Original Article

Results of a Randomized Phase 3 Study of Oral Sapacitabine in Elderly Patients with Newly Diagnosed Acute Myeloid Leukemia (SEAMLESS)

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BACKGROUND: Acute myeloid leukemia (AML) is fatal in elderly patients who are unfit for standard induction chemotherapy. The objective of this study was to evaluate the survival benefit of administering sapacitabine, an oral nucleoside analogue, in alternating cycles with decitabine, a low-intensity therapy, to elderly patients with newly diagnosed AML. **METHODS:** This randomized, open-label, phase 3 study (SEAMLESS) was conducted at 87 sites in 11 countries. Patients aged ≥70 years who were not candidates for or chose not to receive standard induction chemotherapy were randomized 1:1 to arm A (decitabine in alternating cycles with sapacitabine) received 1-hour intravenous infusions of decitabine 20 mg/m^2 once daily for 5 consecutive days every 8 weeks (first cycle and subsequent odd cycles) and sapacitabine 300 mg twice daily on 3 consecutive days per week for 2 weeks every 8 weeks (second cycle and subsequent even cycles) or to control arm C who received 1-hour infusions of decitabine 20 mg/m^2 once daily for 5 consecutive days every 4 weeks. Prior hypomethylating agent therapy for preexisting myelodysplastic syndromes or myeloproliferative neoplasms was an exclusion criterion. Randomization was stratified by antecedent myelodysplastic syndromes or myeloproliferative neoplasms, white blood cell count (<10 × 10^9/L and ≥10 × 10^9/L), and bone marrow blast percentage (≥50% vs <50%). The primary end point was overall survival (OS). Secondary end points were the rates of complete remission (CR), CR with incomplete platelet count recovery, partial remission, hematologic improvement, and stable disease along with the corresponding durations, transfusion requirements, number of hospitalized days, and 1-year survival. The trial is registered at ClinicalTrials.gov (NCT01303796). **RESULTS:** Between October 2011 and December 2014, 482 patients were enrolled and randomized to receive decitabine administered in alternating cycles with sapacitabine (study arm, n = 241) or decitabine monotherapy (control arm, n = 241). The median OS was 5.9 months on the study arm versus 5.7 months on the control arm (P = .8902). The CR rate was 16.6% on the study arm and 10.8% on the control arm (P = .1468). In patients with white blood cell counts <10 × 10^9/L (n = 321), the median OS was higher on the study arm versus the control arm (8.0 vs 5.8 months; P = .145), as was the CR rate (21.5% vs 8.6%; P = .0017). **CONCLUSIONS:** The regimen of decitabine administered in alternating cycles with sapacitabine was active but did not significantly improve OS compared with decitabine monotherapy. Subgroup analyses suggest that patients with baseline white blood cell counts <10 × 10^9/L might benefit from decitabine alternating with sapacitabine, with an improved CR rate and the convenience of an oral drug. These findings should be prospectively confirmed. ***Cancer* 2021;0:1-11**. © *2021 American Cancer Society*.

KEYWORDS: acute myeloid leukemia (AML), decitabine, hypomethylation, sapacitabine, therapy.

INTRODUCTION

Acute myeloid leukemia (AML) is a life-threatening disease characterized by the accumulation of clonal neoplastic hematopoietic precursor cells and impaired normal hematopoiesis. If untreated, patients usually die of infection or bleeding in a matter of weeks.[1]

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AML occurs more commonly in the older population. The median age at diagnosis is 64 years in Europe and 68 years in the United States.[2,3] Standard therapy is intensive induction chemotherapy, consisting of an anthracycline and cytarabine. Despite a complete remission (CR) rate of 40% to 50%, intensive induction chemotherapy does not benefit most older, and particularly elderly, patients.[4] The 5-year survival rate for patients with AML was 46.6% for those aged <65 years but only 7.9% for those aged ≥65 years.[5] The poor outcomes of older patients are caused by patient-related and disease-related factors. Advanced age, poor performance status, comorbidities, and organ dysfunction significantly decrease the tolerance of cytotoxic therapy. Antecedent myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN), a high peripheral white blood cell (WBC) count, cytogenetic risk, and certain genetic mutations, such as *TP53*, diminish the efficacy of cytotoxic therapy.

To address poor tolerance of intensive induction chemotherapy, the European Medicines Agency approved decitabine in 2012 as a low-intensity therapy for patients aged ≥65 years who are not considered candidates for standard, intensive induction chemotherapy by assessment of their treating physicians. The approval was based on a 2.7-month improvement in median overall survival (OS) (7.7 vs 5.0 months) on the decitabine arm versus a control arm of low-dose cytarabine or best supportive care in a randomized phase 3 study. Secondary end points of response rate and progression-free survival and a tertiary end point of event-free survival were also in favor of decitabine.[2]

