# Guadecitabine improved relapse-free survival in high-risk acute myeloid leukemia and myelodysplastic syndrome patients after transplant: phase II results from a single center

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## Abstract

This phase II, single-center clinical trial evaluated the efficacy and safety of guadecitabine, with or without donor lymphocyte infusion, following allogeneic stem cell transplantation in adult patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). The study had three treatment cohorts based on post-transplant disease status. Cohort 1 included patients with hematologic relapse after transplant (N=13). Cohort 2 consisted of patients with minimal residual disease (MRD) detected after transplant (N=18). Cohort 3 compromised patients in remission without MRD within 100 days after transplant (N=24). The primary objectives were achievement of morphological complete remission in cohort 1 and MRD eradication in cohort 2 within six cycles of guadecitabine. Cohort 3 patients received 12 cycles to improve relapse-free survival (RFS). In cohort 1, 21.4% of patients achieved morphological complete remission. In cohort 2, 47.1% achieved MRD eradication. Those who cleared MRD had a 2-year RFS of 62.5%. Cohort 3 patients had a 2-year RFS rate of 62.5% with a median follow-up of 48 months. No unexpected adverse events occurred and no graft failures were observed. Guadecitabine demonstrated efficacy and a favorable safety profile across all cohorts, supporting the investigations of hypomethylating agents.

## Introduction

The hypomethylating agents (HMA) azacitidine and decitabine are widely used in clinical practice as maintenance therapy to prevent relapse or as salvage regimens to treat disease recurrence following allogeneic stem cell transplant (allo-SCT) in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). Most data on the use of HMA in the post-transplant setting primarily come from phase II studies, which have demonstrated encouraging efficacy and a tolerable safety profile.[1,2] However, two randomized clinical trials investigating HMA for post-transplant maintenance reported conflicting results[3,4] raising questions about the of HMA effectiveness in improving relapse-free survival (RFS).

The use of HMA also has been explored in “pre-emptive” and “salvage” settings for AML and MDS patients following allo-SCT. In the “pre-emptive” setting, HMA are administered when post-transplant findings indicate a high risk of imminent hematologic relapse. For instance, Platzbeker and colleagues demonstrated that initiating azacitidine upon detection of minimal residual disease (MRD) delayed morphological relapse by approximately 8 months.[5] Additional studies have supported the efficacy of HMA, with or without donor lymphocyte infusion (DLI), in treating MRD or overt relapse after a transplant.[6-8]

In the “salvage” setting, combining HMA with DLI has proven both safe and effective. Schoereder *et al*. reported an overall response rate of 30% in patients with relapsed AML or MDS following allo-SCT using this combination therapy.[9] Notably, the incidence and severity of graft-*versus*-host disease (GvHD) associated with HMA use have been low, even when the HMA have been combined with DLI. In some studies, azacitidine treatment alone resulted in no GvHD

in patients without a prior history of the condition, while GvHD rates ranged from 17% to37% when azacitidine was combined with DLI. This favorable safety profile may be attributed to the ability of HMA to accelerate the reconstitution of regulatory T cells.[7,10]

Decitabine, a cycle-dependent agent requiring incorporation into DNA, has limited utility due to its short half-life and rapid degradation by cytidine deaminase. Guadecitabine, a next-generation HMA, is a dinucleotide of decitabine and deoxyguanosine designed to resist degradation by cytidine deaminase.[11] This property allows for gradual release after subcutaneous injection, resulting in sustained decitabine levels and prolonged drug exposure.[12] Despite these promising pharmacological features, guadecitabine failed to meet the primary endpoint of improved overall survival (OS) compared with current therapeutic alternatives in the ASTRAL studies.[13,14] Consequently, the pharmaceutical company discontinued its production and availability.

Here, we report the results of a phase II, single-center clinical trial investigating guadecitabine, administered with or without DLI, as maintenance, pre-emptive and salvage therapy for AML and MDS at various stages in the post-transplant setting.

# Methods

## Study design and participation

This prospective study was conducted at the University of Texas, MD Anderson Cancer Center (Clinical Trials.gov identifier: NCT06297629), after obtaining approval from the institutional review board. The study was conducted in accordance with institutional guidelines, the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice standards. The clinical trial was also approved by the Food and Drug Administration, as it was conducted under an Investigational New Drug application. All patients provided written informed consent. Patients with AML or MDS who underwent allo-SCT were enrolled into one of the three cohorts: a cohort of patients with hematologic relapse, a cohort of MRD-positive patients and the third cohort formed of patients on maintenance therapy. Eligible participants were aged 18 years or older, had received allo-SCT from either a matched related or unrelated donor or a single antigen mismatched donor, and had an Eastern Cooperative Group performance status of 0-2 with adequate cardiac, hepatic and renal function.

