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ORIGINAL REPORT

Low-Dose Decitabine Versus Best Supportive Care in Elderly Patients With Intermediate- or High-Risk Myelodysplastic Syndrome (MDS) Ineligible for Intensive Chemotherapy: Final Results of the Randomized Phase III Study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group

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ABSTRACT

Purpose
To compare low-dose decitabine to best supportive care (BSC) in higher-risk patients with myelodysplastic syndrome (MDS) age 60 years or older and ineligible for intensive chemotherapy.

Patients and Methods
Two-hundred thirty-three patients (median age, 70 years; range, 60 to 90 years) were enrolled; 53% had poor-risk cytogenetics, and the median MDS duration at random assignment was 3 months. Primary end point was overall survival (OS). Decitabine (15 mg/m^2) was given intravenously over 4 hours three times a day for 3 days in 6-week cycles.

Results
OS prolongation with decitabine versus BSC was not statistically significant (median OS, 10.1 *v* 8.5 months, respectively; hazard ratio [HR], 0.88; 95% CI, 0.66 to 1.17; two-sided, log-rank $P = .38$). Progression-free survival (PFS), but not acute myeloid leukemia (AML) –free survival (AMLFS), was significantly prolonged with decitabine versus BSC (median PFS, 6.6 *v* 3.0 months, respectively; HR, 0.68; 95% CI, 0.52 to 0.88; $P = .004$; median AMLFS, 8.8 *v* 6.1 months, respectively; HR, 0.85; 95% CI, 0.64 to 1.12; $P = .24$). AML transformation was significantly ($P = .036$) reduced at 1 year (from 33% with BSC to 22% with decitabine). Multivariate analyses indicated that patients with short MDS duration had worse outcomes. Best responses with decitabine versus BSC, respectively, were as follows: complete response (13% *v* 0%), partial response (6% *v* 0%), hematologic improvement (15% *v* 2%), stable disease (14% *v* 22%), progressive disease (29% *v* 68%), hypoplasia (14% *v* 0%), and inevaluable (8% *v* 8%). Grade 3 to 4 febrile neutropenia occurred in 25% of patients on decitabine versus 7% of patients on BSC; grade 3 to 4 infections occurred in 57% and 52% of patients on decitabine and BSC, respectively. Decitabine treatment was associated with improvements in patient-reported quality-of-life (QOL) parameters.

Conclusion
Decitabine administered in 6-week cycles is active in older patients with higher-risk MDS, resulting in improvements of OS and AMLFS (nonsignificant), of PFS and AML transformation (significant), and of QOL. Short MDS duration was an independent adverse prognosticator.

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INTRODUCTION

Epigenetic silencing is a universal mechanism of gene inactivation in malignant cells, probably exceeding mutational events.[1] Recently, treatment approaches targeting the aberrant epigenome of cancer cells have been developed,[2] and low doses of a DNA methylation inhibitor such as

azacytidine and decitabine have shown remarkable activity in older patients with higher-risk myelodysplastic syndromes (MDS).[3,4] Interestingly, both azanucleoside demethylating agents were active also in patients with poor-risk cytogenetic abnormalities (not seen with low-dose cytarabine[5,6]). Translational studies performed on bone marrow cells from patients treated with decitabine or azacytidine have indicated that azanucleosides can revert the aberrant hypermethylation state in vivo.[7-9]

For older patients with MDS, the only curative approach of allogeneic blood stem-cell transplantation is often not available. Until recently, best supportive care (BSC) was considered the only accepted standard treatment because low-dose cytarabine does not result in improved overall survival (OS).[10] On the basis of the encouraging results obtained in large phase II studies of low-dose decitabine,[11,12] the European Organisation for Research and Treatment of Cancer (EORTC) Leukemia Group and German MDS Study Group embarked on a randomized phase III trial comparing decitabine with sole BSC in patients with intermediate-/high-risk MDS ≥ 60 years old who are ineligible for intensive treatment.

PATIENTS AND METHODS

Patients

Eligibility criteria included the following: patients ≥ 60 years old with primary or treatment-related MDS or chronic myelomonocytic leukemia irrespective of WBC counts; International Prognostic Scoring System (IPSS)[13] intermediate-1, intermediate-2, or high risk; bone marrow blasts of 11% to 30% or ≤ 10% and poor cytogenetics (IPSS); and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2. Ineligibility for intensive treatment was judged by the treating physician, with the reason(s), such as comorbid conditions, reduced PS, adverse cytogenetics, wish of the patient, lack of social support system, lack of an HLA-identical donor, and unavailability of a transplantation center, not recorded in the case report forms. Severe cardiovascular disease was an exclusion criterion, whereas previous treatment of MDS was not (except standard chemotherapy or treatment with a hypomethylating agent). The study was performed in accordance with the Declaration of Helsinki, all patients provided written informed consent, and the study was approved by the local ethics committees at all participating trial sites.

Study Design

Patients were randomly assigned (1:1) to receive either decitabine and BSC or sole BSC without subsequent treatment with an azanucleoside (study design prohibited cross over of patients to the experimental arm; Data Supplement). Patients were centrally randomly assigned at the EORTC Data Center, with stratification by IPSS cytogenetics,[13] IPSS risk,[13] MDS type, and institution. Decitabine (15 mg/m^2 in two doses over 2 hours each) was administered intravenously over 4 hours every 8 hours for 3 days. This treatment cycle was repeated every 6 weeks; in case of insufficient regeneration of hematologic parameters to baseline values, the interval could be extended up to 10 weeks. Reasons for exit from study were predefined in the protocol as disease progression, transformation to acute myeloid leukemia (AML; by French-American-British [FAB] criteria), unacceptable toxicity, or normal protocol treatment (eight treatment courses or 10 courses in case complete response [CR] was achieved after eight courses).

