-treat population). (A) Kaplan-Meier curves for RFS in the sorafenib group and the placebo group. In total, 29 RFS events were recorded: 10 in the sorafenib group (8 relapses, 2 deaths) and 19 in the placebo group (17 relapses, 2 deaths). (B) Kaplan-Meier curves for OS in the sorafenib group and the placebo group. Tick marks indicate censoring of data. In total, 27 deaths were recorded, 11 in the sorafenib group and 16 in the placebo group. HR, hazard ratio.

log-rank $P = .013$; Fig 2A). The estimated probability of 24-month RFS was 85.0% (95% CI, 0.70 to 0.93) in the sorafenib group and 53.3% (95% CI, 0.36 to 0.68) in the placebo group, corresponding to an HR for relapse or death of 0.256 (95% CI, 0.10 to 0.65; log-rank $P = .002$). Although the presence of mutated *NPM1* at initial diagnosis positively affected RFS in the sorafenib group (Data Supplement), the *FLT3*-ITD ratio did not influence the treatment effect (Data Supplement). There were overall 14 and 4 deaths after relapse in the placebo and the sorafenib arm, respectively, resulting in a relapse mortality that was significantly higher for patients randomly assigned to the placebo group ($P = .01$; Data Supplement). In contrast, nonrelapse mortality was not different between the 2 treatment arms (Data Supplement).

After a median follow-up duration of 55.1 months, median OS time was not reached in both treatment groups (Fig 2B). The HR for death in the sorafenib group versus the placebo group was 0.52 (95% CI, 0.24 to 1.11; log-rank $P = .086$). The estimated probability of survival at 24 months was 90.5% (95% CI, 0.77 to 0.96) for sorafenib and 66.2% (95% CI, 0.49 to 0.79) for placebo, corresponding to an HR for death of 0.241 (95% CI, 0.08 to 0.74; log-rank $P = .007$; Fig 2B).

Of the 25 relapsing patients, 18 (72%) were treated with sorafenib, 17 patients were treated with chemotherapy (68%), and 6 patients (24%) underwent second HCT with no statistically significant differences between the 2 arms, albeit with small numbers (Data Supplement). There was no significant difference in the frequency and types of administration of relapse therapies between the treatment arms (Data Supplement; Table 2).

Pre- and Post-HCT Minimal Residual Disease Level Governs Sorafenib Response

Active disease at the time of transplantation or the detection of minimal residual disease (MRD) pre- and post-HCT is associated with a high risk of post-HCT relapse and mortality.[37-41] SORMAIN outcome was therefore analyzed according to the molecular and hematologic remission status pretransplantation (Figs 3A and 3B) and the $NPM1^{mut}$- or *FLT3*-ITD–defined MRD level post-HCT (Figs 3C and 3D). MRD-negative patients before HCT derived the strongest benefit from sorafenib maintenance: whereas 5 of 12 MRD-negative patients relapsed under placebo maintenance, none of 9 MRD-negative patients relapsed or died when treated with sorafenib (Fig 3B; $P = .028$). In contrast, after HCT, the benefit from sorafenib was most impressive in the MRD-positive cohort, which had a statistically significantly better RFS with sorafenib than with placebo (Fig 3C; $P = .015$). In contrast, although also patients who were MRD negative after HCT did better with sorafenib than with placebo, with small patient numbers this difference was not statistically significant (Fig 3D).

Safety

Sorafenib was generally well tolerated. Dose reductions were performed in 16 of 40 patients in the placebo group (40.0%) versus in 21 of 43 patients (48.8%) in the sorafenib group (Data Supplement). Study drug discontinuations due to toxicity occurred in 9 patients taking sorafenib (22.0%) compared with 2 placebo-treated patients (5.0%). The most common ≥ 3 adverse events (AEs) in both treatment groups were acute and/or chronic GvHD, which occurred in 32 of 42 patients (76.8%) in the sorafenib