Cohort 1 included patients who experienced hematologic relapse. Cohort 2 consisted of patients in morphological remission with detectable MRD, identified by multicolor flow cytometry, cytogenetics or molecular testing (including next-generation sequencing or reverse transcriptase polymerase chain reaction) during routine post-transplant surveillance. Cohort 3 comprised high-risk patients in remission within 100 days after transplant. High-risk features for AML included therapy-related AML, adverse-risk category defined by the European LeukemiaNet or MRD positivity at transplant. For MDS, high-risk status included therapy-related disease, poor or very poor cytogenetic risk (as defined by Shanz *et al.*[15]), monosomal karyotype,[16] or a history of bone marrow blast count >5% prior to transplant. Patients in this cohort were required to have confirmed complete remission (CR) status with hematologic recovery and resolution of significant transplant-related complications. Details of eligibility criteria are presented in the *Online Supplementary Document*.

## Treatment plan

Patients in cohorts 1 and 2 received guadecitabine subcutaneously at an initial dose of 40 mg/m$^2$/day for 5 consecutive days every 28 days for up to six cycles to achieve a response. The protocol was later amended for cohort 1 to increase the dose to 60 mg/m$^2$/day subcutaneously for 5 consecutive days. DLI was planned in these cohorts if a donor was available and in the absence of contraindications such as active GvHD or low chimerism.

Patients in cohort 3 received guadecitabine at a dose of 30 mg/m$^2$/day subcutaneously for 5 consecutive days every 28 days, for a total of 12 cycles. Dose adjustments and supportive measures, including granulocyte colony-stimulating factor, were permitted based on hematologic recovery and toxicity. Criteria for dose modifications and treatment delays are detailed in the *Online Supplementary Document*.

## Endpoints and assessments

The primary endpoint for cohort 1 was achievement of CR per International Working Group response criteria. For cohort 2, the primary endpoint was MRD eradication, defined as disappearance of the leukemia clone determined by repeat studies including molecular, cytogenetic or flow cytometry findings. For cohort 3, the primary endpoint was RFS. Secondary endpoints across all cohorts included OS, duration of remission, and the incidence of grade 3 and higher adverse events. Bone marrow evaluations were performed at enrollment and at specified intervals during treatment, according to cohort-specific protocols. Adverse events were graded using the Common Terminology Criteria for Adverse Events v. 4.03.

## Statistical analyses

Cohorts 1 and 2 followed a phase II Bayesian design (Thall and Simon[17]), with a maximum of 25 patients each and predefined futility boundaries (see the *Online Supplementary Document* for details). Cohort 3 followed Bayesian monitoring of RFS with a target enrollment of up to 40 patients.[18] Within each cohort, events were tabulated, and the distributions of RFS and OS times were estimated

using the method of Kaplan and Meier.[19]
Despite all interim futility evaluations being deemed acceptable and regulatory agencies approving continued enrollment, we had to terminate the trial prematurely due to the COVID-19 pandemic and the sponsor's withdrawal of support, including discontinuation of the provision of guadecitabine.

## Results

Between August 2016 and August 2020, we prospectively screened and enrolled 56 adult patients with AML or MDS who had undergone allo-SCT at our institution. The patients' demographics and baseline characteristics are detailed in Table 1. Dose modifications on treatment are summarized, per cohort, in the *Online Supplementary Document*.

### Cohort 1 (hematologic relapse)

Thirteen patients (9 with AML and 4 with MDS) were enrolled in cohort 1 following relapse after allo-SCT. Of these, five had relapsed after a second allo-SCT. The median time to relapse after transplant was 237 days (range, 43-1,196 days). Guadecitabine treatment commenced within a median of 15 days after relapse documentation. Notably, none of the three patients enrolled after relapsing within 90 days after allo-SCT responded to guadecitabine, and all died within 6 months after post-transplant relapse had been documented. Following this observation, the protocol was amended to include only patients relapsing more than 90 days after allo-SCT.
Three of 13 patients in cohort 1 achieved CR with the guadecitabine treatment. One AML patient achieved CR after two cycles of guadecitabine and one DLI infusion but died from sudden cardiac arrest after the third cycle (not attributable to the drug) while in CR. One MDS patient achieved CR after two cycles of guadecitabine and one DLI infusion. This patient remains in CR and alive 1,757 days after relapse documentation. The third patient achieved CR but relapsed 107 days later.

### Cohort 2 (minimal residual disease-positive)

Eighteen patients in morphological remission but with documented MRD were enrolled. MRD was detected using multicolor flow cytometry in 14 patients, cytogenetic

