REGULAR ARTICLE

blood advances

Guadecitabine vs TC in relapsed/refractory AML after intensive chemotherapy: a randomized phase 3 ASTRAL-2 trial

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Key Points

- There was no clear survival benefit for guadecitabine over standard-of-care in patients with relapsed/refractory AML.
- Guadecitabine produced higher clinical response rates, with potential survival benefit in several prespecified subgroups.

Guadecitabine is a novel hypomethylating agent (HMA) resistant to deamination by cytidine deaminase. Patients with relapsed/refractory acute myeloid leukemia (AML) were randomly assigned to guadecitabine or a preselected treatment choice (TC) of high-intensity chemotherapy, low-intensity treatment with HMAs or low-dose cytarabine, or best supportive care (BSC). The primary end point was overall survival (OS). A total of 302 patients were randomly assigned to guadecitabine (n = 148) or TC (n = 154). Preselected TCs were low-intensity treatment (n = 233 [77%; mainly HMAs]), high-intensity chemotherapy (n = 63 [21%]), and BSC (n = 6 [2%]). The median OS were 6.4 and 5.4 months for guadecitabine and TC, respectively (hazard ratio 0.88 [95% confidence interval, 0.67-1.14]; log-rank $P = .33$). Survival benefit for guadecitabine was suggested in several prospective subgroups, including age <65 years, Eastern Cooperative Oncology Group performance status 0 to 1, refractory AML, and lower peripheral blood blasts ≤30%. Complete response (CR) + CR with partial hematologic recovery rates were 17% for guadecitabine vs 8% for TC ($P < .01$); CR+CR with incomplete count recovery rates were 27% for guadecitabine vs 14% for TC ($P < .01$). Safety was comparable for the 2 arms, but guadecitabine had a higher rate of grade ≥3 neutropenia (32% vs 17%; $P < .01$). This study did not demonstrate an OS benefit for guadecitabine. Clinical response rates were higher for guadecitabine, with comparable safety to TC. There was an OS benefit for guadecitabine in several prespecified subgroups. This study was registered at www.clinicaltrials.gov as #NCT02920008.

Introduction

Patients with acute myeloid leukemia (AML) who are unable to achieve a complete response (CR) with standard induction therapy (refractory AML) or relapse after achieving an initial remission have a grim

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Study protocol, statistical analysis plan, baseline clinical data, treatment, and end point analysis data will be made available on reasonable request within 30 days. Data requests can be submitted to https://astx.com/contact/ for review and approval.

The full-text version of this article contains a data supplement.

life expectancy, with a 5-year survival rate of ≤10%.[1,2] Factors associated with poor overall survival (OS) after relapse include a shorter duration of remission (<6 months), adverse genetic factors, prior hematopoietic cell transplantation (HCT), older age, and poor performance status.[3] Median survival in several randomized trials of new nontargeted agents ranges between 3.5 and 7.5 months.[4,5] More recently, relapsed or refractory AML with actionable mutations, such as FMS-like tyrosine kinase-3 internal tandem duplication (*FLT-3 ITD*) and isocitrate dehydrogenase (*IDH*), achieved a slightly better median OS of 6 to 9 months in randomized clinical trials.[6,7] Preliminary phase 2 data from these targeted agents also showed durable remissions and longer OS in selected responding patients.[8,9] Other results were, however, not as promising. Single-agent venetoclax treatment was associated with a median survival of ~5 months,[10] and a recent literature review of several venetoclax combination regimens showed a median survival of ~6 to 9 months in relapsed or refractory AML.[11] Data from phase 1 and 2 studies of venetoclax combined with the *FLT-3* inhibitor gilteritinib showed promising response rates, with a median OS of 10 months; however, the median OS in patients who did not proceed to HCT was only 6.3 months.[12] The *IDH-2* inhibitor enasidenib also failed to improve median OS over conventional care regimens in relapsed/refractory AML, with a median survival of 6.5 months.[13] Finding new effective and safe drugs able to prolong survival and/or bridge to HCT as monotherapy or in combination with other agents is still an unmet need for patients with relapsed or refractory AML.

Although not approved for relapsed/refractory AML, the hypomethylating agents (HMAs) azacitidine and decitabine are routinely used in clinical practice to treat such patients. Data from HMAs in relapsed/refractory AML mostly come from small series with variable responses and survival. However, a large international retrospective analysis of 655 patients in 12 centers treated with HMAs showed a CR rate of 11%, CR+CR with incomplete count recovery (CRi) rate of 16%, and median OS of 6.7 months.[14] Decitabine requires incorporation into DNA, making its synthesis phase cycle-dependent.[15] It is, therefore, limited by its shorter half-life and exposure time due to rapid degradation by cytidine deaminase. Guadecitabine is a novel HMA that is a dinucleotide of decitabine and deoxyguanosine resistant to degradation by cytidine deaminase.[16] Gradual release of decitabine from the dinucleotide after subcutaneous injection results in more sustained levels of decitabine, prolonging its exposure window.[17] This should allow more incorporation into the DNA of leukemia cells during the synthesis phase of the cell cycle and is the proposed basis for its potential increased efficacy compared with intravenous decitabine. In addition, the small volume (~1 mL) of subcutaneous injection offers a more convenient administration route than the decitabine 1-hour intravenous infusion. Two schedules of guadecitabine with either 5- or 10-day treatment cycles were investigated in a phase 2 study of 103 patients, with a CR rate of 19% and a CR+CRi rate of 30% with the 10-day regimen. Median OS was 7.1 months for the 10-day schedule. After a median follow-up of 29 months, median OS was not reached for patients who achieved CR or CRi, regardless of subsequent HCT.[18,19]

