

CLINICAL TRIALS AND OBSERVATIONS

International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts

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Key Points

- Azacitidine increased median overall survival by 3.8 months vs current commonly used AML treatments (10.4 vs 6.5 months; $P = .1009$).
- Azacitidine safety in patients age ≥ 65 years with AML (>30% blasts) was consistent with its known safety profile in other trials.

This multicenter, randomized, open-label, phase 3 trial evaluated azacitidine efficacy and safety vs conventional care regimens (CCRs) in 488 patients age ≥ 65 years with newly diagnosed acute myeloid leukemia (AML) with >30% bone marrow blasts. Before randomization, a CCR (standard induction chemotherapy, low-dose ara-c, or supportive care only) was preselected for each patient. Patients then were assigned 1:1 to azacitidine ($n = 241$) or CCR ($n = 247$). Patients assigned to CCR received their preselected treatment. Median overall survival (OS) was increased with azacitidine vs CCR: 10.4 months (95% confidence interval [CI], 8.0-12.7 months) vs 6.5 months (95% CI, 5.0-8.6 months), respectively (hazard ratio [HR] was 0.85; 95% CI, 0.69-1.03; stratified log-rank $P = .1009$). One-year survival rates with azacitidine and CCR were 46.5% and 34.2%, respectively (difference, 12.3%; 95% CI, 3.5%-21.0%). A prespecified analysis censoring patients who received AML treatment after discontinuing study drug showed median OS with azacitidine vs CCR was 12.1 months (95% CI, 9.2-14.2 months) vs 6.9 months (95% CI, 5.1-9.6 months; HR, 0.76; 95% CI, 0.60-0.96; stratified log-rank $P = .0190$). Univariate analysis showed favorable

trends for azacitidine compared with CCR across all subgroups defined by baseline demographic and disease features. Adverse events were consistent with the well-established safety profile of azacitidine. Azacitidine may be an important treatment option for this difficult-to-treat AML population. This trial was registered at www.clinicaltrials.gov as #NCT01074047. (*Blood*. 2015;126(3):291-299)

Introduction

Acute myeloid leukemia (AML) is an aggressive malignancy with poor prognosis. In the United States, an estimated 20 830 new cases are anticipated in 2015 and more than 10 000 people will die of the disease.¹ Older patients, who are at greatest risk of developing AML, have especially poor survival² because of a variety of host- and disease-related adverse prognostic risk factors, such as history of myelodysplastic syndromes (MDSs), unfavorable karyotypes, poor performance status, and comorbidities, which can limit treatment options. As a result, many older patients receive only palliative care.³ Patients age ≥ 65 years with AML have a median overall survival (OS) of only 2 to 8 months.⁴⁻⁸

There is no universally accepted standard approach to treating AML in older patients. Commonly used therapeutic options include best

supportive care (BSC) alone, standard induction chemotherapy (IC), and low-dose ara-c (LDAC). The National Comprehensive Cancer Network (NCCN) guidelines recommend IC for patients with AML age ≥ 60 years with more favorable prognostic features,⁹ but many older patients with AML do not meet these criteria. Older patients considered eligible for IC can have relatively high rates of complete remission (CR); however, no clear survival benefit has been established for IC over less intensive treatment options.^{5,10,11} Those patients considered ineligible for IC because of advanced age or poor performance status are commonly treated with LDAC or BSC alone, which are associated with a median OS of only 5 and 2 months, respectively.^{3,4,12}

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NCCN treatment recommendations for older patients with newly diagnosed AML also include the hypomethylating agents azacitidine and decitabine.⁹ Decitabine was recently approved in Europe for treatment of patients age ≥ 65 years with newly diagnosed AML ($\geq 20\%$ bone marrow [BM] blasts) who are not considered candidates for standard IC. Azacitidine was shown to prolong OS compared with conventional care regimens (CCRs) in the subset of older patients with 20% to 30% BM blasts in the phase 3 AZA-001 trial.¹³ Similarly, azacitidine treatment has been associated with an encouraging median OS of approximately 9 to 10 months in patients with AML who participated in the Austrian Azacitidine Registry^{14,15} or in a French compassionate use program.¹⁶ Reported here are results of the international phase 3 AZA-AML-001 study, the first prospective, randomized clinical study to evaluate the efficacy and safety of azacitidine compared with CCR (doctor's choice of BSC only, LDAC, or standard IC) in patients age ≥ 65 years with newly diagnosed AML and $>30\%$ BM blasts.

Patients and methods

This multicenter, randomized, open-label, parallel-group study conducted in 18 countries was approved by the relevant institutional review boards or independent ethics committees and was conducted according to the Declaration of Helsinki. All patients provided written informed consent. Authors had access to all study data, and analyses were performed by Celgene Corporation, Summit, NJ.

Patients

Eligible patients were age ≥ 65 years with newly diagnosed, histologically confirmed de novo or secondary AML with $>30\%$ BM blasts who were not considered eligible for hematopoietic stem cell transplantation, with intermediate- or poor-risk cytogenetics (NCCN 2009 criteria¹⁷), Eastern Cooperative Oncology Group performance status (ECOG PS) score ≤ 2 , and white blood cell count $\leq 15 \times 10^9/L$. Exclusion criteria included acute promyelocytic leukemia with t(15;17)(q22;q12) and AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22), t(8;21)(q22;q22), or t(9;22)(q34;q11.2); AML arising from previous hematologic disorders other than MDS (eg, myeloproliferative neoplasms); other malignancies; or uncontrolled systemic infection. Patients could not have received prior decitabine, azacitidine, or cytarabine treatment; prior AML therapy (except hydroxyurea, which was allowed up to 2 weeks before the screening hematology sample was taken); or any experimental drug within 4 weeks of starting study treatment.

Study design and treatment

Before randomization, investigators determined which protocol-designated CCR (BSC, LDAC, or IC) was most appropriate for each patient on the basis of age, ECOG PS, comorbidities, and regional guidelines and/or institutional practice. A central, stratified, and permuted block randomization method and interactive voice response system were used to randomly assign patients 1:1 to receive azacitidine or CCR. Randomization was stratified by preselected CCR (BSC, LDAC, or IC), ECOG PS (0-1 or 2), and cytogenetic risk (intermediate or poor). Patients assigned to CCR received their preselected treatment.