**Table 1.** Patients' baseline demographics and clinical/disease characteristics.

| Characteristics | Cohort 1: hematologic relapse N=13 | Cohort 2: MRD$^+$ N=18 | Cohort 3: maintenance N=24 |
|---|---|---|---|
| Median age, years<br>≥65 years, N (%)<br><65 years, N (%) | 64<br>5 (38.5)<br>8 (61.5) | 62.5<br>8 (44.4)<br>10 (55.6) | 63<br>13 (54.2)<br>11 (45.8) |
| Histology, N (%)<br>AML<br>MDS | <br>9 (69.2)<br>4 (30.8) | <br>12 (66.7)<br>6 (33.3) | <br>12 (50)<br>12 (50) |
| ELN adverse risk in AML,* N (%)<br>Poor-risk cytogenetics, N (%)<br>*TP53* mutation, N (%) | 5/9 (55.6)<br>9 (69.2)<br>4 (30.1) | 9/12 (75)<br>12 (66.7)<br>3/18 (16.7) | 9/12 (75)<br>10 (41.7)<br>7/24 (29.2) |
| Disease status at allo-HCT, N (%)<br>CR1/CR2<br>Other | <br>3 (23.1)<br>10 (76.9) | <br>16** (88.9)<br>2 (11.1) | <br>11 (45.8)<br>13 (54.2) |
| MRD status of CR1/CR2 at allo-HCT, N<br>MRD-negative, N (%)<br>MRD-positive, N (%) | 3<br>3 (100)<br>0 | 13/16 evaluable**<br>5/13 (38.5)<br>8/13 (61.5) | 10/11 evaluable***<br>3 (30)<br>7 (70) |
| Previous allo-SCT, N (%) | 5 (38.5) | 5 (27.8) | 3 (12.5) |
| HLA typing (A, B, C, and DRB1), N (%)<br>Matched related donor<br>Matched unrelated donor | <br>7 (53.8)<br>6 (46.2) | <br>7 (38.9)<br>11 (61.1) | <br>9 (37.5)<br>15 (62.5) |
| Conditioning intensity, N (%)<br>Reduced intensity<br>Myeloablative | <br>4 (30.8)<br>9 (69.2) | <br>7 (38.9)<br>11 (61.1) | <br>12 (50)<br>12 (50) |

*Applied only to AML patients. **Of 16 patients transplanted in CR1/CR2 in cohort 2, 13 had MRD evaluation in bone marrow samples at transplant. ***Of 11 patients transplanted in CR1/CR2 in cohort 3, ten had MRD evaluation in bone marrow samples at transplant. AML: acute myeloid leukemia; CR1: first complete remission; CR2: second complete remission; MRD: minimal residual disease; MRD$^+$: MRD detected after allogeneic stem cell transplant; MDS: myelodysplastic syndrome; ELN: European LeukemiaNet; allo-SCT: allogeneic stem cell transplantation.

analyses in two patients, and reverse transcription polymerase chain reaction in two patients. At MRD detection, all but one patient exhibited 100% donor chimerism in both myeloid and T-cell lineages. The median time to MRD detection after transplant was 130 days (range, 28-504 days). Guadecitabine was initiated at a median of 14 days after MRD detection at a dose of 40 mg/m$^2$/day for 5 consecutive days, except for one patient who received 30 mg/m$^2$/day. One patient discontinued during the first cycle and was excluded from outcome evaluation.

Among the 17 evaluable patients, eight (47.1%) achieved response with MRD eradication within the first six cycles of guadecitabine treatment (Figure 1). The median number of treatment cycles before response was observed was three. The 2-year RFS and OS after MRD detection were 29.4% (95% confidence interval [95% CI]: 10.7-51.2%) and 35.3% (95% CI: 18.5-67.2%), respectively (Figure 2A, B). Responders had a 2-year RFS of 62.5% (95% CI: 22.9-86.1%). In contrast, one non-responder survived beyond 1 year after MRD detection.

Of the eight responders, five received DLI in addition to guadecitabine. Response with MRD eradication, regardless of DLI use, was durable with a median duration of 39.4 months (range, 14.2-65.7 months). Two responders relapsed at 14.2 and 16.8 months after their MRD detection. The median remission duration was not reached.

Of the nine non-responders, two had received DLI. All non-responders experienced morphological relapse within a median of 69 days after MRD detection, and all but one died during follow-up.

### Cohort 3 (maintenance)

Twenty-four MDS/AML patients with a high risk of relapse were enrolled to receive guadecitabine maintenance, initiated within 100 days after transplant. Three patients had undergone a previous allo-SCT and received maintenance after their second transplant (Table 1). The median time to maintenance initiation after transplant was 62 days (range, 43-114 days).

The median number of guadecitabine maintenance cycles administered was 7.5 (range, 1-12). Ten patients completed all 12 planned cycles, while two were withdrawn after cycles 9 and 11 due to the investigational agent no longer being available from the sponsor. Seven patients discontinued due to disease progression (MRD detection or hematologic relapse) and five withdrew for reasons including personal preference, COVID-19 travel restrictions, loss of insurance, pneumonia, and prolonged bone marrow suppression.