Sapacitabine, 1-(2-C-cyano-2-deoxy-β-D-arabino-pentafuranosyl)-N^4-palmitoylcytosine (also known as CYC682 or CS-682), is a rationally designed deoxycytidine analogue with a unique mechanism of action.[7] After oral administration, sapacitabine is converted to 2′-C-cyano-2′-deoxy-β(-D-arabino-pentafuranosyl) cytosine (CNDAC). After phosphorylation to the triphosphate form and incorporation into DNA, replication is not inhibited at cytotoxic concentrations in contrast to cytarabine and clofarabine. Instead, after further polymerization, the strong electrophilic properties of the cyano group of CNDAC cause a rearrangement of the nucleotide to a form that lacks a 3′-hydroxyl moiety. This results in a single-strand DNA break that is repaired only to a small extent by the transcription-coupled nucleotide excision pathway. On a subsequent round of DNA replication, unrepaired single-strand DNA breaks are converted to double-strand breaks, causing cell death.[8,9] The palmitoyl side chain on CNDAC allows for improved oral absorption of sapacitabine and protects the N^4 amino group from deamination, which is a major route of inactivation for other nucleoside analogues, such as cytarabine, azacitidine, decitabine, and gemcitabine.[10]

Sapacitabine demonstrated single-agent activity in relapsed or refractory AML with a well tolerated safety profile.[11] Among 35 patients with relapsed or refractory AML enrolled on a phase 1 study of sapacitabine, 8 patients (23%) responded, with 3 CRs, 2 CRs with incomplete platelet count recovery (CRp), and 3 CRs with incomplete hematologic recovery. All 8 patients had been previously treated with other nucleoside analogues, such as cytarabine, decitabine, clofarabine, or fludarabine. A follow-on, large, randomized, phase 2 study of single-agent sapacitabine evaluated 3 different dosing schedules in elderly patients aged ≥70 years with newly diagnosed AML and established the schedule of sapacitabine administered orally twice daily for 3 days each week for 2 weeks of a 28-day cycle as the schedule with the better efficacy profile.[12] To minimize the overlapping toxicities of myelosuppression, a pilot study was designed to evaluate decitabine administered in alternating cycles with sapacitabine in the same population of elderly patients with AML. Among 23 patients who received this regimen, 8 (35%) responded, including 3 who had a CR, 3 who had a partial remission (PR), and 2 who had a major hematologic improvement (HI) in platelets.[13] The current phase 3 study was designed to evaluate the survival benefit of decitabine administered in alternating cycles with sapacitabine versus decitabine monotherapy in elderly patients with newly diagnosed AML.

MATERIALS AND METHODS

Study Design and Participants

This was a randomized, open-label, global phase 3 study conducted in 13 countries after approval by an institutional review board or ethics committee. All patients provided a written informed consent form in accordance with institutional guidelines at participating centers and the ethical principles of the Declaration of Helsinki.

Eligible patients were aged ≥70 years with newly diagnosed AML who were considered unsuitable candidates for intensive induction chemotherapy by assessment of their treating physician. Patients who were suitable candidates but were unwilling to undergo induction chemotherapy could also participate in the study. Patients who had received chemotherapy (except hydroxyurea) or hypomethylating agents for preexisting MDS or MPN were excluded.

Other eligibility criteria included: an Eastern Cooperative Oncology Group performance status of 0 to 2, adequate hepatic function (bilirubin ≤1.5 times the upper limit of normal [ULN] and alanine aminotransferase ≤2 times the ULN), and adequate renal function (creatinine ≤1.5 times the ULN). Exclusion criteria included acute promyelocytic leukemia or extramedullary myeloid tumor without bone marrow involvement; suspected or known central nervous system involvement by leukemia; and uncontrolled illnesses, including symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, cancer requiring systemic therapy in the past 6 months, infection, or HIV. Patients receiving intravenous antibiotics were allowed if infections were under adequate control.

This study initially included a sapacitabine monotherapy arm (arm B), which was removed after a pilot study suggested that decitabine alternating with sapacitabine might be the best possible experimental arm because its 60-day mortality rate of 12% was lower than that of single-agent sapacitabine observed in the phase 2 study and lower than the rates reported in the literature for intensive induction therapy, including clofarabine, decitabine, azacitidine, or low-dose cytarabine. The protocol was amended after receiving agreement from the US Food and Drug Administration according to the Special Protocol Assessment procedure.

Randomization and Masking

There was a lead-in phase to confirm the safety and tolerability of the treatment regimen of decitabine alternating with sapacitabine before opening the randomization phase.[14] Lead-in patients were not randomized and hence were not counted in the intent-to-treat (ITT) population.

Randomization was implemented at the International Drug Development Institute (Louvain-la-Neuve, Belgium) using a fully validated, interactive web-based randomization service. Patients were randomized centrally to 1 of the treatment arms by the method of permuted blocks using the following stratification factors: presence of antecedent MDS or MPN (yes vs no), baseline peripheral WBC count (<10 vs $\geq 10 \times 10^9$/L), and baseline bone marrow blast percentage (≥50% vs <50%). These stratification factors were chosen because they were reported to be prognostic factors for survival in patients with AML.[15,16] Because this was an open-label study, the investigators and patients were not masked.