Azacitidine 75 mg/m² per day was administered subcutaneously for 7 consecutive days per 28-day treatment cycle for at least 6 cycles. CCRs were as follows: BSC only (blood product transfusions and antibiotics, with granulocyte colony-stimulating factor for neutropenic infection); subcutaneous LDAC (20 mg twice per day for 10 days per 28-day treatment cycle for at least 4 cycles); or IC (cytarabine 100-200 mg/m² per day by continuous intravenous infusion for 7 days, plus 3 days of either daunorubicin 45-60 mg/m² per day or idarubicin 9-12 mg/m² per day) for 1 cycle, followed by up to 2 consolidation cycles (ie, the same anthracycline regimen as used at induction and the same cytarabine dose used for induction but administered for 3 to 7 days) for those achieving CR or partial response (PR). Reinduction was not allowed. Azacitidine

and LDAC dosing could be reduced or delayed as needed until the blood count recovered. All study participants could receive BSC, including transient use of hydroxyurea (hydroxyurea was not allowed within 72 hours before or after azacitidine administration).

Patients were scheduled to visit study sites once per week during the first 2 treatment cycles, then every other week thereafter. BM aspirates, BM biopsies, and peripheral blood smears were collected, and cytogenetic testing was performed at screening in the IC group, within 7 days before each treatment cycle; in the azacitidine and LDAC groups, within 7 days before initiation of every second cycle beginning at cycle 3; and in the BSC group, on day 1 of every third cycle (a BSC cycle was defined as 28 days), beginning at cycle 4. Central review of peripheral blood, BM samples, and cytogenetics was conducted by a pathologist and cytogeneticist blinded to treatment. AML classification for each patient was determined by local investigators at study entry.

Efficacy end points

The primary end point was OS, defined as time from randomization to death as a result of any cause. Living patients were censored upon study discontinuation (loss to follow-up, withdrawal of consent) or at the end of the poststudy follow-up. Patients who discontinued randomized treatment could receive subsequent AML therapy during study follow-up according to the investigator's decision. The choice of subsequent therapy was at the discretion of the investigator. A predefined sensitivity analysis evaluated OS in the azacitidine and CCR arms, censoring patients when they began subsequent AML therapy.

Secondary end points included estimated 1-year survival rate and OS in patient subgroups defined by baseline demographic and disease characteristics: age (<75 years vs ≥ 75 years), gender (male vs female), race (white vs Asian), geographic region (North America and Australia/Western Europe and Israel/Eastern Europe/Asia), ECOG PS (0-1 vs 2), baseline cytogenetic risk (intermediate vs poor), World Health Organization classification of AML (AML with recurrent genetic abnormalities vs AML with myelodysplasia-related changes [AML-MRC] vs AML with therapy-related myeloid neoplasms vs AML not otherwise specified), white blood cell count ($\leq 5 \times 10^9/L$ vs $>5 \times 10^9/L$), BM blasts ($\leq 50\%$ vs $>50\%$), and prior history of MDS.

Hematologic responses of CR, morphologic CR with incomplete blood count recovery (CRi), and PR were defined by International Working Group criteria¹⁸ and centrally adjudicated by an independent review committee blinded to treatment assignment. Stable disease was defined as not meeting criteria for any other treatment response (ie, CR, CRi, PR, disease progression, or treatment failure [early death]). Rates of event-free survival (events were progressive disease, relapse after CR or CRi, and death) and relapse-free survival were assessed. Red blood cell (RBC) and platelet transfusion independence (TI), defined as no transfusions for 56 consecutive days on study, was assessed for patients who were transfusion-dependent at baseline (≥ 1 transfusion in the 56 days before study start) and for patients who were TI at baseline and remained TI.

Prospective exploratory end points included OS comparisons within the CCR preselection subgroups. Post hoc multivariate efficacy analyses examined treatment effects on OS adjusted for selected baseline demographic and disease covariates and adjusted for the use of subsequent AML therapy. A separate post hoc analysis evaluated the effect of response (CR) on OS in the azacitidine and CCR groups.

Health-related quality of life (HRQoL) was assessed by using the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), which was to be completed on day 1 of cycle 1 (baseline), every other cycle thereafter, and at the final study visit. HRQoL end points were changes from baseline scores in the Fatigue domain (primary) and in the Physical Functioning, Global Health Status, and Dyspnea domains (secondary) of the QLQ-C30. A 10-point change from baseline was prespecified as the minimally important difference. The HRQoL-evaluable population included patients with a baseline and at least 1 postbaseline assessment. HRQoL was evaluated through cycle 9 because of subsequent small cohort sizes.

Safety

The safety population included all patients who received at least 1 dose of study drug and had at least 1 safety assessment thereafter. Treatment-emergent