With a median follow-up of 48 months (range, 35-70

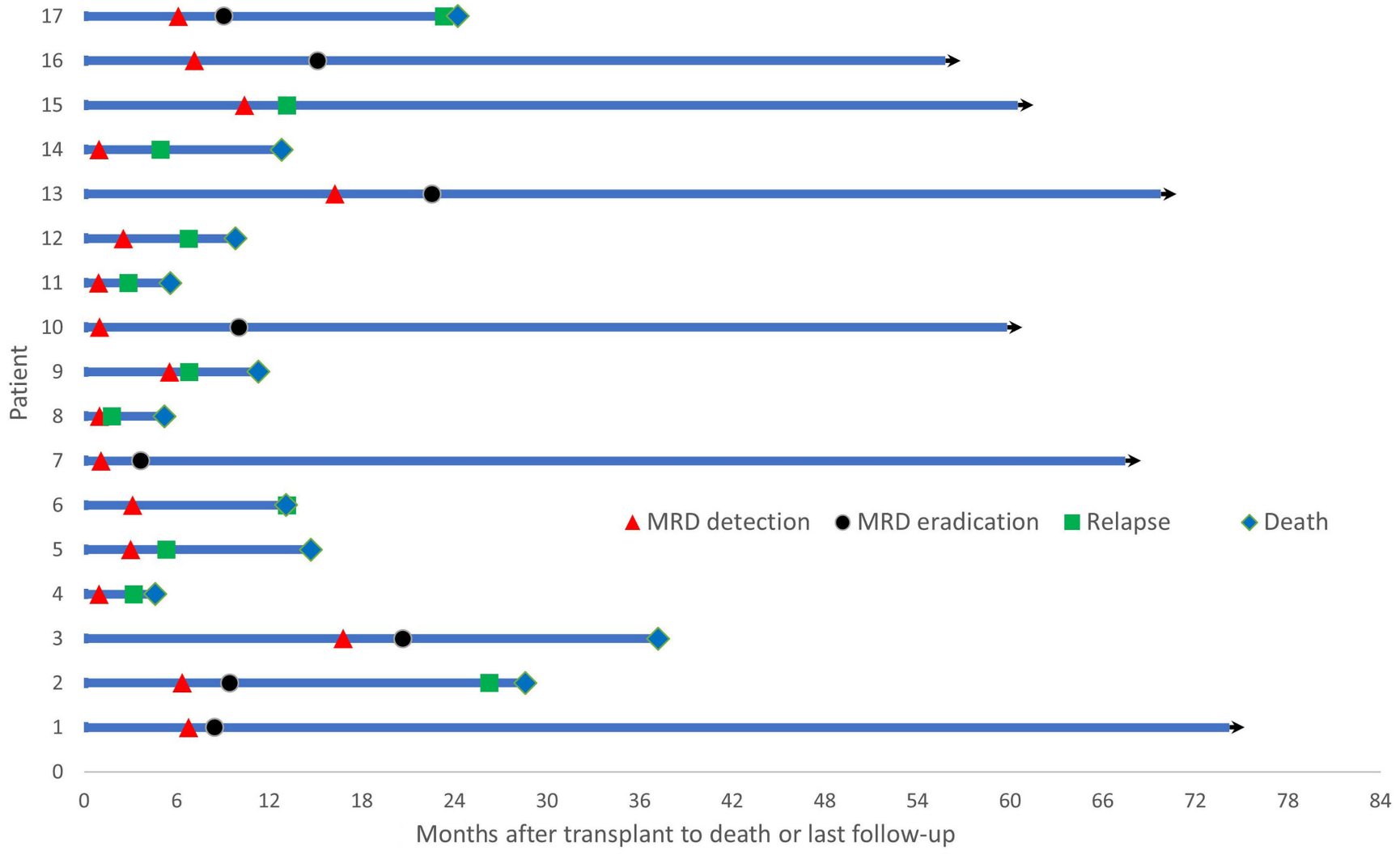


**Figure 1. Swimmer plot for patients with acute myeloid leukemia/myelodysplastic syndrome with minimal residual disease detectable in the post-transplant setting.** The swimmer plot illustrates the time to death or last known alive status for the 17 evaluable patients in cohort 2, who had minimal residual disease (MRD) detected after allogeneic stem cell transplantation and received guadecitabine, with or without donor lymphocyte infusion, for MRD eradication.

months) among survivors, the 2-year RFS and OS rates were 62.5% (95% CI: 40.3-78.4%) and 66.7% (95% CI: 44.3-81.7%), respectively (Figure 3A, B). Most relapses occurred withing the first year, with a 1-year cumulative relapse incidence of 33.3% (95% CI: 14-52.7%) and 2-year cumulative relapse incidence of 37.5% (95% CI: 17.6-56.4%). Non-relapse mortality was 0%.

At the last follow-up, ten of 24 patients (41.7%) had experienced morphological relapse, including seven who relapsed during guadecitabine maintenance (Figure 4). All but two relapses occurred within the first year of transplant. One patient who completed 12 cycles relapsed on day +637 after transplant, and another relapsed on day +791 after withdrawal following two cycles due to pneumonia. Among ten relapsed patients, six had detectable MRD before overt relapse, with a median time to overt relapse of 48 days (range, 30-98 days). Fourteen of 24 patients (58.3%) who received guadecitabine maintenance remain alive and in remission, including three of the seven patients with *TP53* mutation in this cohort.