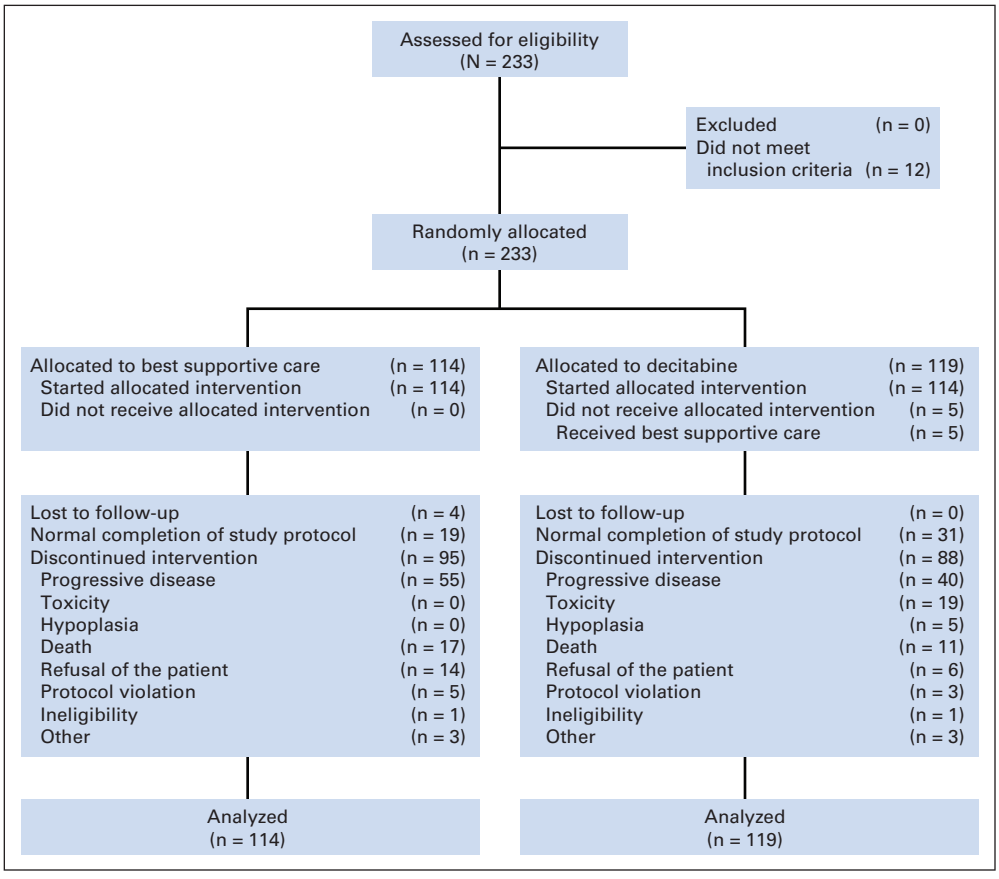

Fig 1. CONSORT diagram of the trial. A total of 12 patients were enrolled onto the trial and later evaluated as ineligible; five patients had a delay between bone marrow study and time of random assignment, two patients had less than 11% blasts in the bone marrow, two patients had received prior treatment that was precluded by the protocol, two patients had insufficient delay between prior myelodysplastic syndrome treatment and random assignment, and one patient had chronic lymphocytic leukemia and heart failure.

End Points

Primary end point was OS (defined as time from random assignment until death from any cause) or last follow-up (censored observation). Secondary end points were AML-free survival (AMLFS; defined as time from random assignment to AML transformation or death from any cause, whichever occurred first), progression-free survival (PFS; defined as time from random assignment to progression, relapse after attainment of CR or partial response [PR], or death, whichever occurred first), best response rate, toxicity, and quality of life (QOL). Responses were assessed according to International Working Group[14] criteria, with bone marrow studies planned after every other course of decitabine and at weeks 24 and 48 for patients on the BSC arm, or earlier in both arms in case of suspected progression. Central review of blood smears, bone marrow aspirates, and biopsies was performed by an expert hematopathologist (H.E.S.), and central cytogenetics review was performed by A.H. Adverse events were scored according to National Cancer Institute Common Toxicity Criteria (version 2.0).

Sample Size Calculation and Statistical Analyses

The aim of this study was to detect a difference in the survival rate at 3 years from 10% (BSC) to 22% (decitabine), corresponding to a hazard ratio (HR) of 0.66. To detect such a difference (two-sided, log-rank test, $\alpha = .05$ and $\beta = .20$) between the two arms, 185 deaths were required. Therefore, a total of 220 patients were to be randomly assigned and observed for at least 2 years.

The Kaplan-Meier method was used to estimate survival-type distributions; SEs of the estimates were obtained via Greenwood formula.[15] The two-sided, log-rank test was used for comparisons of treatment outcome.[15] The Cox proportional hazards model was used to determine independent prognostic importance of several factors, particularly the stratification factors (except center) and the treatment group, and to obtain HR estimates and corresponding 95% CIs.[15] Subgroup analyses were performed using forest plot techniques (Data Supplement). Estimates of incidence of AML progression and death without AML were obtained using the competing risk methods, and the Gray test was used to perform treatment comparisons.[15] For efficacy analyses, the intent-to-treat principle was followed; patients were included in the treatment group assigned by random assignment, independent of the patients' eligibility and the treatment actually received.

QOL Assessment

Patient QOL was assessed at random assignment, then every 6 weeks, and then at the end of treatment using the EORTC Quality of Life Questionnaire C30 (version 3.0). A mixed model with a variable covariance structure was fitted to the longitudinal health-related QOL data to test for differences between the two treatment arms.

RESULTS

Patient Characteristics

Between October 2002 and May 2007, 233 patients from 40 centers in nine European countries were randomly assigned to receive either BSC (114 patients) or decitabine (119 patients; Fig 1). Both groups were well balanced for age, sex, PS, and risk profile (FAB type and IPSS subgroup; Table 1). Overall, 92% of patients had higher-risk disease (IPSS intermediate-2 and high risk), 32% of patients fulfilled WHO criteria of AML (≥ 20% blasts), and 53% of patients with known cytogenetics had poor-risk cytogenetics. Median MDS duration at random assignment was 3 months.