Table 1. Demographics and disease characteristics at baseline

Characteristic	Individual CCR arms									
	Azacitidine (n = 241)		BSC only (n = 45)		LDAC (n = 158)		IC (n = 44)		Combined CCR (n = 247)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years										
Median		75		78		75		70.5		75
Min-max		64-91		67-89		65-88		65-81		65-89
≥75	138	57.3	32	71.1	83	52.5	12	27.3	127	51.4
Male gender	139	57.7	29	64.4	94	59.5	26	59.1	149	60.3
Geographic region										
Western Europe/Israel	116	48.1	26	57.8	74	46.8	22	50.0	122	49.4
North America/Australia	45	18.7	13	28.9	29	18.4	5	11.4	47	19.0
Eastern Europe	46	19.1	0		37	23.4	7	15.9	44	17.8
Asia	34	14.1	6	13.3	18	11.4	10	22.7	34	13.8
AML classification										
Not otherwise specified	153	63.5	22	48.9	95	60.1	26	59.1	143	57.9
With myelodysplasia-related changes	75	31.1	20	44.4	50	31.6	13	29.5	83	33.6
With therapy-related myeloid neoplasms	8	3.3	2	4.4	9	5.7	1	2.3	12	4.9
With recurrent genetic abnormalities*	5	2.1	1	2.2	4	2.5	4	9.1	9	3.6
Prior MDS										
Yes	49	20.3	11	24.4	23	14.6	4	9.1	38	15.4
Secondary	3	1.2	0		3	1.9	0		3	1.2
No	192	79.7	34	75.6	135	85.4	40	90.9	209	84.6
BM blasts†‡										
Median		70		76		74		70		72
Min-max		2-100		9-100		4-100		6-100		2-100
>50%	173	71.8	36	80.0	128	81.0	29	65.9	193	78.1
ECOG PS										
0-1	186	77.2	30	66.6	123	77.9	36	81.8	189	76.8
2	55	22.8	15	33.3	35	22.2	8	18.2	58	23.2
Cytogenetic risk group†§										
Intermediate	155	64.3	29	64.4	104	65.8	27	61.4	160	64.5
Intermediate, cytogenetically normal	113	46.9	23	51.1	65	41.1	17	38.6	105	42.5
Poor	85	35.3	16	35.5	54	34.2	15	34.1	85	34.4
WBC × 10⁹/L 										
Median		3.1		2.3		2.3		2.2		2.3
Min-max		0-33		1-23		0-73		1-90		0-90
ANC × 10⁹/L										
Median		0.3		0.3		0.3		0.3		0.3
Min-max		0-12		0-6		0-20		0-5		0-20
Hgb × 10⁹/L										
Median		95		96		93		89		93
Min-max		50-134		50-135		56-144		68-121		50-144
Platelets × 10⁹/L										
Median		52		52		54		62		56
Min-max		3-585		7-161		6-327		9-273		6-327

ANC, absolute neutrophil count; Hgb, hemoglobin; WBC, white blood cell.

*Excluding the provisional entities of AML with *NPM1* and AML with *CEBPA* mutation (molecular data not available).

†Per central review.

‡Patients were randomly assigned on the basis of local pathology assessment of baseline BM blast count, which was subsequently reviewed by the central pathologist; in a small number of cases, baseline blast count was <30% upon central review.

§Per modified NCCN Clinical Practice Guidelines, 2010 (1 azacitidine patient and 2 CCR patients were missing cytogenetic data).

||In some cases, maximum WBC values were higher than protocol exclusion criteria (WBC value of $\leq 15 \times 10^9/L$). Values shown here are the last nonmissing value before randomization, which may have been obtained after the screening WBC value used for study entry.

adverse events (TEAEs) were defined as new or worsening AEs between the time of first dose (or randomization for BSC only) to the end of the safety follow-up period: 28 days after the last dose of azacitidine or LDAC, 70 days after the last dose of IC, or the day of discontinuation and/or study closure for BSC. To account for differences in treatment exposure, the TEAE incidence rate per 100 patient-years (ie, $100 \times$ [number of patients with a given TEAE/total patient-years of treatment exposure]) was evaluated. The number of patients requiring hospitalization as a result of a TEAE, rate of hospitalization events for a TEAE per patient-year of drug exposure, and number of days hospitalized for TEAEs per patient-year of drug exposure were assessed.

Statistical analyses

The planned sample size was 480 patients (240 per treatment arm), calculated on the assumption of a median OS of 10.5 months in the azacitidine arm and 7.5 months in the CCR arm (40% improvement), with a 1% dropout rate from each treatment arm. This design required 374 deaths to demonstrate a statistically significant OS difference at a 1-sided significance level of 0.025 with at least 90% power to detect a constant hazard ratio (HR) of 0.71.

Efficacy analyses were performed for the intention-to-treat population. Survival distribution functions for each treatment arm, including 1-year survival probability, were estimated by the Kaplan-Meier method. A stratified log-rank