## Safety and toxicity

No unexpected adverse events were observed. In cohorts 1 and 2 (morphological relapse and MRD cohorts), one grade 5 toxicity was reported in each cohort (Table 2). In cohort 1, a patient developed sepsis and died; while in cohort 2, a patient died from respiratory failure. The majority of adverse events observed were hematologic, as expected. Notably, no graft failure occurred in any cohort. Despite frequent bone marrow suppression with decreased neutrophil counts, infections were relatively uncommon, with only 12 grade 3-4 infectious episodes observed in cohort 3 and seven

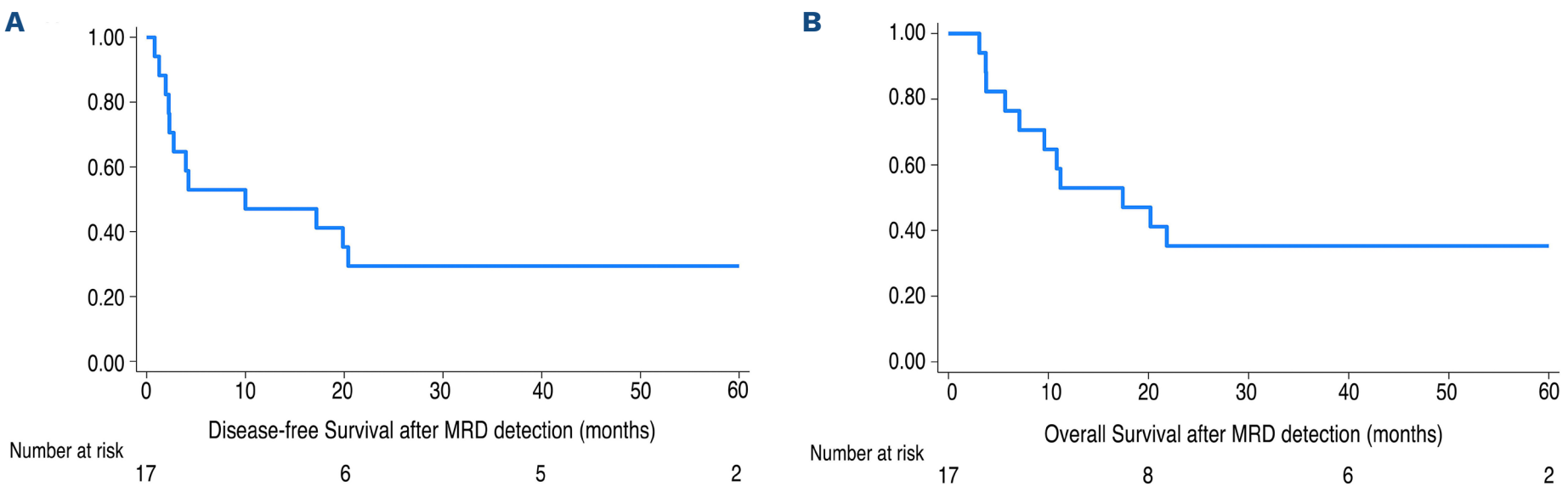


**Figure 2. Kaplan-Meier estimates of disease-free and overall survival distributions after minimal residual disease detection following allogeneic stem cell transplantation in patients who received guadecitabine with or without donor lymphocyte infusion.** (A, B) Kaplan Meier estimates of relapse-free survival (A) and overall survival (B) after minimal residual disease (MRD) detection in cohort 2, comprising patients who had MRD detected following allogeneic stem cell transplantation and received guadecitabine, with or without donor lymphocyte infusion, MRD eradication.