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	BSC (n = 114) No. of Patients	BSC (n = 114) %	Decitabine (n = 119) No. of Patients	Decitabine (n = 119) %
Age, years				
Median	70		69	
Range	60-86		60-90	
≥ 75 years	34	29.8	33	27.7
Sex				
Male	73	64.0	76	63.9
Female	41	36.0	43	36.1
ECOG performance status				
0	25	21.9	29	24.4
1	72	63.2	76	63.9
2	17	14.9	14	11.8
FAB subtype				
RA/RARS	8/2	7.0/1.8	5/3	4.2/2.5
RAEB	64	56.1	61	51.3
RAEB-t	35	30.7	40	33.6
CMMoL	4	3.5	10	8.4
AML	1	0.9	1	0.8
IPSS				
Intermediate-1	8	7.0	8	6.7
Intermediate-2	63	55.3	64	53.8
High	42	36.8	46	38.7
Missing	1	0.9	1	0.8
Cytogenetics				
Good	29	25.4	38	31.9
Intermediate	17	14.9	9	7.6
Poor	51	44.7	57	47.9
Failure	16	14.0	13	10.9
Not assessed	1	0.9	2	1.7
WBC counts, $\times 10^9$/L				
Median	2.7		2.8	
Range	0.6-47.4		0.8-83.8	
≥ 10	11	9.7	23	19.4
Primary or secondary MDS				
Untreated MDS	21	18.4	24	20.3
Pretreated MDS*	79	69.3	80	67.2
Secondary MDS	14	12.3	15	12.6
MDS duration (from diagnosis to random assignment), months				
< 3	58	50.9	59	49.6
≥ 3	56	49.1	60	50.4
Prior malignant disease†	20	17.5	19	15.9
Other prior disease	8	7.0	4	3.4

Abbreviations: BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; FAB, French-American-British; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess blasts; RAEB-t, refractory anemia with excess blasts in transformation; CMMoL, chronic myelomonocytic leukemia; AML, acute myeloid leukemia; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome.

*With transfusions, hydroxyurea, growth factors, immunosuppressive therapy, and so on.

†In total, 34 patients had solid tumors, four patients had malignant lymphoma, one patient had chronic lymphocytic lymphoma, and one patient had a combination of malignancies.

Treatment Applicability

The median number of decitabine courses administered was four courses, equaling approximately 6 months of treatment. Five patients (4.2%) did not receive the study drug; one and two cycles were given to 14.3% and 23.5% of patients, respectively; three or four cycles were given to 18.5% of patients; five, six, or seven cycles were given to 19.3% of patients; and 21% of patients received all eight decitabine courses. Protocol deviations occurred in 81 patients (68.1%) on the decitabine arm compared with 18 patients (15.8%) on the BSC arm and mostly