We report here the results of a randomized phase 3 clinical trial (ASTRAL-2) comparing guadecitabine with standard-of-care physician treatment choice (TC) in the treatment of refractory or relapsed AML.

Methods

Study design

ASTRAL-2 was a phase 3 international, open-label, multicenter, randomized clinical trial (www.clinicaltrials.gov identifier #NCT02920008; EudraCT 2015-005256-97). Patients were randomly assigned 1:1 to guadecitabine or a preselected physician TC of either intensive chemotherapy, low-intensity treatment, or best supportive care (BSC).

Guadecitabine was given as 60 mg/m^2 per day subcutaneously for 10 days for 1 or 2 cycles (based on disease response and hematologic recovery in the first cycle), followed by subsequent 5-day cycles. Cycles were administered every 28 days, unless delayed for hematologic recovery, and continued as long as the patient continued to benefit.

Before randomization, the investigator assigned each patient to one of the following TC options given every 28 days based on the prior treatment received, country approval, and local institutional standard practice:

- High intensity:
  - Intermediate- or high-dose cytarabine (Ara-C), recommended as 1.0 to 1.5 g/m^2 IV every 12 hours or up to 6 g/m^2 per day IV for ≤6 days.
  - Mitoxantrone, etoposide, and Ara-C (MEC regimen): mitoxantrone 6 to 12 mg/m^2 IV (recommended 8 mg/m^2), etoposide 80 to 200 mg/m^2 IV (recommended 100 mg/m^2), and Ara-C 1000 mg/m^2 IV, each daily for 5 days (days 1-5).
  - Fludarabine, Ara-C, and granulocyte-colony stimulating factor, with or without idarubicin (FLAG/FLAG-Ida), with fludarabine 25 to 30 mg/m^2 per day IV on days 1 to 5, ARA-C 12 g/m^2 per day IV for up to 5 days (recommended to be given 4 hours after fludarabine), and subcutaneous granulocyte-colony stimulating factor daily from day 6 up to white cell count recovery, with or without idarubicin 8 mg/m^2 per day IV on days 3 to 5.
- Low intensity:
  - Low-dose Ara-C 20 mg subcutaneous (SC) or IV twice a day on days 1 to 10;
  - Decitabine 20 mg/m^2 per day IV on days 1 to 5; or
  - Azacitidine 75 mg/m^2 per day IV or SC on days 1 to 7.
  - BSC according to local institutional standards.

Randomization was stratified by intensity of preselected TC option (high intensity vs low intensity vs BSC), Eastern Cooperative Oncology Group (ECOG) performance status (PS; 0-1 vs 2), baseline cytogenetics at study entry (poor risk vs other), and study center region (North American vs other international centers).

All patients in the TC arm at any time and those receiving guadecitabine only in the first 30 days could also receive hydroxyurea to control highly proliferative disease at the investigator's discretion.

Eligibility criteria

Adult patients were included if they had an ECOG PS 0-2 and confirmed diagnosis of AML (except acute promyelocytic leukemia), were previously treated with induction-intensive

chemotherapy, including Ara-C and an anthracycline, and did not achieve remission after completing their intensive induction regimen (primary refractory) or relapsed after such induction with or without prior HCT. Patients had to have adequate hepatorenal function (creatinine clearance or glomerular filtration rate ≥30 mL/min and serum bilirubin <2.5× the upper limit of normal).

Patients in their first relapse with a documented remission duration >12 months after initial induction were excluded. Patients were also excluded if they had known clinically active central nervous system or extramedullary AML, except leukemia cutis; a second malignancy requiring active therapy, except breast or prostate cancer stable on endocrine therapy; prior treatment with guadecitabine or with >2 cycles of prior decitabine or azacitidine; refractory congestive heart failure; active infection resistant to all antibiotics; or non-AML–associated pulmonary disease requiring O_2 >2 L/min or any other condition that put the patient at imminent risk of death.

End points and assessments

The primary end point was OS. Secondary end points included 12- and 24-month survival rate; CR; CR with partial hematologic recovery (CRh); CR+CR with incomplete count recovery (CRi); duration of CR+CRh; event-free survival (EFS); transfusion independence rate; HCT rate; and safety.