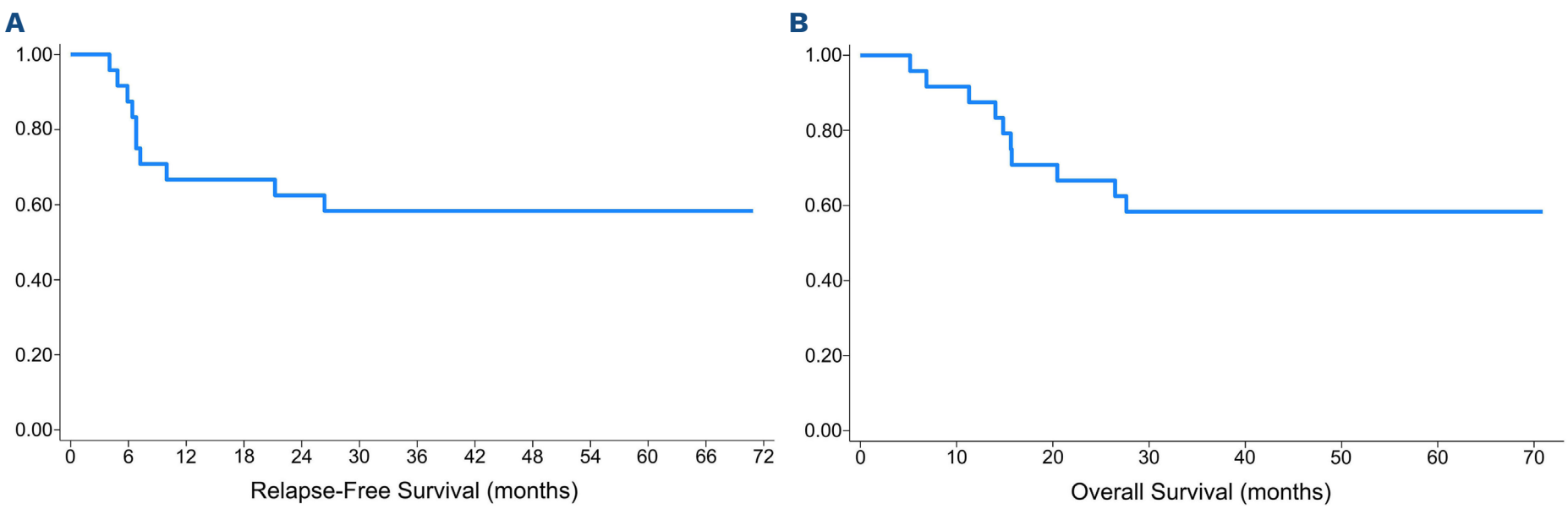


**Figure 3. Outcomes of patients with high-risk acute myeloid leukemia/myelodysplastic syndrome following allogeneic stem cell transplantation who received guadecitabine for maintenance treatment.** (A, B) Kaplan Meier estimates of relapse-free survival (A) and overall survival (B) after allogeneic stem cell transplantation in high-risk acute myeloid leukemia/myelodysplastic syndrome patients who received guadecitabine for post-transplant maintenance in cohort 3.

episodes in cohort 2. Non-hematologic toxicities were rare and gastro-intestinal toxicity was negligible.

Regarding GvHD, in cohort 2 (N=18), two patients developed late acute GvHD: one grade 3 after three cycles of guadecitabine and one DLI infusion, and one grade 2 after six cycles and one DLI. The grade 3 case was taken off the trial and died of GvHD 504 days after GvHD diagnosis. The grade 2 case resolved with treatment; the patient completed all 12 cycles of guadecitabine and no further DLI was given. One case of chronic GvHD occurred after five cycles of guadecitabine and one DLI, was well-controlled, and the patient completed 12 cycles of treatment without additional DLI.

In cohort 3 (N=24), one patient developed late acute GvHD, grade 2, after the fifth cycle which responded to treatment allowing completion of all 12 cycles. Two patients developed chronic GvHD after the fifth and sixth cycles, both were treated successfully and completed 9 and 12 cycles.

## Discussion

In this single-center phase II trial, AML/MDS patients treated with guadecitabine in the post-transplant setting showed promising outcomes. This investigational agent demonstrated efficacy in treating relapse, eradicating MRD, and serving as maintenance therapy, with a tolerable toxicity profile.

HMA are widely used either as monotherapy or in combination with other agents in the treatment of AML and MDS after allo-SCT. Most data on the post-transplant use of HMA are derived from studies utilizing either azacitidine and/or decitabine, administered intravenously or subcutaneously. However, guidelines for optimizing HMA use, either alone or in combination with other anti-leukemia agents, have not yet been established, and results from ongoing trials are eagerly awaited. The phase III, randomized, open-label VIALE-T trial (NCT04161885) is evaluating the safety and efficacy of subcutaneous azacitidine plus venetoclax *versus* best supportive care as maintenance therapy following allo-SCT in AML patients.

Additionally, an oral form of azacitidine has recently been approved for maintenance treatment in patients with AML,[20] and an oral decitabine/cedazuridine combination was approved by the US Food and Drug Administration for the treatment of MDS and chronic myelomonocytic leukemia.[21] The randomized, double-blind, placebo-controlled phase III