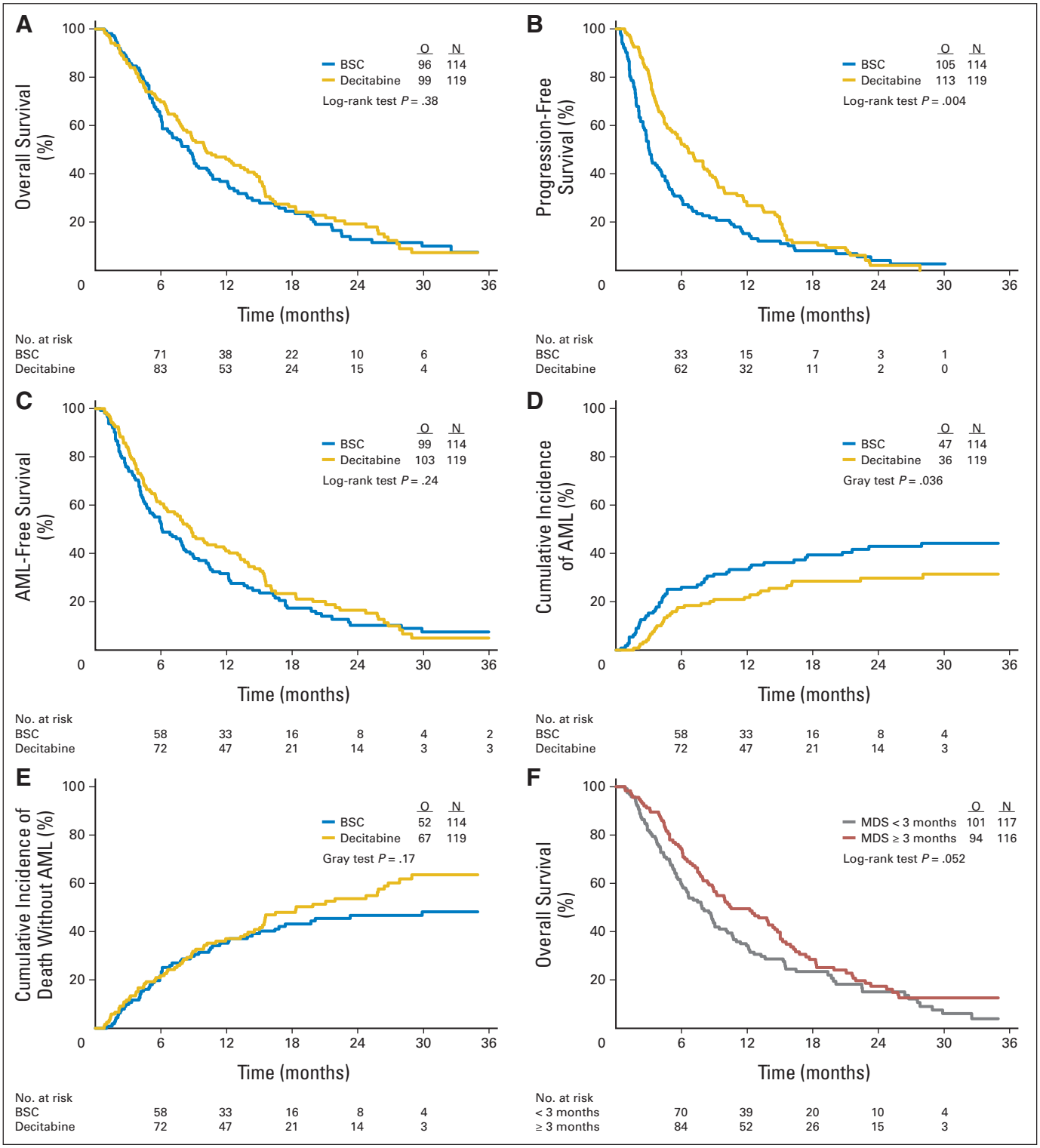

Fig 2. Analyses of survival end points. (A) Overall survival (OS) according to the randomly assigned arm. One-year OS rate was 46% (SE, 4.6%) in the decitabine arm versus 37% (SE, 4.6%) in the best supportive care (BSC) arm, and 2-year OS rate was 19% (SE, 4.0%) in the decitabine arm versus 13% (SE, 3.5%) in the BSC arm. (B) Progression-free survival (PFS) according to the randomly assigned arm. One-year PFS rate was 27% (SE, 4.1%) in the decitabine arm versus 15% (SE, 3.4%) in the BSC arm. (C) Acute myeloid leukemia (AML) –free survival (AMLFS) according to the randomly assigned arm. One-year AMLFS rate was 41% (SE, 4.5%) in the decitabine arm versus 32% (SE, 4.4%) in the BSC arm, 2-year AMLFS rate was 16% (SE, 3.7%) in the decitabine arm and 10% (SE, 3.2%) in the BSC arm. (D) Cumulative incidence of AML according to the randomly assigned arm. Incidence of AML at 1 year was 22% in the decitabine arm versus 33% in the BSC arm; at 2 years, the incidence rates were 30% and 43%, respectively. (E) Cumulative incidence of death without AML according to the randomly assigned arm. Incidence at 1 year was 37% in the decitabine arm versus 35% in the BSC arm; at 2 years, the incidence rates were 54% and 47%, respectively. (F) OS from random assignment according to the time from diagnosis of myelodysplastic syndrome (MDS) until random assignment. Patients randomly assigned less than 3 months from time of diagnosis had a median survival of 7.9 months compared with 10.6 months for patients randomly assigned ≥ 3 months from diagnosis. N, number of patients; O, observed number of events (for OS: deaths; for PFS: progressions or deaths; for AMLFS: AMLs or deaths).

consisted of undertreatment as a result of treatment delays or dose reduction. Reasons for taking patients off the study protocol are given in the Data Supplement. Median time to going off study was 3.7 months in the BSC arm and 5.9 months in the decitabine arm ($P < .001$).

Effects of Decitabine Versus BSC on Survival End Points and Transformation to AML

The positive effect of decitabine on OS did not reach statistical significance ($P = .38$), with a median survival time of 10.1 months in the decitabine arm versus 8.5 months in the BSC arm (HR, 0.88; 95% CI, 0.66 to 1.17; Fig 2A; median follow-up, 2.5 years). PFS was significantly prolonged in patients randomly assigned to the decitabine arm when compared with patients assigned to receive only BSC ($P = .004$, Fig 2B), with more than a doubling of the median PFS (from 3 to 6.6 months) and a reduction of the hazard rate of 32% (HR, 0.68; 95% CI, 0.52 to 0.88). The effect of decitabine on prolongation of AMLFS was not statistically significant ($P = .24$); median AMLFS estimates were 8.8 months in the decitabine arm versus 6.1 months in the BSC arm (HR, 0.85; 95% CI, 0.64 to 1.12; Fig 2C). The cumulative incidence of AML (by FAB criteria) was significantly ($P = .036$) decreased in the decitabine arm versus the BSC arm (22% *v* 33% at 1 year and 30% *v* 43% at 2 years, respectively; Fig 2D), whereas the cumulative incidences of death without AML were similar in both arms (Fig 2E).

Response

In the decitabine arm, 16 (13%) of 119 patients achieved CR, seven patients (6%) achieved PR, and 18 patients (15%) achieved hematologic improvement (HI; Data Supplement). Median time to best response was 3.8 months (range, 1.4 to 11.8 months) for all responders, with a median of 5.8, 2.9, and 3.8 months to reach CR, PR, and HI, respectively. In the BSC arm, two (2%) of 114 patients achieved HI.

Time From MDS Diagnosis to Random Assignment Is a Prognostic Factor for Survival

In a retrospective analysis (performed after initiation of the present trial) of five phase II trials of decitabine in MDS (177 patients),[12] shorter MDS duration before decitabine was associated with significantly shorter survival from treatment start. Applying this parameter post hoc, by taking the median MDS duration at random assignment (ie, 3 months) as the cut point to separate the entire cohort into two groups, patients with ≥ 3 months of MDS duration had longer survival from random assignment than patients with less than 3 months of MDS duration (10.6 *v* 7.9 months, respectively; $P = .052$; Fig 2F).

Multivariate Analyses

Multivariate analyses (Cox model) showed that treatment comparison adjusted for stratification factors used for random assignment yielded results similar to those provided by univariate analyses (data not shown). Additional multivariate analyses considering IPSS risk groups, cytogenetics as reported on case report forms, MDS duration, and baseline PS indicated that the following features were of independent poor prognosis regarding OS, PFS, and AMLFS: IPSS high risk, poor cytogenetics, less than 3 months of MDS duration, and ECOG PS of 1 or 2 (Table 2). The estimated treatment HR adjusted by these factors remained unchanged compared with that based on univariate analysis for OS and PFS but was slightly higher regarding AMLFS (HR, 0.90).

Subgroup Analyses

For exploratory purposes, we performed a limited number of subgroup analyses according to prognostic factors (Table 2) and patient age. Possible interactions between initial features and the magnitude of the treatment effect regarding the three end points were also investigated. For OS and AMLFS, the benefit of decitabine over BSC seemed more apparent for patients less than 75 years old than for patients ≥ 75 years old and for patients with an MDS duration of ≥ 3 months than patients with an MDS duration of less than 3 months (test for heterogeneity: $P = .08$; Figs 3A and 3C). Kaplan-Meier curves for OS, PFS, and AMLFS according to treatment by MDS duration and a summary of outcome comparisons according to MDS duration and treatment arm are provided in the Data Supplement. Cox multivariate analysis revealed that, adjusting for IPSS high-risk group, cytogenetics, and initial PS, treatment differences were in fact quite consistent within each

Table 2. Results of Cox Univariate and Multivariate Analysis Regarding OS, PFS, and AMLFS