Peripheral blood (PB) was assessed at screening and on day 1 of each cycle for response evaluation. Bone marrow (BM) aspirate or biopsy was performed at screening and at the end of cycles 1, 3, and 6 unless PB showed persistence of ≥5% leukemic blasts, which excluded the possibility of a marrow response. After cycle 6, BM assessment by BM aspirate or biopsy was repeated every 3 months for the first year of the study and every 6 months thereafter until PB or BM assessment showed disease progression or relapse.

Evaluation of response was determined based on PB and BM data listings at each visit using International Working Group response criteria[20] with the addition of CRh (defined as <5% of BM blasts, no evidence of disease, partial recovery of PB counts [platelets >50 000/μL], and absolute neutrophil count >500/μL).

Adverse events (AEs) were recorded at each visit in all patients who received treatment and were reported using Common Terminology Criteria for Adverse Events v4.03.

Statistical analyses

To provide a statistical power ≥90% to detect a difference in survival with a hazard ratio (HR) of ~0.692 (median OS of 6.5 months for guadecitabine vs 4.5 months for TC) using a stratified log-rank test at an overall 0.05 α level with a 1:1 randomization, the trial would have required 315 death events and ~404 patients to be randomly assigned.

Efficacy analyses included all randomly assigned patients (intent to treat [ITT]). Survival was calculated from the date of randomization to the date of death. OS curves were estimated using the Kaplan-Meier method and formally compared between the 2 treatment groups using a 2-sided, stratified log-rank test using the randomization stratification factors. Subgroups for OS analysis that were prespecified in the statistical analysis plan included: age (< vs ≥ 65 years), sex (men vs women), baseline ECOG PS (0-1 vs 2), baseline cytogenetic risk (poor risk vs all others), response to initial induction (refractory vs first relapse vs second or subsequent relapses), disease burden as defined by baseline BM blasts (≤ vs >40%) and baseline PB blasts (≤ vs >30%), geographic region (North America vs all others), race (White vs Black vs Asian vs other), and preselected TCs (high intensity vs low intensity vs BSC).

Response rates were compared between the 2 groups using a Cochran Mantel-Haenszel test, stratified by the randomization stratification factors and an α level of 0.05. Transfusion independence was defined as no red blood cells or platelet transfusion for ≥8 consecutive weeks after the start of treatment, and the rates were compared using the stratified Cochran Mantel-Haenszel test. The same method was used to compare HCT rates between the 2 groups.

EFS was calculated from the date of randomization to the date of treatment discontinuation for whatever reason, the start of another antileukemia treatment (except HCT), or death, whichever came first. Disease progression as determined by the treating physicians was not included in the EFS definition because there was no consensus on the definition of disease progression, particularly in the setting of patients receiving ongoing HMA treatment with clinical benefit without an objective response. One- and 2-year survival rates were estimated using the Kaplan-Meier procedure.

AEs were recorded and compared for the 2 groups in all patients who received treatment.

Study oversight

The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. Institutional review board/ethics committee approval was obtained before the start of the trial in each participating center, and all patients provided written informed consent before being randomly assigned. An independent data monitoring committee (DMC) was established before the start of the trial, composed of 2 clinical and 1 statistical expert who did not participate in any of the ASTRAL guadecitabine trials. The committee met at regular intervals to review unblinded efficacy and safety data in closed sessions, followed by an open session with sponsor representatives (without any unblinded data) to provide recommendation on study conduct. In September 2018, with data from 278 randomly assigned patients and 107 deaths reported from the planned 315 deaths, the DMC estimated that the HR for OS at that time was 1.32 and that the trial would be highly unlikely to reach its targeted HR of 0.692 when all patients were randomly assigned. The DMC recommended that the sponsor stop further enrollment and provide the information to all investigators and patients but continue to treat and follow patients already randomly assigned according to their individual response and benefit from treatment, and after receiving reconsent from patients. By the time this was implemented by the sponsor, 302 of the planned 404 patients were enrolled. All enrolled patients were followed for ≥1 year from randomization, with a data cutoff in January 2020.

Results

Patients and treatment

Ninety-eight study centers in 15 countries contributed to this study (supplemental Table 1). Patient disposition is shown in Figure 1.