Procedures

Treatments were administered in 28-day cycles. Patients assigned to the study arm of decitabine in alternating cycles with sapacitabine (arm A) received 1-hour intravenous infusions of decitabine 20 mg/m^2 once daily for 5 consecutive days every 8 weeks (first cycle and subsequent odd cycles) and sapacitabine 300 mg twice daily on 3 consecutive days per week for 2 weeks every 8 weeks (second cycle and subsequent even cycles). Patients assigned to the control arm (arm C) received 1-hour infusions of decitabine 20 mg/m^2 once daily for 5 consecutive days every 4 weeks.

Dosing on day 1 of each treatment cycle and sapacitabine dosing on day 8 of a sapacitabine treatment cycle did not start until clinically significant and drug-related nonhematologic toxicities had resolved to grade ≤1 or baseline. After recovery, a dose reduction of sapacitabine was required for grade 3 and 4 drug-related nonhematologic toxicities caused by sapacitabine. Dose reductions of sapacitabine for hematologic toxicities were guided by findings from bone marrow and the time to absolute neutrophil count and platelet count recovery. A dose reduction of 50 mg twice daily was required for a delay in blood count recovery to the best level on study beyond day 42 if bone marrow blasts decreased ≥25% from baseline but remained >10%. If blasts were ≤10%, dose reduction of 100 mg twice daily was required for persistent cytopenias. In addition, temporary dose reduction of sapacitabine was allowed for grade 2 toxicity in a frail patient. Decitabine dose reduction was guided by the commercial label or package insert approved by regulatory agencies.

Patients could continue treatment indefinitely as long as there was no evidence of clinically significant AML progression. After discontinuation from treatment, patients were contacted by the study staff for survival status approximately every 3 months.

A bone marrow biopsy and/or aspirate was performed at baseline, before starting cycle 2, and as clinically indicated thereafter. Adverse events (AEs) were graded according to National Cancer Institute Common Terminology for Adverse Events (CTCAE) version 4.0 and the relationship to decitabine or sapacitabine were determined by investigators. Safety was assessed using the 30-day mortality rate, AEs, serious AEs (SAEs), and OS.

Outcomes

The primary end point was OS, which was measured from the date of randomization to the date of death or was censored at the last follow-up date when patients were known to be alive. Secondary end points were the rates of CR, CRp, PR, HI, and stable disease (SD) and the corresponding durations, transfusion requirements, number of hospitalized days, and 1-year survival.

A CR was defined as normalization of the blood and bone marrow with ≤5% bone marrow blasts, independence of transfusions, a granulocyte count ≥1.0 × 10^9/L, and a platelet count ≥100 × 10^9/L.[17,18] A PR was defined by the same blood count as a CR but with a decrease ≥50% in bone marrow blasts to a level of ≥6%. A CRp was defined the same as a CR but without platelet count recovery to ≥100 × 10^9/L. HI was defined according to the International Working Group criteria.[19] SD was defined as no evidence of clinically significant progression for over 16 weeks without achieving at least HI. Transfusion requirement for each patient was defined as the number of units of packed red blood cells (PRBCs) and/or platelet transfusions administered per 8-week period before the first dose of study drug and through the date of treatment discontinuation. Hospitalized days were the days spent in the hospital for receiving decitabine or sapacitabine and/or the treatment of a medical condition regardless of its relationship to study drugs.

Survival analyses were performed in subgroups of patients with de novo AML versus an antecedent MDS or MPN, those with baseline WBC counts ≥10 versus <10 × 10^9/L, those with baseline bone marrow blast percentages ≥50% versus <50%, and with unfavorable-risk cytogenetics according to the Southwest Oncology Group (SWOG)[17] versus without unfavorable-risk cytogenetics. These subgroups were selected because differences in treatment outcomes have been reported in the literature.[15,16]

The following baseline patient and disease characteristics, which might be potentially related to survival, were selected as covariates for exploratory analysis of OS: age, Eastern Cooperative Oncology Group performance status, treatment choice of low-intensity therapy as recommended by the investigator, significant concomitant medical illness measured by the Hematopoietic Cell Transplantation-Comorbidity Index (HCTCI) score,[20] type of AML, time since AML diagnosis, peripheral WBC count, absolute neutrophil count, platelet count, hemoglobin level, bone marrow blast percentage, bone marrow cytogenetic risk according to the SWOG, units of PRBCs transfused, and units of platelets transfused.

Statistical Analysis

The planned sample size was 485 patients, with approximately 243 per arm over an estimated accrual period of 24 months, requiring ≥424 events to detect a 27.5% reduction in the risk of death with ≥90% power and a significance level of .0249 (1-sided). The median survival was assumed to be 8 months on arm C. An interim analysis was planned when approximately 212 deaths were observed. A Pampallona-Tsiatis boundary with power equal to 0.2 was used for the interim analysis. The boundary for futility would be reached if the *P* value of the 1-sided test comparing the OS of arm A versus arm C was >.287, ie, hazard ratios >0.926 or a benefit of <0.6 month in median survival.[21,22]

To prevent premature early termination, the Data Safety Monitoring Board (DSMB) was guided by a conservative criterion requiring a (1-sided) *P* value < .0001 for extreme evidence of superiority of arm A relative to arm C on OS while monitoring the trial.