TABLE 2. AML Pretreatments and Transplantation Characteristics

AML Risk and Prior Treatments	All Patients (N = 83)	Placebo (n = 40)	Sorafenib (n = 43)
Cytogenetic risk			
Low	0 (0)	0 (0)	0 (0)
Intermediate	76 (91.56)	36 (90.0)	40 (93.03)
High	4 (4.82)	3 (7.5)	1 (2.33)
Unknown	3 (3.61)	1 (2.5)	2 (4.65)
Intensive chemotherapy cycles before transplantation[a]			
1	12 (14.46)	6 (15.0)	6 (13.95)
2	45 (54.22)	24 (60.0)	21 (48.84)
3	14 (16.87)	3 (7.5)	11 (25.58)
> 3	12 (14.46)	7 (17.5)	5 (11.63)
Transplantation timing			
CHR1	59 (71.08)	27 (67.5)	32 (74.42)
Outside CHR1	24 (28.92)	13 (32.5)	11 (25.58)
Remission status at transplant			
CHR, no mCR	46 (55.42)	19 (47.5)	27 (62.79)
mCR	21 (25.3)	12 (30.0)	9 (20.93)
No CHR	16 (19.28)	9 (22.5)	7 (16.28)
Conditioning therapy			
Full	37 (44.58)	19 (47.5)	18 (41.86)
Reduced intensity	46 (55.42)	21 (52.5)	25 (58.14)
Donor (%)			
MUD	63 (75.9)	28 (70.0)	35 (81.4)
FAM	20 (24.1)	12 (30.0)	8 (18.6)
Donor lymphocyte infusion[b]	12 (14.46)	6 (15.0)	6 (13.95)

NOTE. All data are No. (%) unless otherwise indicated.

Abbreviations: AML, acute myeloid leukemia; CHR1, first complete hematologic remission; FAM, 10/10 matched sibling donor; mCR, molecular complete remission; MUD, matched unrelated donor, that is, 9/10 or 10/10 match.

[a]One patient with "unknown" donor lymphocyte infusion (DLI) status, therefore coded as no DLI.

[b]One patient with missing number of consolidation therapy cycles, although consolidation therapy was given.

group and in 23 of 39 patients (59.8%) in the placebo group. The other common grade ≥ 3 AEs occurring in ≥ 10% of sorafenib-treated patients were infections in 11 of 42 patients (26.2%), GI toxicity in 6 patients (14.3%), electrolyte alterations in 6 patients (14.3%), and skin toxicity in 5 patients (11.9%). In the placebo group, the common grade ≥ 3 AEs were infections in 9 patients (23.1%) and GI toxicity in 6 patients (15.4%; Table 3). Only 2 of 16 deaths that occurred during the treatment period were unrelated to AML. Both deaths occurred in the placebo arm.

DISCUSSION

Patients with *FLT3*-ITD–positive AML who undergo HCT have a high risk of dying as a result of relapse.[9] Whether *FLT3*-ITD–specific TKI maintenance therapy post-HCT[30-33] can improve outcome was unknown. In spite of recruiting fewer patients than intended and the phase II design, to our knowledge, SORMAIN—with its more than 4.5 years of median follow-up—provides the first placebo-controlled evidence that post-HCT maintenance therapy can reduce the risk of relapse and death. Of note, SORMAIN did not only include patients who underwent transplantation in the first CHR, but also included high-risk patients in the second or subsequent CHR.

Several other aspects of the SORMAIN trial are important. First, 4 of 10 RFS events occurred after the end of sorafenib treatment and might be preventable by longer maintenance duration. Equally important, however, sorafenib treatment effects extended beyond the time of actual therapy because by log-rank analysis, which compared RFS for the entire observation period of almost 42 months, sorafenib-treated patients fared better than placebo-treated patients.

Second, 63% of the patients in the sorafenib group were either not in CHR or were not in molecular remission at the time of HCT, and one third of the patients with *NPM1*^{mut} AML continued to be MRD positive at the time of randomization. Considering that MRD positivity before and