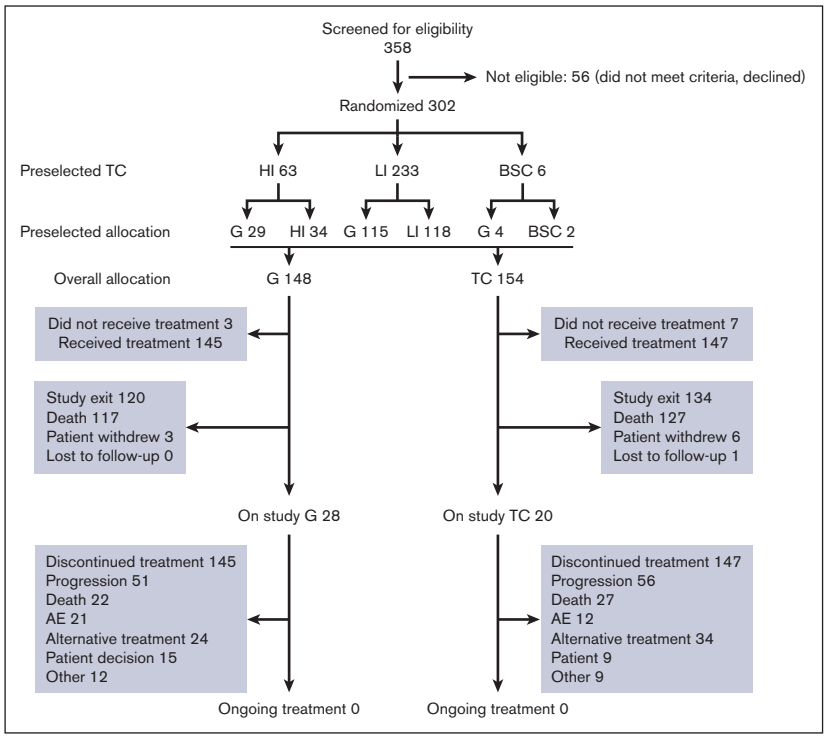

Figure 1. Patient disposition. G, guadecitabine; HI, high intensity; LI, low intensity.

The ITT population comprised 302 patients, of whom 148 were randomly assigned to guadecitabine and 154 to TC. Of those patients, 233 (77%) were preselected to be randomly assigned in the low-intensity group (115 to guadecitabine and 118 to low intensity), 63 (21%) in the high-intensity group (29 to guadecitabine and 34 to high intensity), and only 6 (2%) in the BSC group (4 to guadecitabine and 2 to BSC). Of the 118 patients randomly assigned to receive low-intensity treatment, 100 (85%) received HMAs (64 receiving azacitidine and 36 decitabine). Baseline variables presented in Table 1 were generally balanced between the 2 arms, with no statistically significant differences. Median ages were 65 and 63 years for guadecitabine and TC, respectively. More patients with guadecitabine vs TC were aged ≥65 years (51% vs 40%) and had refractory AML (45% vs 33%), whereas fewer had ECOG PS 2 (16% vs 21%) and prior HCT (18% vs 26%). There were 41% of patients in second or subsequent relapse (39% and 44% for guadecitabine and TC, respectively). The median numbers of treatment cycles were 3 (range, 1-24) and 2 (range, 1-17) for guadecitabine and TC, respectively. The most common causes of treatment discontinuation with guadecitabine vs TC were disease progression as determined by the treating physician (35% vs 38%) and death (15% vs 18%).

Primary outcome and other survival analyses

Median follow-up was 21.6 months. Figure 2 shows Kaplan-Meier survival curves, and Figure 3 shows a forest plot of the prespecified subgroup OS analyses. There was no statistically significant difference between the guadecitabine and TC arms in the ITT population. Median OS durations were 6.4 and 5.4 months for guadecitabine and TC, respectively (HR 0.88 [95% confidence interval (CI), [0.67-1.14]; log-rank P = .33). There was no significant difference in median OS between guadecitabine (6.4 months), high-intensity treatment (6.2 months), and low-intensity treatment (5.3 months).

Several prespecified subgroups suggested a survival benefit for the guadecitabine arm. These included patients aged <65 years (n = 164; HR 0.68 [95% CI, 0.47-0.97]), those with ECOG PS 0-1 (n = 247; HR 0.76 [95% CI, 0.57-1.00]), those with refractory AML (Figure 4A; n = 117; median OS 10.5 months for guadecitabine, 4.6 months for TC, HR 0.58 [95% CI, 0.38-0.89]; log-rank P = .01), or PB blasts ≤30% (Figure 4B; n = 178; median OS 9.2 months for guadecitabine, 6.2 months for TC, HR 0.65 [95% CI, 0.46-0.92]; log-rank P = .01), and those who received ≥ 4 cycles (n = 94; HR 0.59 [95% CI, 0.36-0.95]). The 12- and 24-month survival rates trended higher for guadecitabine (32% and 19%, respectively) vs TC (26% and 10%, respectively). There were no prespecified molecular genetic subgroups, but a survival analysis of patients with *TP53* mutations showed no significant difference between guadecitabine and TC (n = 58; HR 0.85 [95% CI, 0.48-1.49]).

Other secondary outcomes

There was no significant difference between guadecitabine and TC in EFS (median EFS: 3.0 months for guadecitabine and 2.4 months for TC). The CR, CR+CRh, and CR+CRi rates were almost double with guadecitabine compared with TC, with both CR+CRh and CR+CRi rates significantly higher (P < .01 for both; Table 2). The median duration of CR+CRh was twice as long for guadecitabine compared with TC (4.1 vs 2.1 months). The transfusion independence rate was also higher for guadecitabine compared with TC (20% vs 13%), whereas the proportions of patients who underwent HCT were similar for the 2 treatment arms (18% for guadecitabine and 16% for TC).