The ITT population consisted of all randomized patients. The primary analysis compared OS between arm A and arm C in the ITT population. The safety population comprised all patients who had received at least 1 dose of sapacitabine or decitabine. OS was measured from the date of randomization to the date of death. Patients who were alive at study closure were censored at the last follow-up date when they were known to be alive. The distribution of OS and 1-year survival was estimated using the method of Kaplan and Meier. A log-rank analysis stratified by the presence of antecedent MDS or MPN (yes vs no), baseline peripheral WBC count (<10 vs ≥10 × 10^9/L), and baseline bone marrow blast percentage (≥50% vs <50%) was used to compare OS between arm A and arm C.

The response rates of CR, CRp, PR, HI, or SD were compared between the 2 arms using the Fisher exact test. The mean number of transfusion-free weeks and the mean number of units of PRBCs and platelet transfusions were compared between the 2 arms using the 2-sample Wilcoxon test. The mean number of hospitalized days was compared between the 2 treatment arms using the Wilcoxon test. Days alive and out of hospital over the first 90, 180, 240, and 360 days after randomization while on study for each patient were compared between arms using the Wilcoxon test. The percentage of days alive and out of hospital was defined as the number of days alive and out of hospital divided by the number of days alive on study for each patient and also was compared among the 2 treatment arms at the above time points.

A multivariate Cox proportional hazard model was used for survival analysis in subgroups. The SIDES (Subgroup Identification based on Differential Effect Search) methodology was used in the exploratory analysis of predictive factors for survival. The optimal cutoffs for each covariate were based on the standard differential-effect slitting criterion, which aimed at maximizing the difference between the test statistics in the subgroups

TABLE 1. Patient Characteristics

Characteristic	No. of Patients (%)	
	Arm A-ITT: Decitabine/Sapacitabine, n = 241	Arm C-ITT: Decitabine, n = 241
Age (years, Median [range]	78 [70-92]	77 [70-92]
70-74	77 (32.0)	70 (29.0)
75-79	69 (28.6)	99 (41.1)
≥80	95 (39.4)	72 (29.9)
Sex		
Men	139 (57.7)	146 (60.6)
Women	102 (42.3)	95 (39.4)
ECOG PS		
0-1	185 (76.8)	172 (71.4)
2	48 (19.9)	58 (24.1)
HCTCI		
0-2	124 (51.5)	129 (53.5)
≥3	117 (48.5)	112 (46.5)
Low-intensity therapy recommended by investigator	223 (92.5)	219 (90.9)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HCTCI, Hematopoietic Cell Transplantation-Comorbidity Index[22]; ITT, intent-to-treat population.

associated with a particular split.[23] A 2-sided *P* value < .1 was used to select the significant factors to be included in the multivariate analyses. A 2-sided *P* value < .05 was considered significant. Statistical computations were done using the SAS statistical software package (SAS 14.1).

Role of Funding Source

The sponsor of the study, H.M.K., and M.B. designed the trial. Clinical data were collected by the investigators who had full access to raw data of their sites. Data were analyzed and interpreted by the sponsor and the authors. The corresponding author (H.M.K.) had full access to the data and the final responsibility for the decision to submit the article for publication.

RESULTS

Between October 2011 and December 2014, 482 patients were randomized to receive decitabine administered in alternating cycles with sapacitabine (arm A) or decitabine monotherapy (arm C) at 87 sites in 11 countries.

At the planned interim analysis for futility in December 2014, the DSMB found that the planned futility boundary was crossed after 247 events had occurred and it would be unlikely for the study to reach a statistically significant improvement in survival. The DSMB found no safety concerns in 470 randomized patients and recommended that all recruited patients stay on their assigned treatment to complete the study. Enrollment to the study was stopped shortly after the DSMB meeting.

The primary analysis of OS was based on 424 projected deaths. There were 444 deaths at the time of clinical data cutoff in June 2017, which was approximately 2.5 years after the last patient was randomized in December 2014.

The efficacy analysis was based on the ITT population of 241 patients randomized to arm A and 241 patients randomized to arm C. Thirteen patients did not receive treatment, including 5 on arm A and 8 on arm C. The safety analysis was based on 469 patients, including 236 on arm A and 233 on arm C.

Patient characteristics were similar between treatment arms in the ITT population, except that there were more patients aged ≥80 years on arm A than on arm C (Table 1).[20] Disease characteristics were similar between the treatment arms (Table 2).

Survival

At the time of the final analysis, 444 patients had died, including 226 on arm A and 218 on arm C. The median OS in the ITT population was 5.9 months in arm A (95% CI, 4.7-8.0 months) versus 5.7 months in arm C (95% CI, 4.9-8.2 months), which did not reach statistical significance (Fig. 1). One-year survival was similar between the arms, 33.6% on arm A (95% CI, 27.7%-39.6%) and 34.7% on arm C (95% CI, 28.8%-40.8%).