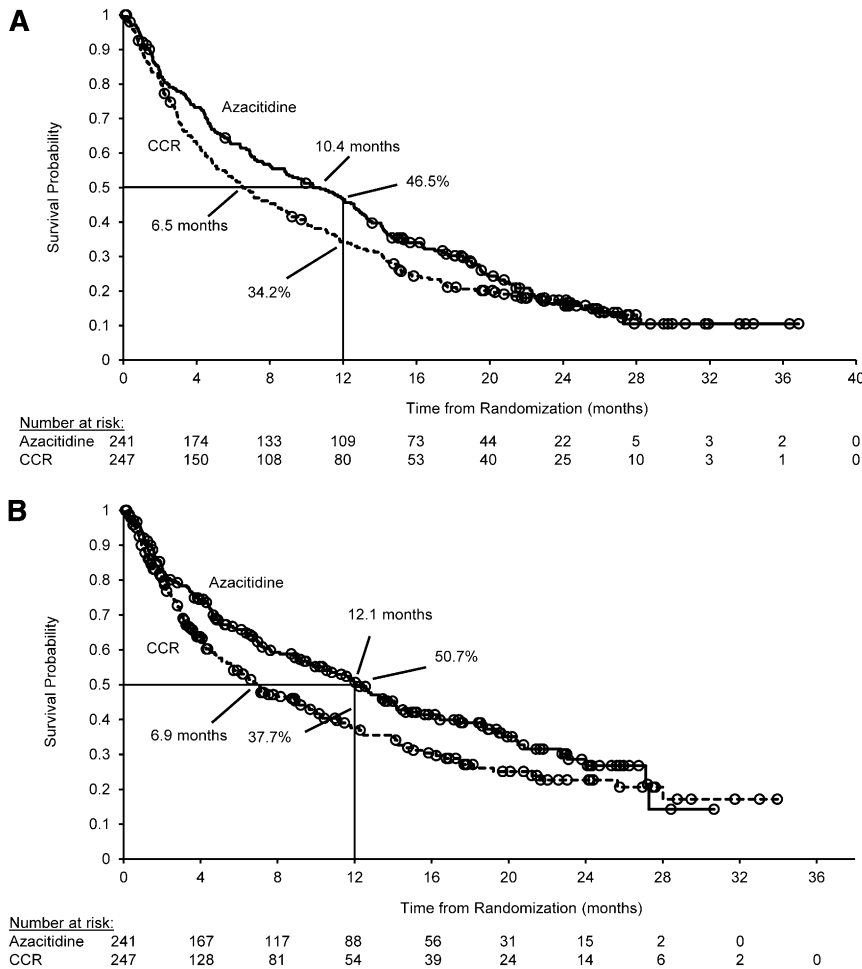


Figure 1. Primary and preplanned sensitivity analyses for OS of AML therapy. (A) Primary analysis: OS for the intention-to-treat population. Median OS was 10.4 months (95% CI, 8.0-12.7 months) for the azacitidine arm and 6.5 months (95% CI, 5.0-8.6 months) for the CCR arm. In the analysis stratified by ECOG PS and cytogenetic risk, the HR was 0.85 (95% CI, 0.69-1.03; log-rank $P = .1009$). One-year survival was 46.5% for the azacitidine arm and 34.2% for the CCR arm (difference, 12.3%; 95% CI, 3.5%-21.0%). Median follow-up for OS was 24.4 months. There were 193 deaths in the azacitidine arm (80.1%) and 201 deaths in the CCR arm (81.4%). (B) Preplanned sensitivity analysis: OS censored for subsequent AML therapy (67 azacitidine patients and 75 CCR patients were censored at the time they received subsequent AML therapy). Median OS was 12.1 months (95% CI, 9.2-14.2 months) for the azacitidine arm and 6.9 months (95% CI, 5.1-9.6) for the CCR arm. In the analysis stratified by ECOG PS and cytogenetic risk, the HR was 0.76 (95% CI, 0.60-0.96; log-rank $P = .0190$). CIs for the difference in 1-year survival probabilities were derived by using Greenwood's variance estimate. (○) Censored patient.

test, with ECOG PS and cytogenetic risk as stratification factors, compared OS between azacitidine and CCR. A stratified Cox proportional hazards model was used to generate HRs and 95% confidence intervals (CIs). Time-to-event secondary end points were analyzed by using the same methods but without stratification. Secondary analyses were not controlled for multiplicity. Exploratory analyses comparing azacitidine with individual CCRs within treatment preselection groups (IC, LDAC, or BSC) were not powered to detect statistical differences between treatments, and results should be interpreted with caution. All reported log-rank or Fisher's exact test P values for secondary and exploratory end points are nominal.

In post hoc analyses, OS with azacitidine vs CCR was estimated by using Cox proportional hazards models to adjust for variables that were preselected on the basis of their known potential to influence outcomes because of confounding and/or heterogeneity. These Cox models were adjusted for (1) selected baseline demographic and disease covariates known to influence prognosis (eg, cytogenetic risk), (2) covariates for subsequent therapy (time-varying; yes or no) and treatment-by-subsequent-therapy (time-varying) interaction, and (3) all covariates in models (1) and (2). HRs, 95% CIs, and P values were estimated from these Cox models.

Results

Patient disposition

The study was conducted between October 2010 and January 2014; the database was locked in March 2014. A total of 488 patients were randomly assigned at 98 clinical sites. Before random assignment, LDAC

was preselected for most patients (64%), whereas BSC and IC were each preselected for 18% of patients (supplemental Figure 1 available at the *Blood* Web site). Overall, 241 patients were randomly assigned to receive azacitidine and 247 to receive CCR. In the CCR arm, 45 patients were assigned to BSC, 158 to LDAC, and 44 to IC.

The most common reasons for early discontinuation were AEs (azacitidine, $n = 89$ [37%]; CCR, $n = 66$ [28%]) and death (azacitidine, $n = 53$ [22%]; CCR, $n = 58$ [24%]) (supplemental Figure 2).

Baseline demographic and disease characteristics were generally balanced between treatment arms (Table 1). More than half of all patients (54%) were age ≥ 75 years, median BM blasts at baseline were 72%, and 35% of patients had poor-risk cytogenetics. Patients received a median of 6 (range, 1-28) azacitidine treatment cycles, 2 (range, 1-3) IC cycles, and 4 (range, 1-25) LDAC cycles, and the median exposure to BSC only was 65 (range, 6-535) days. In the azacitidine and LDAC groups, 52.5% and 35.9% of patients, respectively, received 6 or more treatment cycles, and 32.2% and 17.6% received 12 or more treatment cycles. Cumulative patient-years of study drug exposure were 174.9 for azacitidine, 82.9 for LDAC, 14.1 for IC, and 9.6 (ie, time on study) for BSC.

Efficacy

Survival. The median duration of follow-up was 24.4 months. By study end, 394 deaths (80.7%) had occurred (azacitidine, $n = 193$ [80.1%]; CCR, $n = 201$ [81.4%]). Median OS for patients receiving azacitidine and CCR was 10.4 and 6.5 months, respectively; stratified HR was 0.85 (95% CI, 0.69-1.03; $P = .1009$) (Figure 1A).