Table 1. Baseline characteristics

Characteristic	Guadecitabine	Treatment choice	Total
Patients randomly assigned	148	154	302
Median age, y	65	63	63
≥65 y, n (%)	76 (51)	62 (40)	138 (46)
<65 y, n (%)	72 (49)	92 (60)	164 (54)
Men, n (%)	86 (58)	78 (51)	164 (54)
ECOG PS, n (%)			
0	42 (28)	45 (29)	87 (29)
1	83 (56)	77 (50)	160 (53)
2	23 (16)	32 (21)	55 (18)
Poor risk cytogenetics, n (%)	66 (45)	65 (42)	131 (43)
TP53 mutations	31 (21)	27 (18)	58 (19)
BM blasts, n (%)			
≤40%	95 (64)	92 (60)	187 (62)
>40%	52 (35)	62 (40)	114 (38)
PB blasts, n (%)			
≤30%	87 (59)	91 (59)	178 (59)
>30%	36 (24)	35 (23)	71 (24)
Total WBC counts >20 000/μL, n (%)	16 (11)	14 (9)	30 (10)
Median platelet count, $\times 10^9$/L (range)	34 (2-295)	42 (4-812)	37 (2-812)
Response to induction, n (%)			
Refractory	66 (45)	51 (33)	117 (39)
1st relapse	25 (17)	35 (23)	60 (20)
Subsequent relapse	57 (39)	68 (44)	125 (41)
Prior HCT, n (%)	27 (18)	40 (26)	67 (22)

WBC, white blood cell.

Safety

Table 3 shows a summary of safety results. Similar treatment-emergent AE rates were observed with guadecitabine and TC (both 97%). The incidence rates of grade ≥3 AEs were similar for the 2 groups (89% for guadecitabine and 84% for TC). Of grade ≥3 AEs that occurred at an incidence rate >5%, neutropenia incidence was significantly higher with guadecitabine vs TC (32% vs 17%; $P < .01$).

Discussion

In this international randomized phase 3 trial, patients treated with guadecitabine in the ITT analysis did not have a better OS than those treated with TC. Patients in the TC arm were mainly treated with HMAs and intensive chemotherapy. Nonetheless, several prespecified subgroups appear to show a potential survival benefit for guadecitabine over TC. Furthermore, secondary clinical response end points, including CR+CRh and CR+CRi rates, were significantly higher with guadecitabine compared with TC. The overall incidence of grade ≥3 AEs was comparable for the 2 arms, but guadecitabine was associated with a significantly higher neutropenia incidence.

The HMAs are widely used as monotherapy or in combination with other agents in the treatment of AML after the failure of intensive chemotherapy. Recently, an oral form of azacitidine was approved for AML maintenance,[21] and an oral decitabine/cedazuridine form was US Food and Drug Administration-approved for myelodysplastic syndromes and chronic myelomonocytic leukemia.[22] It remains, however, important to identify the best HMA to be investigated in current and future combinations in the treatment of relapsed/refractory AML. Guadecitabine is a novel HMA that has shown promising clinical activity in newly diagnosed and relapsed/refractory AML.[18,23] In a phase 2 study by Roboz et al[18] investigating multiple guadecitabine regimens, guadecitabine given as a 10-day regimen in the first few cycles and followed by a 5-day regimen produced a CR+CRi rate of 30% in a heavily pretreated population. More importantly, long-term follow-up in that study showed 2-year survival rates of 57% for patients who achieved CR and 50% for those who achieved CR or CRi. Median survival was not reached in patients with CR or CRi, regardless of whether they received HCT postresponse.[19]

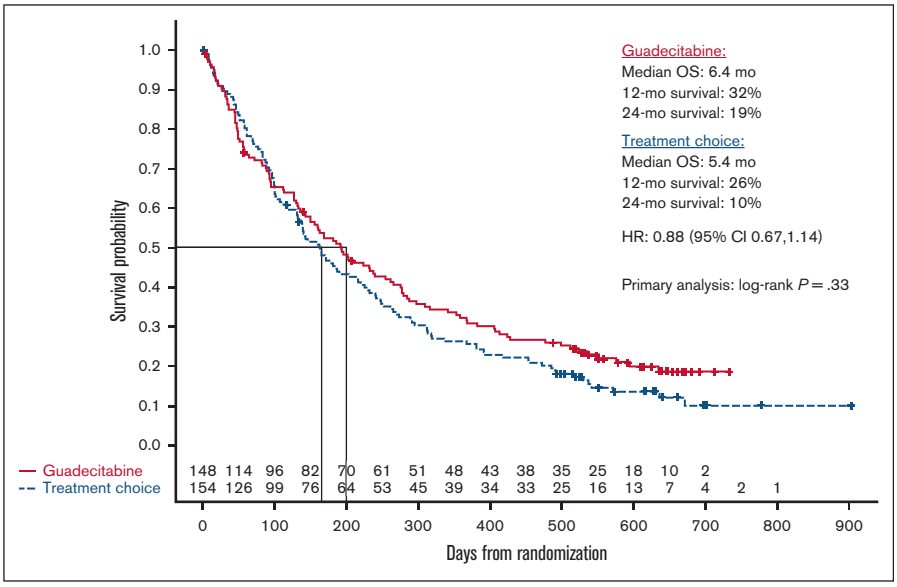

Figure 2. Primary end point: OS; and secondary end points: 12- and 24-month survival.