In an exploratory subgroup analysis using a multivariate Cox proportional hazard model, a trend of improved survival favoring arm A was observed in patients with peripheral WBCs $<10 \times 10^9$/L. The opposite was observed in the subgroup with WBCs $\geq 10 \times 10^9$/L, for which longer survival was observed on arm C (Fig. 2).

Responses

Forty patients achieved CR on arm A (16.6%; 95% CI, 12.1%-21.9%), and 26 achieved CR on arm C (10.8%;

TABLE 2. Disease Characteristics

Characteristic	No. of Patients (%)	
	Arm A-ITT: Decitabine/ Sapacitabine, n = 241	Arm C-ITT: Decitabine, n = 241
Type of AML		
De novo	163 (67.6)	154 (63.9)
Preceded by AHD	66 (27.4)	70 (29)
Treatment-related	12 (5.0)	17 (7.1)
WBCs, $\times 10^9$/L		
<10	157 (65.1)	162 (67.2)
≥10	84 (34.9)	79 (32.8)
Bone marrow blasts, %		
<50	123 (51.0)	131 (54.4)
≥50	118 (49.0)	110 (45.6)
Cytogenetic risk: SWOG		
Favorable	6 (2.5)	2 (0.9)
Intermediate	120 (49.8)	129 (53.5)
Unfavorable	100 (41.5)	94 (39.0)
Unknown	1 (0.4)	0 (0.0)
Failed to grow/not done or missing	14 (5.8)	16 (6.6)

Abbreviations: AHD, antecedent hematologic disorder; AML, acute myeloid leukemia; ITT, intent-to-treat population. SWOG, Southwest Oncology Group; WBC, white blood cell count.

95% CI, 7.2%-15.4%). The difference did not reach statistical significance. The median time to response was 2.6 months on arm A and 3.4 months on arm C. The 10.8% CR rate on arm C was consistent with that reported in the DACO-016 study (15.7%) (ClinicalTrials.gov identifier NCT00260832) considering that this study enrolled more patients who were aged ≥80 years and included patients with WBCs $>40 \times 10^9$/L who were excluded from the DACO-016 study (Table 3).

In the subgroup with WBCs $<10 \times 10^9$/L, significantly more CRs occurred on arm A compared with arm C, whereas the opposite was observed in the subgroup with WBCs $\geq 10 \times 10^9$/L, consistent with the trends of OS in these subgroups (Table 4).

Transfusion and Hospitalization

Transfusion and hospitalization requirements for patients who received at least 1 dose of study drug were similar between treatment arms (Table 5).

Predictive Factors for OS and Response Rate

An exploratory analysis using the SIDES methodology[23] found that patients with peripheral WBCs $<4.1 \times 10^9$/L; SWOG favorable-risk, intermediate-risk, or unknown-risk cytogenetics; or HCTCI scores ≤2 benefitted the most by being treated with decitabine administered in alternating cycles with sapacitabine as measured by OS, 1-year survival, and the rate of CR/CRp.

Toxicity

Two hundred thirty-six patients on arm A and 233 on arm C received a median of 3 treatment cycles. The median duration of treatment was 3.5 months for arm A and 3.3 months for arm C, with 16.9% patients on arm A and 15.5% on arm C having received ≥12 cycles. Dose reductions for decitabine were similar on both arms: 18.2% of patients on arm A had a dose reduction for sapacitabine.

Four hundred sixty-eight patients (99.8%) reported at least 1 AE. The most common grade 3 or 4 AEs, regardless of causalities, were similar between the arms (Table 6).

The most common SAEs were pneumonia (arm A, 26.7%; arm C, 27.9%), febrile neutropenia (arm A, 20.8%; arm C, 22.7%), sepsis or septic shock (arm A, 16.9%; arm C, 15.9%), and disease progression (arm A, 13.1%; arm C, 8.2%). Among 199 patients who had at least 1 SAE on arm A, 44 only received the first cycle of decitabine and never received sapacitabine (Table 7).

The first cycle of treatment was decitabine on both arms. Twenty-one patients randomized to arm A (8.9%) and 18 randomized to arm C (7.7%) died within 30 days. Sixty-day mortality was 22.0% on arm A and 20.6% on arm C.

Eighty-five patients (36%) treated on arm A and 57 (24.5%) treated on arm C had AEs with an outcome of death during treatment or within 28 days after last dose of study drug. Among 85 patients who died from AEs on arm A, 30 only received decitabine during the first cycle and did not receive sapacitabine (Table 8).

DISCUSSION

This is the first large, randomized, controlled, phase 3 trial designed to evaluate the survival benefit of an oral drug, sapacitabine, given in alternating cycles with the best available standard-of-care therapy of an intravenous drug in elderly patients with newly diagnosed AML who were unfit for or refused intensive induction therapy. In the ITT population, the study arm that received decitabine/sapacitabine with decitabine given in the first and subsequent odd cycles and oral sapacitabine in the second and subsequent even cycles did not reach a statistically significant improvement in OS versus the control arm of decitabine monotherapy (median, 5.9 vs 5.7 months; $P = .8902$). The CR rate was 16.6% on the study arm versus 10.8% on the control arm ($P = .15$). Median durations of CR were similar between the 2 arms.