Variable	OS			PFS			AMLFS		
	HR*	95% CI	*P*	HR*	95% CI	*P*	HR*	95% CI	*P*
Univariate analysis									
Treatment: decitabine *v* BSC	0.88	0.66 to 1.17	.38	0.68	0.52 to 0.88	.004	0.85	0.64 to 1.12	.24
Multivariate analysis									
Treatment: decitabine *v* BSC	0.88	0.66 to 1.18	.40	0.68	0.51 to 0.89	.005	0.90	0.67 to 1.19	.46
IPSS: high risk *v* others	1.55	1.13 to 2.12	.007	1.42	1.05 to 1.93	.02	1.72	1.26 to 2.35	< .001
Cytogenetics									
Poor *v* good	1.75	1.22 to 2.50	.002	1.39	0.99 to 1.95	.06	1.68	1.18 to 2.40	.004
Intermediate *v* good	0.93	0.53 to 1.62	.79	0.90	0.53 to 1.51	.69	1.11	0.65 to 1.90	.69
Unknown *v* good	1.32	0.81 to 2.15	.27	1.22	0.77 to 1.92	.39	1.38	0.86 to 2.21	.19
Months from MDS diagnosis to random assignment: < *v* ≥ 3	1.34	1.01 to 1.78	.04	1.33	1.01 to 1.74	.04	1.48	1.12 to 1.96	.007
ECOG PS									
1 *v* 0	1.48	1.02 to 2.14	.04	1.37	0.97 to 1.92	.07	1.48	1.03 to 2.12	.04
2 *v* 0	1.48	0.89 to 2.46	.14	1.62	1.01 to 2.61	.05	1.80	1.11 to 2.94	.02

Abbreviations: OS, overall survival; PFS, progression-free survival; AMLFS, acute myeloid leukemia–free survival; HR, hazard ratio; BSC, best supportive care; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; ECOG, Eastern Cooperative Oncology Group; PS, performance status.
*HR > 1 corresponds to a worse prognosis.

MDS duration subgroup, and conversely, in each treatment arm, patients with MDS duration of ≥ 3 months consistently had a better outcome than patients with MDS duration of less than 3 months. This consistency was assessed by including an interaction term (treatment × duration of MDS) in the Cox model (Data Supplement). For each of the three end points, this was not significant (OS, $P = .67$; PFS, $P = .38$; AMLFS, $P = .90$).

Regarding PFS, the advantage of decitabine over BSC was consistent throughout the subgroups of these factors, except for age; in patients ≥ 75 years old, treatment results were similar (Fig 3B). In patients with high-risk IPSS and/or poor cytogenetics, a significant benefit of decitabine versus BSC was observed (Data Supplement), as in patients without these high-risk features (Data Supplement).

Toxicity

Grade 3 or 4 infections were the most frequent adverse events on both arms (Table 3), followed by grade 1 to 3 nausea and vomiting (more frequent in patients treated with decitabine). Grade 3 or 4 toxicities also included infection with grade 3 or 4 neutropenia (47.4% of patients on decitabine arm *v* 35.0% of patients on BSC arm) and fatigue (8.8% of patients on decitabine arm *v* 14.0% of patients on BSC arm). Febrile neutropenia was noted in 25.4% of patients receiving decitabine compared with 7.1% of patients receiving BSC.

Postprogression Treatment: Possible Effects on OS

Approximately 25% of patients who experienced progression on both study arms received postprogression treatment (azacytidine, induction chemotherapy, and allografting; Data Supplement). Although inclusion criteria defined eligible patients as not being candidates for intensive treatment, patients on the decitabine arm may have benefited from the study drug to a degree as to be eventually judged fit enough to be offered intensive treatment after progression or as consolidation when in remission. Similarly, BSC alone may have stabilized patients enough to proceed to more aggressive treatment.

QOL

Patients on the decitabine arm showed a significant improvement in their self-reported fatigue and physical functioning (Fig 4), with borderline improvement of global health status, whereas no apparent effect was seen on dyspnea. Supportive analyses revealed that for most other QOL scales, the trend was also in favor of decitabine (data not shown). However, missing data were an issue (baseline