Table 2. Post hoc OS analyses: results of multivariate Cox models

Covariates	HR	95% CI	P
Cox model 1, adjusted for baseline covariates*			
Treatment (azacitidine vs CCR)	0.80	0.66-0.99	.0355
Cytogenetic risk status (intermediate vs poor)	0.42	0.34-0.52	<.0001
ECOG performance status (0-1 vs 2)	0.62	0.48-0.79	.0001
BM blasts (%)†	1.01	1.01-1.01	<.0001
Preselected treatment			
BSC vs IC	1.88	1.32-2.69	.0005
LDAC vs IC	1.14	0.84-1.53	.3990
Geographic area			
Asia vs Western Europe	1.19	0.86-1.64	.2915
Eastern Europe vs Western Europe	1.73	1.30-2.31	.0002
North America/Australia vs Western Europe	1.16	0.88-1.52	.3036
Age (years)†	1.02	1.00-1.04	.0219
AML classification (AML with myelodysplasia-related changes vs all other AML types)	0.83	0.67-1.03	.0973
Cox model 2, adjusted for subsequent treatment			
Treatment (AZA vs CCR)	0.75	0.59-0.94	.0130
Subsequent therapy (yes vs no)	1.62	1.16-2.25	.0043
Treatment × subsequent therapy interaction	2.19	1.40-3.42	.0006
Cox model 3, adjusted for baseline covariates and subsequent treatment			
Treatment (azacitidine vs CCR)	0.69	0.54-0.88	.0027
Subsequent therapy (yes vs no)	1.67	1.19-2.34	.0028
Treatment × subsequent therapy interaction	2.75	1.72-4.38	<.0001
Cytogenetic risk status (intermediate vs poor)	0.41	0.33-0.51	<.0001
ECOG performance status (0-1 vs 2)	0.60	0.46-0.76	<.0001
BM blasts (%)†	1.01	1.01-1.02	<.0001
Preselected treatment			
BSC vs IC	2.37	1.64-3.42	<.0001
LDAC vs IC	1.24	0.92-1.67	.1667
Geographic area			
Asia vs Western Europe	1.15	0.84-1.59	.3804
Eastern Europe vs Western Europe	1.84	1.38-2.45	<.0001
North America/Australia vs Western Europe	1.11	0.84-1.47	.4669
Age (years)†	1.02	1.00-1.04	.0741
AML classification (AML with myelodysplasia-related changes vs all other AML types)	0.81	0.65-1.00	.0554

*Covariates included in the model were selected by using a stepwise variable selection procedure in which covariates were selected incrementally into a Cox model with the significance level for inclusion set to $P \leq .25$. After each addition of a covariate to the model, the contribution of each covariate present in the model at that step was evaluated; significance level for retention in the model was set to $P \leq .15$. Patients with a missing value for any covariate in the final model ($n = 10$ [2.0%]) were excluded from analysis. Additional covariates that were considered for inclusion but that did not meet the criterion for selection into the model were gender (male, female), WBC (continuous, log-transformed), and prior history of MDS (yes or no). †Continuous variables.

A total of 69 patients (28.6%) in the azacitidine group and 75 patients (30.4%) in the CCR group received subsequent AML therapy after discontinuing randomized study treatment. The most common subsequent therapies received in the azacitidine and CCR groups, either alone or in combination, included a cytarabine-based regimen (16.6% and 11.3%, respectively), azacitidine (4.6% and 13.0%, respectively), and/or decitabine (0.8% for each group). In the prespecified sensitivity analysis, 67 azacitidine-treated patients (the start date of subsequent treatment was not available for 2 azacitidine-treated patients) and 75 CCR-treated patients were censored at the time they began subsequent therapy. Median OS in the azacitidine arm was 12.1 vs 6.9 months in the CCR arm (stratified HR, 0.76; 95% CI, 0.60-0.96; $P = .0190$) (Figure 1B). Post hoc Cox regression analyses supported results of the sensitivity analysis; when adjusted for use of subsequent AML therapy as a time-dependent variable, azacitidine improved OS compared with

CCRs (HR, 0.75; 95% CI, 0.59-0.94; $P = .0130$) (Table 2). Baseline covariates retained in the post hoc multivariate Cox regression model were cytogenetic risk, ECOG PS, percentage of BM blasts, geographic area, age, investigator preselection of CCR, and World Health Organization AML classification (Table 2). When adjusted for these factors, the HR for OS with azacitidine vs CCR was 0.80 (95% CI, 0.66-0.99; $P = .0355$). Furthermore, when subsequent AML therapy as a time-dependent variable and baseline covariates were included in the same multivariate model, the HR for azacitidine relative to CCR was 0.69 (95% CI, 0.54-0.88; $P = .0027$) (Table 2).

One-year survival rates in the azacitidine and CCR groups were 46.5% and 34.2%, respectively, a difference of 12.3% (95% CI, 3.5%-21.0%). In the sensitivity analysis that censored patients who received subsequent AML therapy, 1-year survival proportions were 50.7% in the azacitidine arm and 37.7% in the CCR arm, a difference of 13.0% (95% CI, 3.3%-22.7%).

Univariate OS analyses showed favorable trends for azacitidine compared with CCR across all subgroups (Figure 2). Median OS in patients with poor-risk cytogenetics was 6.4 months in the azacitidine

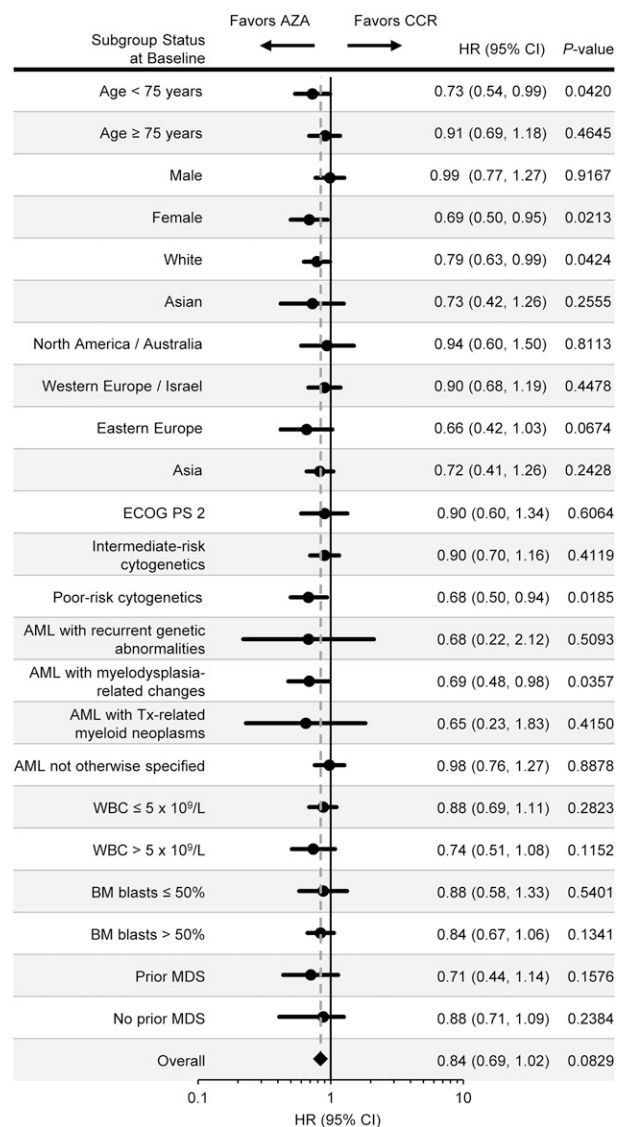


Figure 2. Overall survival in univariate analyses of patient subgroups. Patient subgroups were defined by baseline demographic and disease characteristics. The dotted line represents the overall unstratified HR for azacitidine vs CCR.