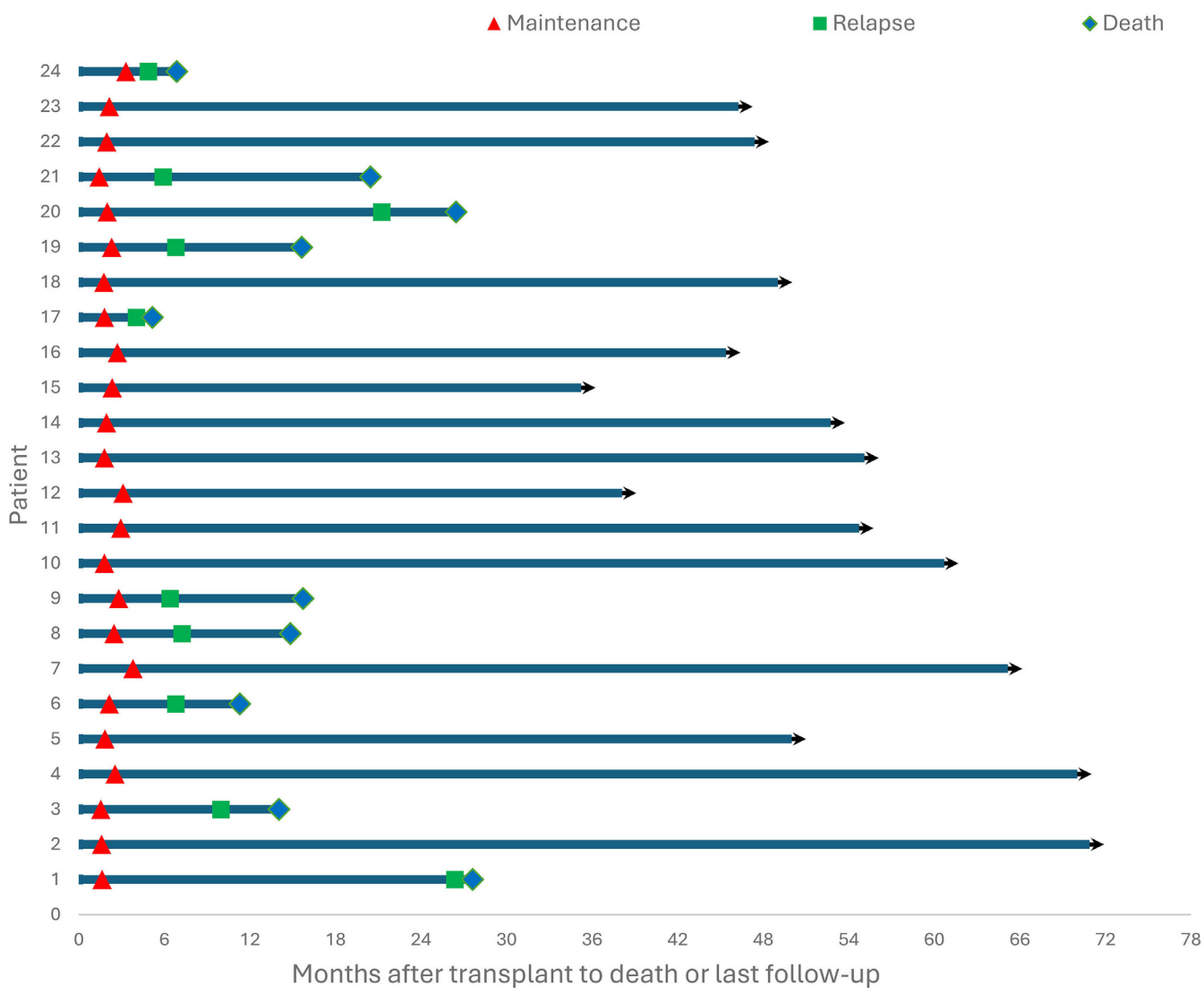


**Figure 4. Swimmer plot for patients with acute myeloid leukemia or myelodysplastic syndrome in remission without minimal residual disease detectable in the post-transplant setting who received guadecitabine maintenance.** The swimmer plot illustrates the time to death or last known alive status for the 24 high-risk acute myeloid leukemia/myelodysplastic syndrome patients who received post-transplant maintenance with guadecitabine (cohort 3). All eligible patients in this cohort were in complete remission with no detectable minimal residual disease at the initiation of maintenance therapy.

**Table 2.** Most common treatment-related adverse events.*

| Adverse events | N of events in cohort 1 | | | N of events in cohort 2 | | | N of events in cohort 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Grade 1-2 | Grade 3-4 | Grade 5 | Grade 1-2 | Grade 3-4 | Grade 5 | Grade 1-2 | Grade 3-4 | Grade 5 |
| Hematologic | | | | | | | | | |
| Anemia | - | 2 | - | 2 | 4 | - | 5 | 5 | - |
| Neutrophil count decreased | - | 9 | - | - | 16 | - | - | 21 | - |
| WBC decreased | - | 7 | - | 1 | 14 | - | 2 | - | - |
| Thrombocytopenia | - | 5 | - | 1 | 12 | - | 5 | 17 | - |
| Non-hematologic | | | | | | | | | |
| Diarrhea | - | 1 | - | 1 | 2 | - | 5 | - | - |
| Nausea | 3 | 2 | - | 4 | - | - | 5 | - | - |
| Vomiting | - | - | - | 3 | 1 | - | 3 | - | - |
| Transaminase elevation | - | 1 | - | 2 | - | - | 11 | 1 | - |
| Febrile neutropenia | - | 5 | - | - | 3 | - | - | 2 | - |
| Pneumonia | - | 1 | - | - | 1 | - | - | 5 | - |
| Sepsis | - | - | 1 | - | 1 | - | - | 1 | - |
| Other infections | - | 5 | - | - | - | - | 5 | 7 | - |
| Cardiac arrest | - | - | 1 | - | - | - | - | - | - |

*A total of 54 cycles of guadecitabine were administered in cohort 1, 106 cycles in cohort 2, and 162 cycles in cohort 3. WBC: white blood cell count.

AMADEUS trial (NCT04173533) is evaluating the safety and efficacy of oral azacitidine for AML and MDS maintenance therapy, with accrual now complete.

Given the expanding range of available regimens, identifying the optimal HMA for investigation in current and future post-transplant combinations remains critical.