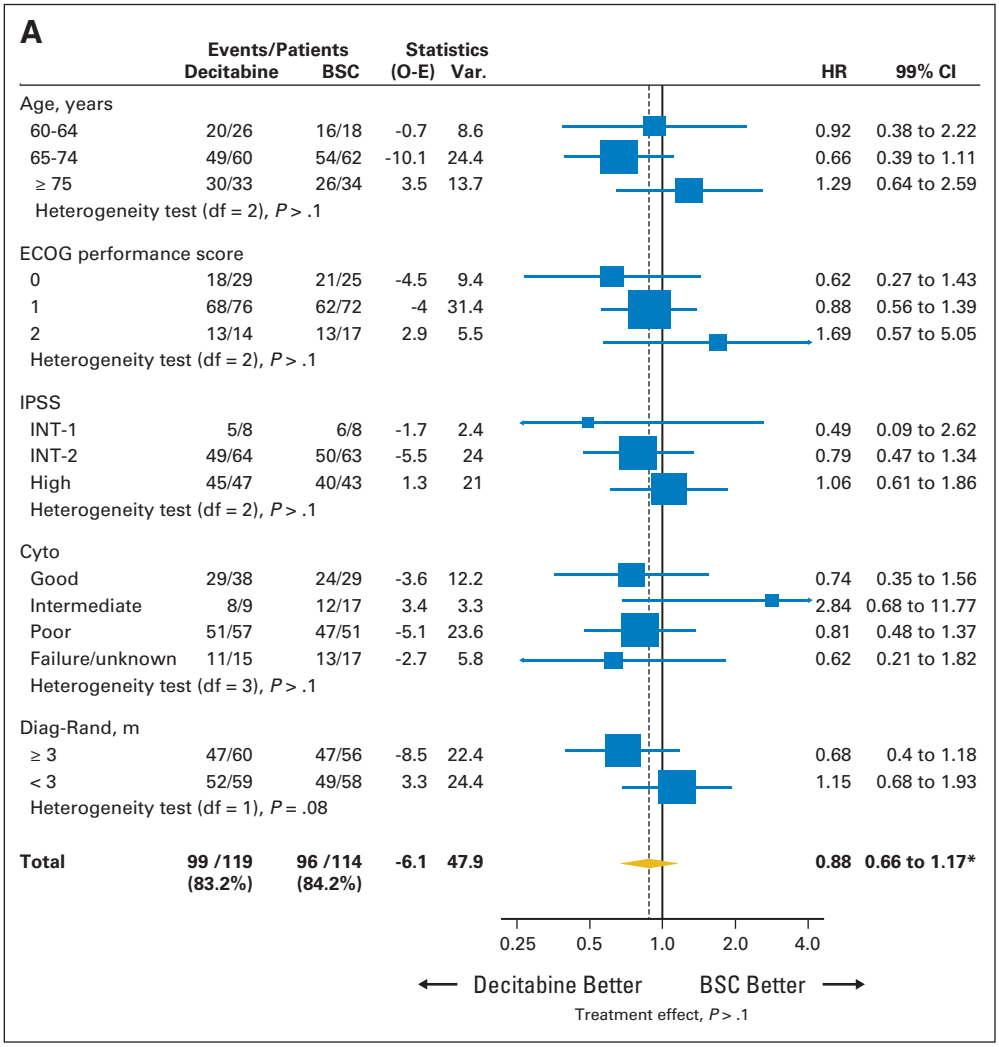

Fig 3. Forest plots depicting (A) overall survival, (B) progression-free survival, and (C) acute myeloid leukemia–free survival by random assignment arm. Host factors of patient age and performance status and disease-specific factors of International Prognostic Scoring System (IPSS) risk, cytogenetic risk, and duration of myelodysplastic syndrome (MDS) at time of random assignment were analyzed. HR, hazard ratio; BSC, best supportive care; O, observed; E, expected; ECOG, Eastern Cooperative Oncology Group; INT, intermediate; Cyto, cytogenetics; Interm, intermediate; UNK, unknown; Diag, diagnosis; Rand, random assignment. (*) Ninety-five percent CIs for totals and subtotals; 99% CIs elsewhere.

compliance was only 60%, decreasing from 50% to 30% during the first year), and the observed treatment differences could not be confirmed consistently when imputing the missing data.

DISCUSSION

This trial confirms the activity of intravenous decitabine in higher-risk MDS,[3,11,12,16,17] with a 19% rate of CR+PR and an overall 34% response rate when also including HI (15%). The primary end point of OS and secondary end point of AMLFS did not reach statistical significance, whereas PFS was significantly prolonged. Decitabine treatment was associated with only limited nonhematologic toxicity. Myelosuppression was the major adverse effect, particularly during early treatment (prolonged cytopenias in some patients necessitated delay of subsequent treatment or even termination). Improvements in QOL with decitabine treatment were noted for patients' self-reported fatigue and physical functioning, with a borderline positive effect on global health status, in line with data previously reported for decitabine[3] and azacytidine.[18]

Older patients with MDS are frequently burdened by comorbidities, reduced PS, and often high-risk cytogenetics.[19] To advance a nonintensive treatment approach in this difficult-to-treat patient group, eligibility criteria of this academic trial explicitly targeted patients with poor-risk cytogenetics and/or treatment-related MDS, did not impose an upper age limit, and systematically included patients with newly diagnosed advanced MDS. Thus, the majority of patients had poor-risk cytogenetics, 29% of patients were ≥ 75 years old, 15% of patients had a prior malignancy, almost 80% of patients had a reduced PS, and 50% of patients had MDS diagnosed less than 3 months before random assignment. These features are reflected by the limited PFS and OS of patients in the control arm (3 and 8.5 months, respectively). Notably, patients with poor-risk cytogenetics clearly derived clinical benefit from decitabine. In addition, azacytidine has shown activity in patients with poor-risk cytogenetics,[4,20] and because both drugs are DNA hypomethylating agents,[21] this may be a class effect. Patients with treatment-related MDS had comparable PFS and OS as patients with primary MDS (data not shown).

Compared with other decitabine response predictors, prior MDS duration has received only limited attention,[12,22] with conflicting results. We now addressed, in a post hoc fashion (implementation to stratify for MDS duration in the ongoing trial was not possible), our