Table 3. Kaplan-Meier estimated median OS and 1-y survival comparisons within preselected treatment subgroups

	No. of patients	OS							1-y survival			
		Median		Difference		HR	95% CI	P	%	95% CI	Difference	95% CI
		Months	95% CI	Months	95% CI							
Preselected for BSC only	89											
Azacitidine	44	5.8	3.6-9.7	2.1	-1.0-5.2	0.60	0.38-0.95	.0288	30.3	17.5-44.2	11.7	-6.3-29.8
BSC	45	3.7	2.8-5.7						18.6	8.7-31.4		
Preselected for LDAC	312											
Azacitidine	154	11.2	8.8-13.4	4.8	1.7-7.9	0.90	0.70-1.16	.4270	48.5	40.3-56.2	14.5	3.5-25.5
LDAC	158	6.4	4.8-9.1						34.0	26.6-41.6		
Preselected for IC	87											
Azacitidine	43	13.3	7.2-19.9	1.1	-5.4-7.6	0.85	0.52-1.38	.5032	55.8	39.8-69.1	4.9	-16.2-26.0
IC	44	12.2	7.5-15.1						50.9	35.2-64.6		

arm and 3.2 months in the CCR arm (HR, 0.68; 95% CI, 0.50-0.94; $P = .0185$). Median OS in patients with AML-MRC who received azacitidine was 12.7 months and 6.3 months for patients who received CCR (HR, 0.69; 95% CI, 0.48-0.98; $P = .0357$).

In preplanned exploratory analyses, OS in patients who had been preselected to receive BSC alone but were randomly assigned to azacitidine was improved compared with that for patients who received BSC only (5.8 vs 3.7 months, respectively; $P = .0288$) (Table 3 and supplemental Figure 3). Patients who were preselected to receive LDAC treatment but were randomly assigned to receive azacitidine showed a 4.8-month increase in median OS compared with those who received LDAC (11.2 vs 6.4 months, respectively; $P = .4270$). Those preselected to receive IC but who received azacitidine had a median OS

similar to that of patients who received IC (13.3 and 12.2 months, respectively). Estimated 1-year survival rates within preselected groups ranged from 30.3% to 55.8% in the azacitidine groups and from 18.6% to 50.9% in the CCR groups.

Hematologic response. Overall response (CR + CRi) rates were comparable in the azacitidine (27.8%) and CCR (25.1%) arms ($P = .5384$) (Table 4). Within the CCR arm, overall response rates were 0% (BSC), 25.9% (LDAC), and 47.7% (IC). In the azacitidine and CCR treatment arms, 29.5% and 23.9% of patients, respectively, had stable disease as their best response during treatment. Higher proportions of patients who were transfusion dependent at baseline in the azacitidine treatment arm attained RBC TI (38.5% vs 27.6% in the CCR arm) or platelet TI (40.6% vs 29.3%). Total numbers of

Table 4. Treatment response and secondary end points

	Azacitidine (n = 241)		CCR (n = 247)		HR	95% CI	P
	No.	%	No.	%			
Hematologic response*							
CR + CRi	67	27.8	62	25.1			.5384
CR	47	19.5	54	21.9			.5766
CRi	20	8.3	8	3.2			.0191
CRc-20	5	2.1	14	5.7			.0589
PR	3	1.2	3	1.2			1.0
Stable disease	71	29.5	59	23.9			.1833
Progressive disease	20	8.3	20	8.1			1.0
Early death	18	7.5	29	11.7			—
No confirmed AML†	18	7.5	12	4.9			—
Not assessable‡	44	18.3	62	25.1			—
Other secondary end points							
EFS, mo§					0.87	0.72-1.05	.1495
Median		6.7		4.8			
Min-max		5.0-8.8		3.8-6.0			
RFS, mo					1.11	0.75-1.66	.5832
Median		9.3		10.5			
Min-max		6.7-12.4		7.3-12.3			
Relapse after CR or CRi	43	64.2	35	56.5			.4712
Duration of CR or CRi, mo							—
Median		10.4		12.3			
Min-max		7.2-15.2		9.0-17.0			
Transfusion independencell							
RBC	65	38.5	45	27.6			
Platelets	41	40.6	24	29.3			

CRc-20, cytogenetic complete remission in at least 20 metaphases; EFS, event-free survival; RFS, relapse-free survival.

*Hematologic response was defined by International Working Group criteria¹⁸ and was adjudicated by an independent review committee. Stable disease was defined as a clinical state that did not meet criteria for any other treatment response (eg, CR, CRi, disease progression, or treatment failure).

†Patients included on the basis of local review had <30% BM blasts at central review.

‡Patients were missing BM aspirate or hematology assessment.

§Events included treatment failure, progressive disease, relapse after CR or CRi, or death.

llNo transfusions for 56 consecutive days on study for patients who were transfusion dependent at baseline (≥ 1 transfusion in the 56 days before study start).