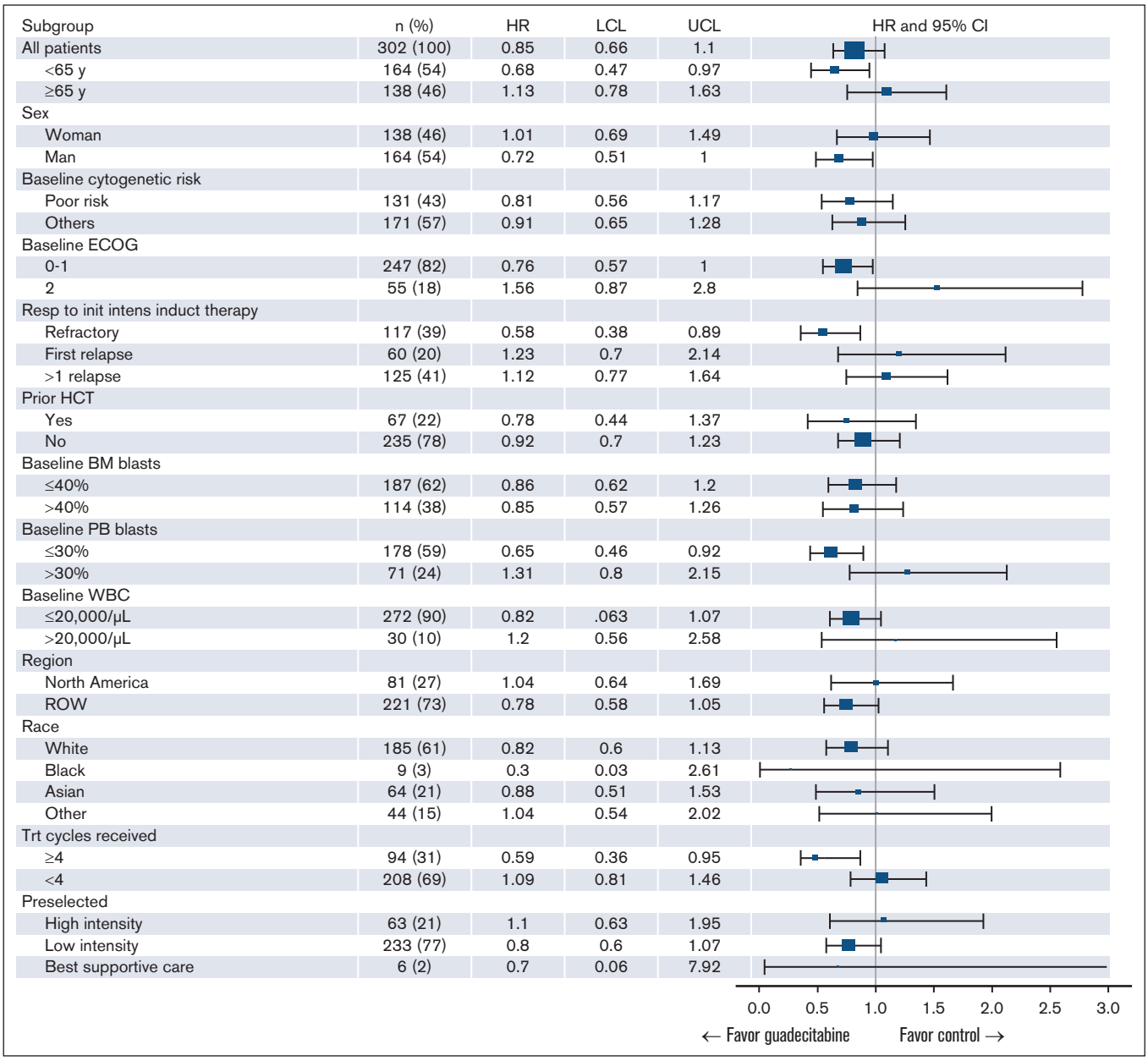

Figure 3. Survival prospective subgroups: multiple subgroups showed significant benefit for guadecitabine (OS 95% CI HRs upper confidence limit [UCL] ≤1).
Resp to init intens induct, response to initial intensive induction; LCL, lower confidence limit; ROW, rest of the world; Trt, treatment.