The study arm of decitabine/sapacitabine was well tolerated. The median number of treatment cycles was similar between the 2 arms; 16.9% of patients on decitabine/

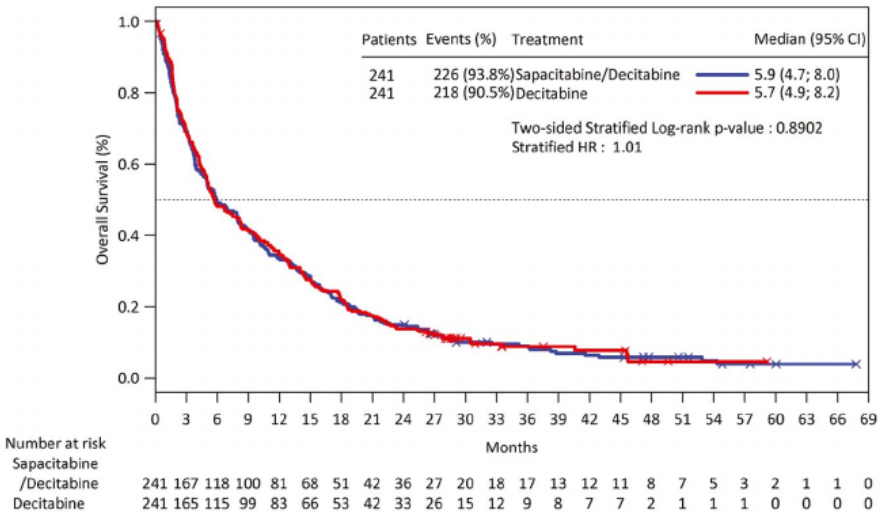

Figure 1. Kaplan-Meier survival curves illustrate survival in the intent-to-treat population according to treatment received. HR indicates hazard ratio.

Exploratory Subgroup	*Stratified HR [95% CI]*	*Sap/Dec better ← → Decitabine better*	*Sap/Dec Event/ N*	*Sap/Dec Median, mos*	*Decitabine Event/ N*	*Decitabine Median, mos*	*P*
Antecedent MDS/MPD	0.85 [0.59, 1.24]		60/66	6.4	65/70	5.0	0.409
De novo / Rx-related	1.08 [0.86, 1.35]		166/175	5.9	153/171	6.7	0.515
Interaction test	*P=0.396*						
WBC <10,000	0.84 [0.66, 1.06]		145/157	8.0	146/162	5.8	0.145
WBC ≥10,000	1.57 [1.12, 2.19]		81/84	3.8	72/79	5.5	0.007
Interaction test	*P=0.011*						
BM Blasts <50%	1.00 [0.77, 1.30]		113/123	9.5	114/131	9.8	0.986
BM Blasts ≥50%	1.01 [0.77, 1.32]		113/118	3.9	104/110	3.9	0.957
Interaction test	*P=0.885*						
CG unfavorable	1.27 [0.94, 1.73]		97/100	3.8	87/94	5.7	0.116
CG other	0.89 [0.69, 1.15]		129/141	8.2	131/147	5.7	0.377
Interaction test	*P=0.142*						

Figure 2. Survival analyses in subgroups from the current study are illustrated. BM indicates bone marrow; CG, cytogenetics; HR, hazard ratio; MPD, myeloproliferative disorder; MDS, myelodysplastic syndrome; mos, months; Rx-related, drug-related; Sap/Dec, sapacitabine and decitabine; WBC, white blood cell count.

sapacitabine received at least 12 cycles versus 15.5% on the control arm. Grade 3 or 4 AEs (regardless of causality) for the study arm were similar to those for the control arm and were consistent with the known safety profile of decitabine and sapacitabine. Eighty-five patients (36%) treated with decitabine/sapacitabine and 57 (24.5%) treated with decitabine monotherapy had AEs with an outcome of death during treatment or within 28 days after the last dose. Among 85 patients randomized to receive decitabine/sapacitabine who died from treatment-emergent AEs, 30 received only decitabine during the first cycle and did not receive sapacitabine, suggesting the presence of heterogeneity in patient and disease characteristics despite the use of stratification factors for randomization.