Table 5. Grade 3 to 4 TEAEs occurring in ≥10% of patients in any treatment group (by decreasing frequency in the azacitidine arm)

Preferred term*	Individual CCR arms							
	Azacitidine (n = 236)		BSC only (n = 40)		LDAC (n = 153)		IC (n = 42)	
	No.	%	No.	%	No.	%	No.	%
Febrile neutropenia	66	28.0	11	27.5	46	30.1	13	31.0
Neutropenia	62	26.3	2	5.0	38	24.8	14	33.3
Thrombocytopenia	56	23.7	2	5.0	42	27.5	9	21.4
Pneumonia	45	19.1	2	5.0	29	19.0	2	4.8
Anemia	37	15.7	2	5.0	35	22.9	6	14.3
Leukopenia	16	6.8	0		13	8.5	6	14.3
Hypokalemia	12	5.1	1	2.5	10	6.5	7	16.7

TEAEs were coded by using the Medical Dictionary for Regulatory Activities and were graded for severity by using the National Cancer Institute's Common Toxicity Criteria for Adverse Events v4.0.

*To be considered treatment-emergent, an AE must have been a new occurrence or the worsening of a preexisting AE.

patients in the azacitidine and CCR groups who remained RBC TI or became RBC TI on treatment were 105 (43.6%; 95% CI, 37.2%-50.1%) and 76 (30.8%; 95% CI, 25.1%-36.9%), respectively, and who remained or became platelet TI were 142 (58.9%; 95% CI, 52.4%-65.2%) and 106 (42.9%; 95% CI, 36.7%-49.3%), respectively.

Post hoc analysis to explore the potential influence of CR on OS showed that when patients who attained CR (19.5% in the azacitidine group and 21.9% in the CCR group) were excluded from analysis, median OS in the azacitidine and CCR groups was 6.9 months (95% CI, 5.1-8.9 months) vs 4.2 months (95% CI, 3.2-5.1 months; HR, 0.77; 95% CI, 0.62-0.95; stratified log-rank $P = .0170$). The estimated 1-year survival rates for patients who did not achieve CR were 33.8% in the azacitidine arm and 20.4% in the CCR arm, a difference of 13.4% (95% CI, 4.5%-22.4%).

HRQoL. The population that was evaluable for HRQoL initially comprised 291 patients (azacitidine, 157; CCR, 134). This patient subset decreased over time in both groups, but at a faster rate in the CCR arm after cycle 3, and there was large variation in QLQ-C30 responses within each treatment group. Change from baseline scores for primary and secondary domains of the QLQ-C30 generally improved over 9 treatment cycles in both arms (supplemental Table 1). No HRQoL detriment was seen with azacitidine or CCR at the group level during treatment. The few changes that met the minimally important difference threshold were Fatigue (cycles 7 and 9) and Global Health Status/QoL (cycle 9) in the CCR group.

Safety

The safety population comprised 471 patients (azacitidine, 236; CCR, 235); 5 patients randomly assigned to azacitidine and 7 patients randomly assigned to CCR did not receive study treatment, and 5 patients in the CCR arm had no post-dose safety assessment. Most patients experienced a TEAE during the study (99.2% in the azacitidine arm and 100% in the CCR arm). TEAEs leading to study drug-dose reduction occurred for 3.4%, 1.3%, and 4.8% of patients in the azacitidine, LDAC, and IC arms, respectively; TEAEs leading to dose interruption occurred in 49.2%, 39.9%, and 9.5% of patients, respectively. Drug-related TEAEs leading to study discontinuation occurred in 22 patients (9.3%) in the azacitidine arm, 20 patients (13.1%) in the LDAC arm, and 5 patients (11.9%) in the IC arm; those that occurred in >1 patient in the azacitidine and LDAC arms, respectively, included pneumonia (3.0% and 2.0%), febrile neutropenia (1.3% in each arm), pyrexia (0% and 1.3%), and sepsis (0% and 1.3%).

Among the most frequent drug-related TEAEs in the azacitidine, LDAC, and IC groups, respectively, were nausea (27.1%, 22.2%, and 42.9%), neutropenia (19.9%, 22.9%, and 31.0%), and thrombocytopenia (17.4%, 22.2%, and 21.4%) (supplemental Table 2). Accounting for patient-years of treatment exposure, incidence rates of anemia, febrile neutropenia, neutropenia, and thrombocytopenia were substantially lower in the azacitidine arm than in the LDAC and IC arms (supplemental Table 3). Grades 3 and 4 hematologic TEAEs occurred with approximately equal frequency in the azacitidine and LDAC groups (Table 5). In both the azacitidine and LDAC groups, hematologic TEAEs (any grade) decreased in frequency as treatment continued (supplemental Table 4). The most frequent serious TEAEs occurred with similar frequency in the azacitidine, LDAC, and IC arms and included febrile neutropenia (25.0%, 24.8%, and 24.3%, respectively), pneumonia (20.3%, 19.0%, and 14.9%), and pyrexia (10.6%, 10.5%, and 8.9%) (supplemental Table 5). Notably, 30-day mortality rates in the azacitidine and CCR arms were 6.6% and 10.1%, respectively, and 60-day mortality rates were 16.2% and 18.2%.

In the azacitidine and CCR arms, 165 patients (69.9%) and 157 patients (66.8%), respectively, were hospitalized for a TEAE. Rates of hospitalization for TEAEs per patient-year of drug exposure in the azacitidine and CCR arms were 1.96 and 2.39, respectively (relative risk, 0.82; 95% CI, 0.70-0.960; $P = .0083$). Times spent in the hospital for TEAEs were 28.5 days and 38.3 days per patient-year of drug exposure in the azacitidine and CCR arms, respectively (relative risk, 0.74; 95% CI, 0.71-0.78; $P < .0001$).

Discussion

This randomized trial in older patients (median age, 75 years) with newly diagnosed AML compared subcutaneous azacitidine with commonly used treatments for AML (LDAC, intensive chemotherapy, or BSC alone) and showed that azacitidine was associated with a clinically meaningful improvement in median OS (10.4 vs 6.5 months) and 1-year survival (46.5% vs 34.2%) vs CCR, although the primary end point was not met (stratified HR, 0.85; 95% CI, 0.60-1.03; $P = .1009$), influenced by the convergence of the Kaplan-Meier curves at around 22 months. Such convergence is not unexpected in a disease with no cure and a patient population with poor OS.