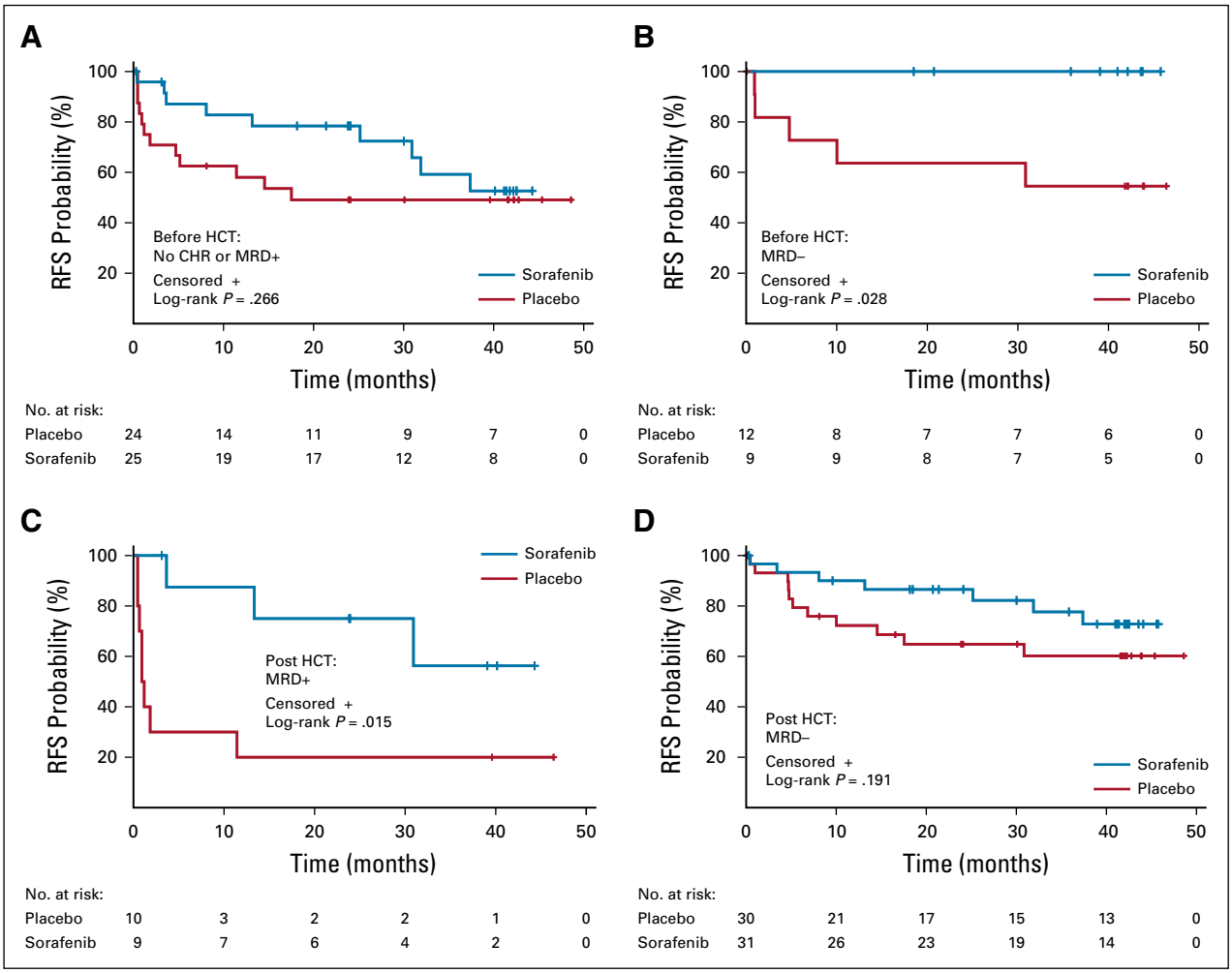

FIG 3. Distribution of relapse-free survival (RFS) in the sorafenib and placebo treatment groups by minimal residual disease level pre– and post–stem cell transplantation. (A) Kaplan-Meier curves for RFS probabilities in non–complete hematologic remission (CHR) patients or CHR patients with detectable minimal residual disease (MRD; no CHR or MRD+) versus (B) undetectable MRD (MRD−) before hematopoietic stem cell transplantation (HCT). MRD was defined as detectable nucleophosmin 1 mutations (*NPM1*^{mut}) mRNA, or, in *NPM1* wild type acute myeloid leukemia, FMS-like tyrosine kinase 3–internal tandem duplication mRNA. (C) Kaplan-Meier curves for RFS probabilities in the sorafenib group and the placebo group with detectable MRD (MRD+) or (D) undetectable MRD (MRD−) post-HCT at the time of randomization. Tick marks indicate censoring of data. Survival differences were assessed using log-rank tests.

after HCT is strongly predictive of poor survival,[37-41] a relapse rate of only 15% after 2 years in the sorafenib arm (Fig 2A) appears to be a clinically meaningful improvement. Interestingly, MRD-negative patients before HCT but also MRD-positive patients after HCT apparently derived the strongest benefit from sorafenib maintenance (Fig 3). One possible implication from these MRD data could be that novel treatment strategies that induce MRD negativity before HCT might synergize with post-HCT sorafenib maintenance.