The strength of this study is the randomized assignment to 2 treatment arms, with the control arm being the

TABLE 3. Response Rate and Duration: Intent-to-Treat Population

	No. of Patients (%)	
	Arm A-ITT: Decitabine/Sapacitabine, n=241	Arm C-ITT: Decitabine, n=241
CR (95% CI), %	16.6 (12.1 - 21.9): $P = 0.1468$	10.8 (7.2 - 15.4)
Time to response, Median, mos	2.6	3.4
Duration, Median (95% CI)	9.5 (6.1 - 13.6)	10.4 (8.1 - 14.0)
CRp (95% CI), %	2.1 (0.7 - 4.8)	2.1 (0.7 - 4.8)
Time to response, Median, mos	4.9	4.5
Duration, Median (95% CI)	9.5 (3.1 - 20.7)	5.7 (3.0 - 12.5)
PR (95% CI), %	5.0 (2.6 - 8.5)	3.3 (1.4, 6.4)
Time to response, Median, mos	2.1	1.4
Duration, Median (95% CI), mos	2.2 (1.2 - 9.9)	1.9 (0.5, 9.8)
HI (95% CI), %	17.0 (12.5- 22.4)	15.8 (11.4 - 21.0)
Time to response, Median, mos	1.3	2.3
Duration, Median (95% CI), mos	5.8 (2.7 - 17.0)	4.8 (3.4 - 7.2)
SD (95% CI), %	8.7 (5.5 - 13.0)	12.9 (8.9 - 17.8)
Duration, Median (95% CI), mos	23.3 (9.1 - 33.2)	14.8 (10.6 - absent)

Abbreviations: CI, confidence interval; CR, complete remission; CRp, complete remission with incomplete platelet recovery; HI, hematologic improvement; ITT, intent-to-treat population; PR, partial remission; SD, stable disease.

TABLE 4. Response Rate and Duration According to White Blood Cell Count

Response	Arm A: WBCs $<10 \times 10^9$/L, n = 157	Arm C: WBCs $<10 \times 10^9$/L, n = 162	Arm A: WBCs $\geq 10 \times 10^9$/L, n = 84	Arm C: WBCs $\geq 10 \times 10^9$/L, n = 79
CR (95% CI), %	21 (14.9-28.2); $P = .0017$[a]	8.6 (4.8-14.1)	8.3 (3.4-16.4)	15.2 (8.1-25.0); $P = .1819$
Time to response: Median, mo	3.0	3.4	1.9	3.2
Duration: Median (95% CI), mo	12.9 (6.9-16.4)	10.4 (5.8-22.8)	4.7 (1.1, absent)	10.1 (1.6-13.1)
CRp, %	3.2	1.9	0.0	2.5
Time to response: Median, mo	4.9	1.8	—	Not estimable
Duration: Median, mo	9.5	7.7	—	Not estimable
PR, %	3.8	2.5	7.1	5.1
Time to response: Median, mo	1.7	1.0	2.1	2.8
Duration: Median, mo	2.2	1.2	3.3	1.9
HI, %	18.4	15.4	14.3	16.5
Time to response: Median, mo	1.3	2.8	1.8	1.1
Duration: Median, mo	4.4	4.7	5.8	6.2
SD, %	7.0	14.8	11.9	8.9
Duration, median, mo	33.2	14.8	11.0	6.4

Abbreviations: CI, confidence interval; CR, complete remission; CRp, complete remission with incomplete platelet recovery; HI, hematologic improvement; PR, partial remission; SD, stable disease; WBCs, white blood cells.
[a]This *P* value indicates a statistically significant difference.

TABLE 5. Transfusion and Hospitalization Requirements

Requirement	Arm A: Decitabine/Sapacitabine, n = 236	Arm C: Decitabine, n = 233
Average no. of RBC units transfused per wk while on treatment: Median	0.8	0.8
Average no. of platelet units transfused per wk while on treatment: Median	0.3	0.2
Median no. of transfusion-free wks	13	12.3
Median percentage of days alive and out of hospital while on treatment		
First 90 d	83.3	81.1
First 180 d	86.4	83.3
First 240 d	86.9	83.3
First 360 d	87.8	84.0

Abbreviation: RBC, red blood cell.

best available treatment in current clinical practice. The limitation of the study is the open-label design, which is necessary when the experimental treatment is an oral drug given in alternating cycles with an intravenously infused drug. The median OS of 5.7 months on the control arm of decitabine monotherapy was lower than the median OS of 7.7 months reported in the phase 3 decitabine study (DACO-016), possibly because of differences in patient populations,

TABLE 6. Grade 3 or 4 Adverse Events Occurring in ≥10% of Patients

Event	Arm A: Decitabine/Sapacitabine, n = 236	Arm C: Decitabine, n = 233
No. of patients with ≥1 grade 3 or 4 TEAE, %	205 (86.7)	213 (91.4)
Hematologic		
Anemia	114 (48.3)	103 (44.2)
Neutropenia	105 (44.5)	87 (37.3)
Febrile neutropenia	62 (26.3)	62 (26.6)
Thrombocytopenia	122 (51.7)	120 (51.5)
Nonhematologic		
Pneumonia	63 (26.7)	70 (30.0)
Sepsis/septic shock	20 (8.5)	2 6 (11.2)
Hyponatremia	14 (5.9)	25 (10.7)

Abbreviation: TEAE, treatment-emergent adverse event.
[a]One patient could have multiple grade 3 or 4 TEAEs; grade was of the worst severity regardless of cycles.