The patient population in the present phase 3 study was rigorously selected, with 80% of patients having either refractory AML or AML in ≥2nd relapse. This explains the large proportion of patients who were preselected to be randomly assigned to the low-intensity TC group, most of whom (85%) received HMAs. The other TC comparators included established second-line intensive chemotherapy with the MEC regimen[24,25] and FLAG-Ida,[26] and high-dose Ara-C at standard doses. Only 6 patients were preselected for the BSC group, of whom only 2 actually received BSC. There were 43% of patients with poor-risk cytogenetics, and 22% had prior HCT. Although guadecitabine did not show significant improvement in OS in the overall population, an OS benefit was suggested in several of the prespecified subgroups (Figure 3). This provided a patient profile that may achieve survival benefit with guadecitabine: younger (aged <65 years), more fit (ECOG PS 0-1), refractory to induction chemotherapy, and lower PB blast burden (PB blasts ≤30%). The aforementioned patient profile is also more prone to receive an optimal duration of ≥4 cycles of HMA treatment, another subgroup that showed survival benefit. An exploratory analysis from the international randomized phase 3 trial of guadecitabine vs standard-of-care TC in newly diagnosed AML (ASTRAL-1) did not show an OS benefit of guadecitabine vs TC, but a post hoc exploratory analysis suggested better survival outcomes with guadecitabine in patients receiving ≥4 cycles of treatment.[27] This observation may have also contributed to the discordance between the early OS HR estimated by the DMC (1.32) and the final, more

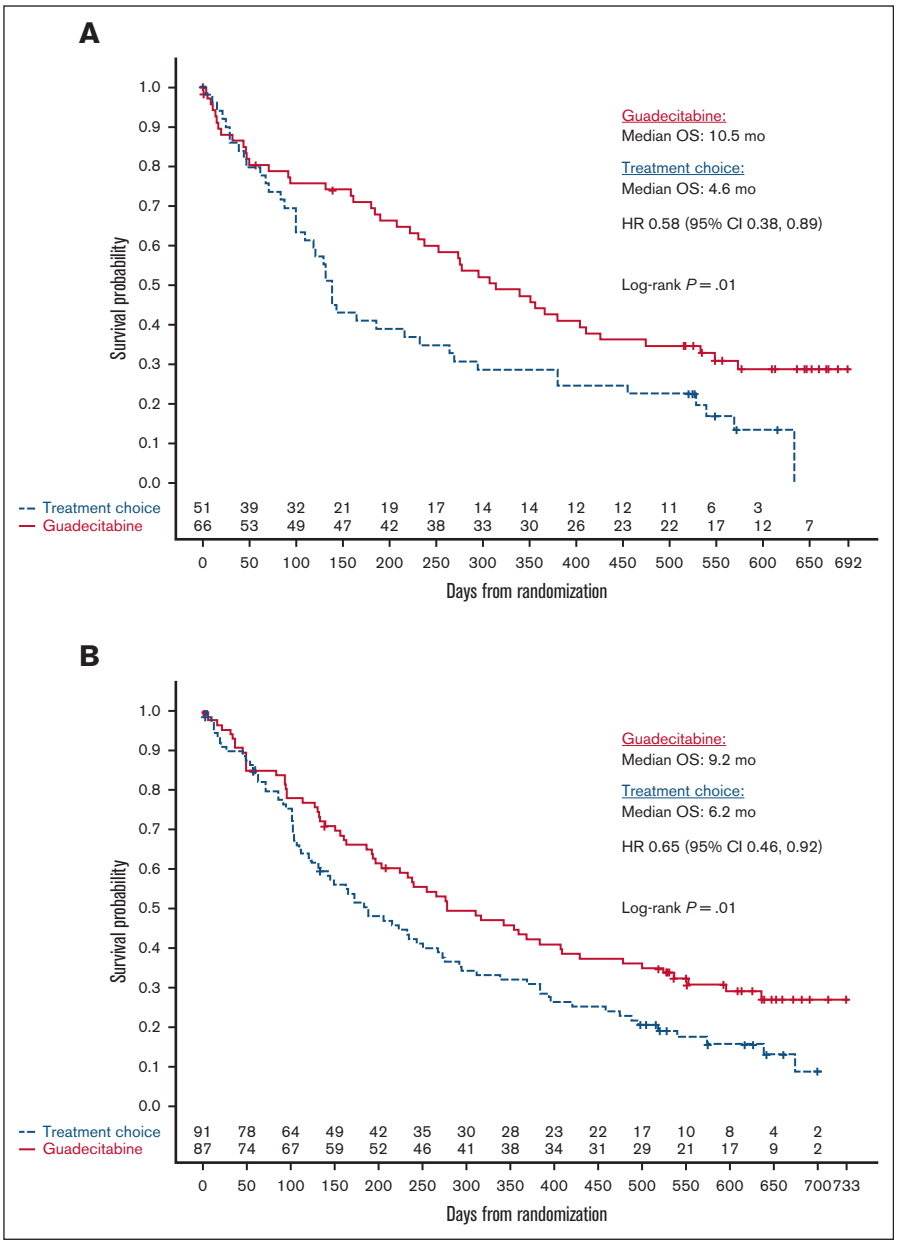

Figure 4. Overall survival in prespecified subgroups. Kaplan-Meier OS plots of patients with refractory AML (A; n = 117) and PB blasts ≤30% (B; n = 178).