Sorafenib maintenance treatment after HCT was not associated with significantly more toxicity than placebo. Especially the frequency of skin and GI toxicity were similar in both treatment arms. Adverse effects were managed with dose reductions, which occurred in approximately half of the patients in both treatment arms. However, considering the beneficial overall outcome in the sorafenib group, reported moderate dose reductions did not seem to abolish sorafenib efficacy.

Nine SORMAIN patients were treated upfront with midostaurin. Hence, it is unclear to which extent results from SORMAIN apply also to patients undergoing midostaurin plus chemotherapy induction therapy. However, given the strong benefit of sorafenib for patients who were MRD negative before HCT (Fig 3A), an intriguing possibility could be that a chemotherapy/midostaurin induction treatment—if it yields higher rates of MRD negativity before HCT—could potently synergize with sorafenib maintenance.

A limitation of SORMAIN was its premature termination because of inadequate enrollment. A major reason for this was that many patients received sorafenib

TABLE 3. Incidence of AE (safety population)

	Sorafenib (n = 42[a])		Placebo (n = 39[a])	
Grade 3 and 4 AE Type	**All**	**Drug Related**	**All**	**Drug Related**
Neutropenia	1 (2.4)	1 (2.4)	1 (2.6)	1 (2.6)
Thrombocytopenia	2 (4.8)	0	1 (2.6)	0
Liver toxicity: ALT, AST increased	2 (4.8)	0	2 (5.1)	2 (5.1)
GI toxicity (vomiting, nausea, diarrhea)	6 (14.3)	2 (4.8)	6 (15.4)	3 (7.7)
Skin toxicity	5 (11.9)	2 (4.8)	1 (2.6)	1 (2.6)
Infections	11 (26.2)	1 (2.4)	9 (23.1)	2 (5.1)
Overall GvHD rate	32 (76.8)	—	23 (59.8)	—
aGvHD (grade ≥ 2)	10 (24)		7 (18.2)	
cGvHD (mild/moderate)	18 (42.9)	—	14 (35.9)	—
cGvHD (severe)	8 (19.2)	—	4 (10.4)	—
Cardiotoxicity and renal insufficiency	4 (9.5)	1 (2.4)	1 (2.6)	0
Electrolyte alterations	6 (14.3)	3 (7.1)	1 (2.6)	0
Other	33 (78.6)	8 (19.1)	22 (56.4)	4 (10.3)

NOTE. All data are No. (%) unless otherwise indicated.
Abbreviations: AE, adverse event; aGvHD, acute graft versus host disease; cGvHD, chronic graft versus host disease.
[a]Safety population (patients who received at least 1 time study medication).

maintenance therapy off label outside of a clinical trial based on results from uncontrolled studies and expert recommendations.[30,42-46]

In conclusion, SORMAIN establishes targeted maintenance therapy as a novel efficacious treatment paradigm with the potential to meaningfully improve outcome after HCT. Ongoing post-HCT maintenance therapy studies use more FLT3-specific TKIs, such as quizartinib or gilteritinib.[47,48] They could help to better understand to which extent FLT3 selectivity versus immune-stimulatory off-target activities[27-29,49] govern the overall efficacy of sorafenib.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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DATA AVAILABILITY STATEMENT

Access to anonymized individual participant-level data collected during the trial, in addition to supporting clinical documentation, will be available. Study-related supporting documents, such as the protocol, amendments, and statistical analysis plan, will be provided. Access to data will be available for 10 years following publication of the primary manuscript. Research proposals to conduct a scientifically relevant analysis of the study data should be submitted to burchert@staff.uni-marburg.de. The research proposal will be reviewed by members of the steering committee of the study. After approval of the research proposal, access to the study data are granted after receipt of a signed Data Sharing Agreement.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Sorafenib Maintenance After Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia With *FLT3*–Internal Tandem Duplication Mutation (SORMAIN)

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