TABLE 7. Serious Adverse Events Occurring in ≥5% Patients

Event	Arm A: Decitabine/Sapacitabine, n = 236	Arm C: Decitabine, n = 233
No. of patients with ≥1 SAE, %	199 (84.3)	188 (80.7)
Anemia	11 (4.7)	14 (6.0)
Febrile neutropenia	49 (20.8)	53 (22.7)
Cellulitis	10 (4.2)	11 (4.7)
Pneumonia	63 (26.7)	65 (27.9)
Sepsis/septic shock	40 (16.9)	37 (15.9)
Disease progression	31 (13.1)	19 (8.2)

Abbreviation: SAE, serious adverse event.

as shown in Table 9. This study had more patients aged ≥75 years. Such patients had a lower median OS (6.3 months) in the DACO-016 study.[12] In addition, this study included patients with WBCs >40× 10^9/L who were excluded from DACO-016. Patients with proliferative AML (WBCs >10 × 10^9/L) are known to have worse outcomes.[15]

It appears that the decitabine/sapacitabine arm performed better in patients who had low peripheral WBC counts. In the subgroup with WBCs <10 × 10^9/L (n = 319), a trend toward improved OS (median, 8.0 vs 5.8 months; hazard ratio, 0.84 [95% CI, 0.66-1.06]; P = .14) and a significantly higher CR rate (21.0% vs 8.6%; P = .0017) were observed in patients who were randomized to the decitabine/sapacitabine arm. The opposite was observed in the subgroup with WBCs ≥10 × 10^9/L (n = 163), in which longer survival (median, 5.8 vs 3.8 months; hazard ratio, 1.57 [95% I, 1.12-2.19]; P = .007) and a trend toward a higher CR rate (15.2% vs 8.3%; P = .18) were observed on the decitabine monotherapy arm.

Decitabine dose density has been known to influence the CR rate and median OS. In the phase 2 study of single-agent decitabine administered at 20 mg/m^2 daily for 5 days every 4 weeks, the CR rate was 24%, and the median OS was 7.7 months.[24] In the phase 2 study of decitabine administered at 20 mg/m^2 daily for 10 days every 4 weeks, the CR rate was 47%, and the median OS was 13 months.[25] It is possible that, for highly proliferative disease (ie, a high peripheral WBC count), the dose density of decitabine must be ≥20 mg/m^2 daily for 5 days every 4 weeks instead of every 8 weeks to control the disease. Treatment effect heterogeneity was further explored using the SIDES methodology. The optimal cutoff points for the peripheral WBC count, SWOG cytogenetic risk category, and HCTCI score were identified and could be used to design future studies.

In conclusion, the results of this large, multicenter, global study demonstrated that the regimen of decitabine administered in alternating cycles with sapacitabine was active and well tolerated but did not significantly improve OS compared with decitabine monotherapy. Subgroup analyses suggested that patients with baseline WBCs <10 × 10^9/L might benefit from the regimen of decitabine alternating with sapacitabine, which improved the CR rate and had the greater convenience of an oral drug. For patients with proliferative AML (WBCs ≥10 × 10^9/L), delivery of a higher dose density of decitabine by concomitant administration of decitabine and sapacitabine should be considered.

On July 7, 2020, the US Food and Drug Administration approved an oral combination of decitabine and cedazuridine (INQOVI; Astex Pharmaceuticals, Inc) for adult patients with MDS based on decitabine exposure equivalence between oral combination and intravenous decitabine.[26] The availability of oral decitabine administration may facilitate the future development of an entirely oral treatment regimen for elderly patients

TABLE 8. Adverse Events With an Outcome of Death

Event	Arm A: Decitabine/Sapacitabine, n = 236	Arm C: Decitabine, n = 233
AE with outcome of death, %	36 (12.7[a])	24.5
Disease progression	12.3 (2.1[a])	7.7
Pneumonia	2.5 (1.3[a])	1.7
Sepsis/septic shock	9.7 (4.2[a])	4.7
Others	11.4 (5.1[a])	11.1

Abbreviation: AE, adverse event.
[a]This value indicates the percentage of patients who died after receiving only decitabine in the first cycle.

TABLE 9. Patients Randomized to Decitabine: DACO-016 and CYC682-12

	No. of Patients (%)	
Variable	Decitabine Arm From DACO-016, n = 242	Decitabine Monotherapy Arm From CYC682-12, n = 241
Age: Median [range], y	73 [64-89]	77 [70-92]
70-74	76 (31.4)	70 (29.0)
75-79	65 (26.9)	99 (41.1)
≥80	30 (12.4)	72 (29.9)
WBCs: Median, $\times 10^9$/L	3.1	3.6
$>40 \times 10^9$/L	Excluded from trial according to eligibility criteria	29 (12.0)

Abbreviations: CYC682-12, A Study of Oral Sapacitabine in Elderly Patients With Newly Diagnosed Acute Myeloid Leukemia (SEAMLESS; ClinicalTrials.gov identifier NCT01303796); DACO-016, Trial of Decitabine in Patients With Acute Myeloid Leukemia (ClinicalTrials.gov identifier NCT00260832); WBCs, white blood cells.

with AML, allowing them to enjoy good quality of life at home without being burdened with the inconveniences associated with intravenous infusions.

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