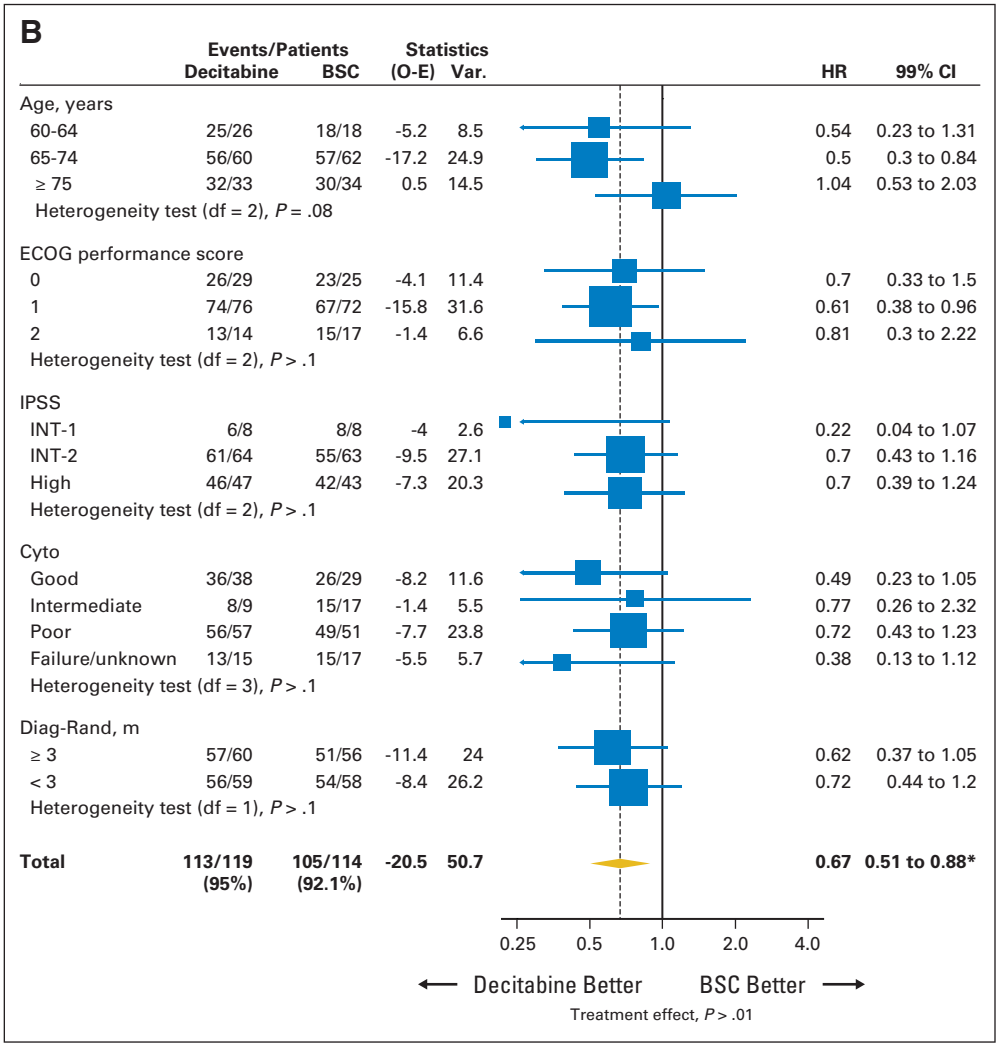

Fig 3. (continued)

finding that short duration of MDS may be a novel factor linked to poor outcome.[12] Indeed, short MDS duration was associated with a worse outcome after decitabine or BSC. This finding is in sharp contrast to the adverse prognostic impact of antecedent disease duration in patients who received intensive chemotherapy.[23] It is supported by a similar analysis of patients with AML from MDS treated on the 00331 phase II multicenter decitabine trial; patients with longer MDS duration before decitabine also had a better outcome (manuscript submitted). Application of this discriminator in the evaluation of other decitabine schedules and MDS treatments seems warranted.

Median time to best response was more than 3 months (median time to CR, 5.8 months). Because this is well established for both hypomethylating agents,[24] it calls for administration of repeated treatment courses. Still, a substantial number of patients received only one or two decitabine courses (only 26% of patients received all eight courses). Thus, it appears mandatory to not limit treatment duration to increase the likelihood of obtaining a best response and to maintain responses until progression or resistance.

Recently, alternative decitabine dosing (1-hour infusions on 5 consecutive days, repeated every 28 days) has resulted in a notable response rate in the Alternative Dosing for Outpatient Treatment (ADOPT) trial[16,25] with a median of nine courses administered. Whether this schedule is superior to the one used in the present study can only be clarified within a prospective randomized trial.

Compared with patients treated with azacytidine (and randomly assigned against BSC) on the phase III trial (Aza-001) of azacytidine versus standard treatment (ie, either BSC, low-dose cytarabine, or induction chemotherapy), OS with decitabine was shorter (10.1 months with decitabine *v* 21.1 months with azacytidine).[4] However, patients on the BSC arm of the present trial also had a shorter OS than patients randomly assigned to BSC in the Aza-001 trial (8.5 *v* 11.5 months, respectively). What may be the reasons for these differences? The median age of patients was identical, and the Aza-001 trial included even more IPSS high-risk patients. However, the present trial recruited more patients with poor-risk cytogenetics, an ECOG PS of 1 or 2, treatment-related MDS, and a leukocyte count of more than 13×10^9/L. Notably, we found that previous MDS duration strongly contributed to treatment outcome; median MDS duration at random assignment was only 3 months (*v* 12 months in the Aza-001 trial) because immediate enrollment after diagnosis was possible. The early and steep decrease of the curves depicting PFS during the first 3 months from random assignment