favorable HR of 0.88. At the early DMC analysis, very few patients had received at least 4 cycles. The study did not include molecular subgroups in the prespecified OS subgroup analyses. There was, however, no survival difference between guadecitabine and other low-intensity treatments in different molecular subgroups (*FLT-3, NPM1,* and *TP53*) in the previous guadecitabine randomized trial in newly diagnosed AML.[27]

To our knowledge, the ASTRAL-2 phase 3 trial is the first study to identify a baseline patient profile that is most likely to benefit from guadecitabine. In the subgroup OS analysis, it is noteworthy that the OS HR with guadecitabine fared better vs low-intensity therapy (OS HR, 0.80) than vs high-intensity therapy (OS HR, 1.10), although the size of the high-intensity subgroup was small (n = 63) with a wide HR, 95% CI, (0.63-1.95). This may suggest a better benefit in patients who are refractory to intensive chemotherapy. Indeed, refractory AML is one of the prospective subgroups that showed the best survival advantage for guadecitabine (OS HR, 0.58 [95% CI, 0.38-0.89]). Another large subgroup that showed survival benefit was patients with PB blasts ≤30% (n = 178; OS HR, 0.65 [95% CI, 0.46-0.92]). In a previous multivariate analysis of 128 patients with relapsed or refractory AML treated with guadecitabine in phase 1 and 2 trials, higher PB blasts were significantly associated with a lower response.[28] It is also noteworthy that the retrospective study of a large international cohort of patients with relapsed or refractory AML treated with HMAs also identified lower PB disease burden as one of the most significant predictors of response and survival to HMAs in this population.[14]

Table 2. Clinical response

	Guadecitabine	TC	*P* value*
Patients randomly assigned, n	148	154	
Best response, n (%)			
CR	19 (13)	11 (7)	.051
CR + CRh	25 (17)	12 (8)	.01
CR + CRi	40 (27)	22 (14)	<.01
Median duration of CR+CRh, mo	4.1	2.1	

*Cochran Mantel-Haenszel test.

Both the rates for CR (13%) and CR+CRi (27%) for guadecitabine in this phase 3 trial were comparable to those achieved in the previous phase 2 trial (19% and 30%, respectively).[18] The CR rate for TC (7%) is lower than would be expected from prior small series but comparable to large international cohorts or randomized trials showing a CR rate for similar TC options of 12%[5] and a CR rate of 11% for HMAs.[14] It is unclear why the higher response rate did not translate to an OS benefit in the ITT population. One possible explanation is the shorter treatment duration in the ITT population (median 3 cycles for guadecitabine), resulting in more than half the patients not receiving an optimal HMA treatment duration of ≥4 cycles. This is probably expected in this high-risk AML population. Further, stopping enrollment early because of a perceived lack of survival benefits may have prompted some investigators to stop the experimental treatment early after that decision. Despite this, selected prospective subgroups seemed to benefit from guadecitabine treatment. It should also be noted that the trial enrollment stopped at 302 patients (short of the planned 404), which reduced the trial power to detect a significant survival benefit.

The higher incidence of grade ≥3 neutropenia with guadecitabine probably reflects a more potent cytotoxic effect at this recommended dose of guadecitabine compared with standard US Food and Drug Administration-approved doses of decitabine, azacitidine, and low-dose Ara-C. A similar observation was reported in the previous randomized guadecitabine trial vs standard-of-care treatment composed of other HMAs and low-dose Ara-C in newly diagnosed AML.[27]

Table 3. AEs (irrespective of causality)

	Guadecitabine	TC
Patients treated, n	145	147
Patients with any AE, n (%)	140 (97)	143 (97)
Patients with any grade ≥3 AE, n (%)	129 (89)	124 (84)
AEs grade ≥3 occurring at >5%, n (%)		
Febrile neutropenia	56 (39)	56 (38)
Neutropenia*	47 (32)	25 (17)
Thrombocytopenia	41 (28)	44 (30)
Anemia	31 (21)	36 (24)
Pneumonia	27 (19)	30 (20)
Sepsis	17 (12)	16 (11)
Hypokalemia	11 (8)	14 (10)
Leukopenia	12 (8)	12 (8)

*$P < .01$.

In conclusion, this phase 3 trial did not demonstrate a clear survival benefit for guadecitabine over standard-of-care TC options in patients who were heavily pretreated with relapsed or refractory AML. Nonetheless, patients treated with guadecitabine seemed to benefit from higher clinical response rates and durations of response. The OS subgroup analyses identified potential survival benefits from guadecitabine in several important prespecified subgroups. Optimizing the use of guadecitabine and other HMAs should remain an area of active research in the treatment of patients with AML.

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Authorship

Contribution: All authors treated and contributed patients' data in the trial except M.A., Y.H., and H.N.K; G.J.R. chaired the study steering committee; G.J.R., G.S., E.A.G., H.D., and M.A. wrote the first draft of the manuscript; and all authors had access to the data, and reviewed and approved the manuscript.

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