Azacitidine was generally well tolerated; more than half the azacitidine-treated patients received 6 or more treatment cycles, and one-third received 12 or more cycles. TEAEs occurred with comparable frequency and were similar to those reported for azacitidine in patients with MDS, and similar reductions in hematologic toxicity were observed as azacitidine treatment continued.¹⁹⁻²¹ Rates and days of hospitalization for TEAEs by study drug exposure were lower in the azacitidine arm compared with CCR. During treatment, azacitidine and CCR were associated with general improvement in HRQoL, with improvement exceeding the threshold for a minimally important difference with CCR at cycles 7 and 9 for Fatigue and at cycle 9 for Global Health Status. Importantly, there was no meaningful HRQoL deterioration in the primary or secondary QLQ-C30 domains during treatment in either arm. Interpreting HRQoL outcomes is challenging because the population evaluable for HRQoL was smaller than the intention-to-treat population. Consequently, there is a risk that the protection of randomization was lost as the evaluable groups became smaller in number, which could introduce bias to the results.

Because subsequent therapy is a known confounding factor in survival studies,²² a sensitivity analysis censoring patients who received subsequent antileukemic treatment was prospectively included in the

study design. In this analysis, median OS with azacitidine was extended by more than 5 months vs CCR (12.1 vs 6.9 months; stratified HR, 0.76; 95% CI, 0.60-0.96; $P = .0190$). This finding is supported by results of the post hoc Cox model that controlled for use of subsequent treatment, showing a 25% reduced risk of death in the azacitidine arm. In the multivariate Cox analysis adjusting for baseline disease and demographic characteristics as well as subsequent treatment, azacitidine reduced risk of death by 31% vs CCR (HR, 0.69; 95% CI, 0.54-0.88; $P = .0027$).

Univariate subgroup analyses showed that the overall HR for OS was within the 95% CIs for the HRs for each subgroup comparison. Although univariate analysis suggested improved OS in some azacitidine-treated demographic cohorts (eg, females), these characteristics dropped out of the multivariate Cox models, which retained only the most significant influences on OS as covariates, including cytogenetic risk, ECOG PS, and BM blast count. Remarkably, azacitidine was superior to CCR in subgroups with biologically poor risk factors. IC and LDAC provide no OS benefit in older patients with AML and poor cytogenetics^{5,10,12,23}; median OS with these treatments in this population was approximately 2 to 3 months.¹² In patients with poor-risk cytogenetics in this study, median OS with azacitidine (6.4 months) was twofold higher than that of patients who received CCR (3.2 months) and was nominally significant vs CCR in both univariate and multivariate analyses. As the only AML treatment yet shown to improve OS in older patients with poor-risk cytogenetics, azacitidine may be the treatment of choice for these patients. Azacitidine was also associated with improved OS in patients with AML-MRC, consistent with findings that azacitidine significantly improves OS in patients with higher-risk MDSs.²¹

The individual CCR preselection groups likely reflect 3 different patient populations with regard to performance status, frailty, and comorbidities, which play an important part in selection of treatment of older patients with AML. As might be expected, patients preselected to receive IC had the best OS, followed by patients in the LDAC preselection group, and patients preselected to receive BSC only had the worst OS outcomes. Although the study was not powered to demonstrate significant differences for comparisons within preselection groups, such comparisons allow assessment of treatment effects in patients with generally similar prognoses and clinical features because preselection of the preferred CCR occurred before randomization. Patients preselected to receive IC who received azacitidine or IC had comparable OS (13.3 vs 12.2 months, respectively) and 1-year survival (55.8% vs 50.9%). Thus, low-intensity azacitidine treatment may benefit older patients with AML who, although they are eligible for IC, choose to forego intensive therapy. In the LDAC preselection group, azacitidine demonstrated an improvement in median OS of 4.8 months (11.2 vs 6.4 months; $P = .4270$) and a 1-year survival advantage of 14.5% vs LDAC. Notably, in this study, patients received a median of 4 LDAC treatment cycles, which is double the reported median LDAC exposure in most large clinical trials.^{4,6,12} A survival improvement with azacitidine was also seen in patients preselected to receive BSC alone (5.8 vs 3.7 months).

Azacitidine has demonstrated an OS benefit in patients with higher-risk MDS in the absence of CR.²⁴ Similarly, in these older patients with AML, a nominally significant increase in OS was seen in azacitidine-treated patients who did not achieve CR (6.9 vs 4.2 months with CCR; $P = .0170$).

Decitabine was evaluated in a trial with 485 patients age ≥ 65 years with AML and $\geq 20\%$ BM blasts randomly assigned to receive either decitabine or physicians' choice of treatment (LDAC or BSC).⁴ The primary analysis for that trial demonstrated a nonsignificant survival increase with decitabine (7.7 vs 5.0 months), whereas a later unplanned

analysis at ~ 3 years demonstrated a nominally significant P value for unchanged OS outcomes. Although cross-trial comparisons are problematic because of differences in populations, comparator arms, and LDAC regimens, the median OS in the azacitidine arm of this trial of 10.4 months is encouraging.

Combination treatment regimens may further improve outcomes for older patients with AML. Results of early trials of azacitidine in combination with lenalidomide,^{25,26} panobinostat,²⁷ or sorafenib²⁸ as first-line or salvage therapy in older patients with AML are promising, with overall response rates of approximately 30% to 40%. Larger studies are needed to confirm these findings.

In conclusion, results of this study suggest that azacitidine may provide an important additional treatment option for older patients with newly diagnosed AML.

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Authorship

Contribution: H. Dombret, J.F.S., R.M.S., M.D.M., and H. Döhner contributed to study design; H. Dombret, J.F.S., A.B., A.W., D.S., J.H.J., R.K., J.C., A.C.S., A.C., C.R., I.S., T.B.d.C., H.K.A.-A., G.M., J.F., R.N., and H. Döhner enrolled study participants, clinically managed study participants, and collected and reviewed data; H.M., S.S., L.M.L., and C.L.B. analyzed the data and L.M.L. provided statistical support; and all authors participated in manuscript development and revision. The primary author (H. Dombret) is responsible for manuscript content and gave approval to submit the manuscript.

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