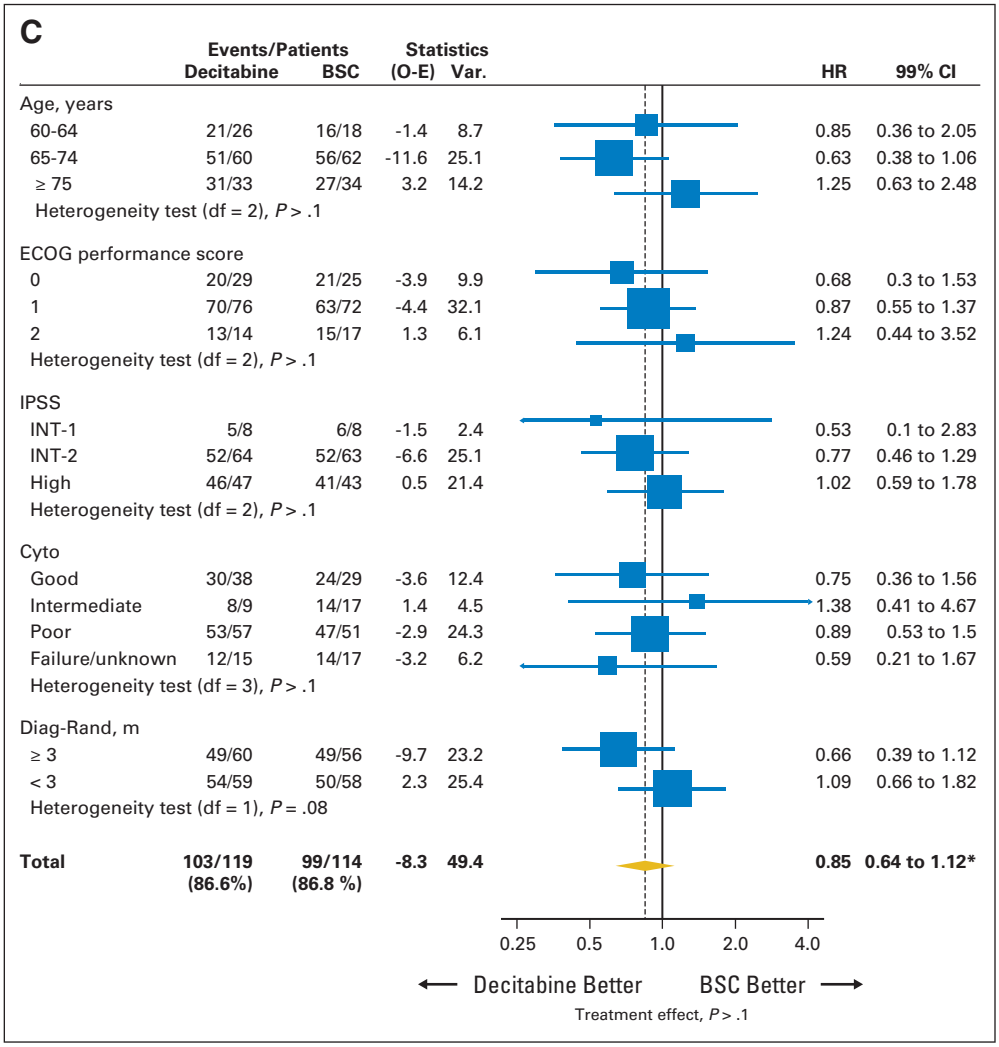

Fig 3. (continued)

Table 3. Adverse Events

Adverse Event	BSC (n = 114) No. of Patients	BSC (n = 114) %	Decitabine (n = 114)* No. of Patients	Decitabine (n = 114)* %
Febrile neutropenia				
Grade 3	6	5.3	25	21.9
Grade 4	2	1.8	4	3.5
Infection with grade 3/4 neutropenia				
Grade 3	33	28.9	35	30.7
Grade 4	7	6.1	19	16.7
Infection				
Grade 3	45	39.5	44	38.6
Grade 4	12	10.5	22	19.3
Hemorrhage				
Grade 3	14	12.3	15	13.2
Grade 4	4	3.5	5	4.4
Fatigue				
Grade 3	12	10.5	5	4.4
Grade 4	4	3.5	5	4.4
Nausea				
Grade 1	9	7.9	25	21.9
Grade 2	8	7.0	8	7.0
Grade 3	1	0.9	2	1.8
Vomiting				
Grade 1	3	2.6	13	11.4
Grade 2	7	6.1	5	4.4
Grade 3	1	0.9	1	0.9
Diarrhea				
Grade 1	9	7.9	12	10.5
Grade 2	9	7.9	17	14.9
Grade 3	5	4.4	4	3.5

Abbreviation: BSC, best supportive care.
*Patients randomly assigned in the decitabine arm who received at least one decitabine infusion were included in this analysis.

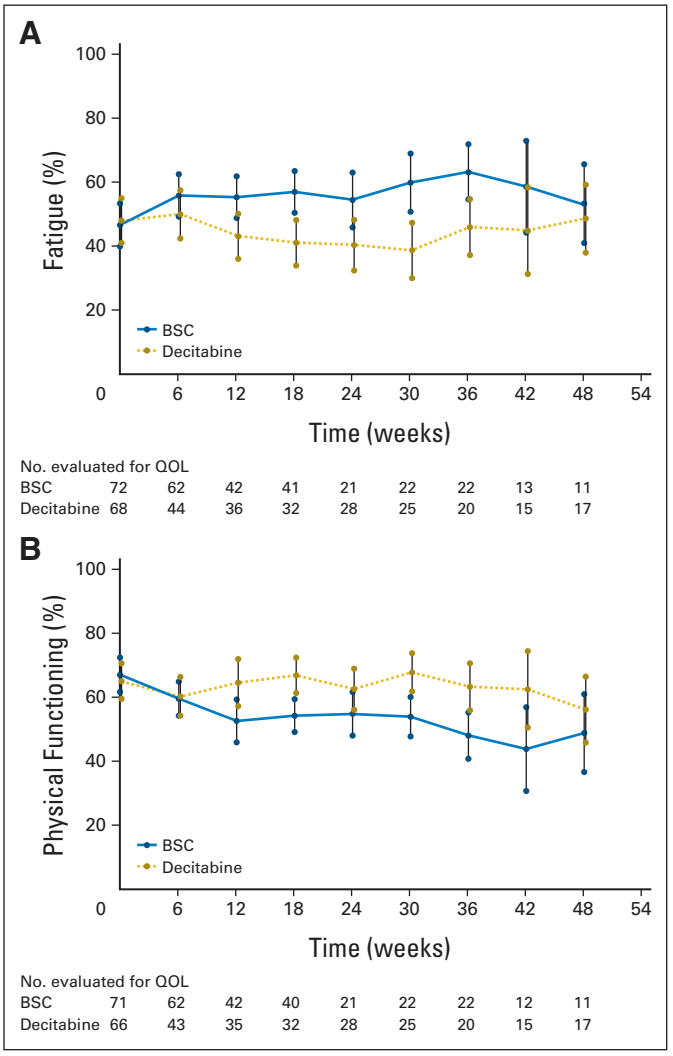

Fig 4. Results (mean ± 95% CI) of the quality-of-life (QOL) studies before and after random assignment in the decitabine versus best supportive care (BSC) arms. Dimensions depicted are (A) fatigue and (B) physical functioning. Scores were computed according to the procedures outlined in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 scoring manual. Compliance was limited during follow-up, constraining the generalizability of the results, which nonetheless support the conclusion that decitabine treatment leads to improvement in health-related QOL dimensions.

(mostly composed of progression events; Fig 2B) implies that many patients had MDS already in progression at random assignment. In contrast to a similar comparison of previous MDS duration, in which CR rate (albeit not survival) was superior in patients with MDS of longer duration,[22] patients on the present trial had not received chemotherapy before random assignment. In total, these differences in patient populations most likely account at least in part for the differences in outcome between the 06011 and Aza-001 trials.

In conclusion, this is the second phase III study demonstrating activity of low-dose decitabine given in 6-week cycles in patients with higher-risk MDS, with a study cohort reflective of the numerous poor-risk features common in this patient group (older age, reduced PS, treatment-related myelodysplasia, poor-risk cytogenetics, and often progressive MDS). Significantly prolonged PFS and decreased AML transformation rate, as well as improvements in QOL, demonstrate that this treatment, with an acceptable toxicity profile, is beneficial in this patient group, warranting further studies (eg, a comparison with the 4-week decitabine schedule, combinations with histone deacetylase inhibitors, and maintenance treatment with lower-dose schedules).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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