Guadecitabine is a novel HMA that has demonstrated promising clinical activity in newly diagnosed and relapsed/refractory AML.[22] In a previous phase II study of a heavily pretreated population of patients, guadecitabine achieved a CR+CR with incomplete count recovery rate of 50-57%. The median survival was 574 days for patients who achieved CR and 476 days for those who achieved CR with incomplete count recovery. These encouraging results led to the design of the current clinical trial, which aims to define and establish the efficacy and safety of guadecitabine, with or without DLI, across various disease stages in the post-transplant setting.

Despite promising early findings, results of a randomized phase III clinical trial (ASTRAL-2) comparing guadecitabine to standard-of-care treatment in refractory or relapsed AML did not show a clear OS benefit.[13] However, the trial reported higher response rates, improved response duration and survival benefit in certain groups treated with guadecitibine. Following the ASTRAL-2 study results, which demonstrated no superiority of guadecitabine over standard-of-care treatment,[13] we were compelled to close our study prematurely. This decision was driven by the sponsor's choice to discontinue provision of the investigational agent, despite the promising interim outcomes.

The treatment cohorts in this study represented high-risk patients, even after undergoing allo-SCT. The low response rate observed in the hematologic relapse cohort was not unexpected but served as proof of concept for guadecitabine's potential efficacy in the post-transplant setting. In contrast, cohort 2, consisting of patients with MRD detected after transplant, showed more promising outcomes. Guadecitabine, with or without DLI, appeared to postpone or prevent hematologic relapse. Previously, we reported that most patients developed hematologic relapse within a median of 49-56 days after MRD detection by multicolor flow cytometry if no intervention was applied.[23] That study also found that approximately half of the patients whose relapses occurred more than 6 months after allo-SCT had detectable MRD in earlier bone marrow samples. Recent research has reinforced this finding. A study using droplet digital polymerase chain reaction for MRD detection in post-transplant MDS patients revealed that 42 of 54 relapses were preceded by positive MRD, with a median lead time of 71 days.[24] These results underscore the importance of timely MRD monitoring and effective interventions to prevent hematologic relapses after transplant.

In our current study, among 17 evaluable patients with post-transplant MRD, eight achieved MRD eradication with guadecitibine treatment, and only two of these patients relapsed (at 14.2 and 16.8 months after MRD detection). In contrast, the group who did not respond to guadecitabine developed hematologic relapse within 2 months of MRD detection.

The third cohort, included to evaluate the efficacy and safety of guadecitabine as maintenance therapy, demonstrated the most promising results. Among 24 evaluable high-risk patients, ten experienced hematologic relapses during follow-up. With a median follow-up of 4 years, RFS was 62.5% and no non-relapse mortality was observed.

Clinical trials focusing on maintenance therapies typically target high-risk populations. However, these trials often have an inherent selection bias, as participants must

have good graft function and be free of infection, GvHD and organ dysfunction. This selection bias contributes to extremely low transplant-related mortality rates, usually less than 10%, reported in maintenance trials. While low transplant-related mortality enhances RFS, it may dilute the observed maintenance effect.

In our maintenance cohort, we similarly targeted a population at high risk of relapse. Among AML patients, 75% had adverse-risk features according to European LeukemiaNet criteria. For MDS patients, 50% had a revised International Prognostic Scoring System score of 4.5 or higher, indicating a high or very high-risk prognostic group. Despite these adverse prognostic factors, the 2-year relapse incidence was 37.5%, which compares favorably to historical data showing relapse rates of 45% or higher, sometimes up to 70%, in high-risk AML and MDS populations without intervention.[25-27] While our results are encouraging, determining the true efficacy of any maintenance intervention requires a randomized trial.

Based on our findings, guadacitibine appears to be well-tolerated and no graft failure or non-relapse mortality was observed. These observations support the notion that HMA, alone or in combination with other anti-leukemic agents, have promising potential for maintenance therapy after allo-SCT.

Our study had several limitations. It was not a randomized trial which limited our ability to draw definitive conclusions. Additionally, we had a small sample size and we were unable to meet our accrual goal due to multiple challenges. During the COVID-19 pandemic, travel restrictions prevented many patients from participating, as they were out town or even out of state. Due to difficulties in closely monitoring patients and ensuring their safety, we paused enrollment. When we later attempted to resume, the sponsor withdrew support and stopped providing the investigational agent. The sponsor's decision was based on findings from the ASTRAL-2 and ASTRAL-3 studies, in which guadecitabine failed to show superiority over standard treatments in relapsed/refractory AML and MDS/chronic monomyelocytic leukemia, respectively. Following these results, our study was terminated early, and the sponsor ultimately discontinued guadecitabine development.

Despite these limitations, our study demonstrated a proof of concept and highlighted the potential efficacy and safety of guadecitibine with or without DLI across three distinct cohorts based on post-transplant disease status. The long-term follow-up data uniquely suggest that early intervention following MRD detection can effectively prevent hematologic relapse when applied promptly.

**Disclosures**

*BO and RC received research grants from ASTEX Pharmaceuticals during the study period.*

**Contributions**

*BO and RC designed and performed research, analyzed data and wrote the paper. PT and RB designed research, analyzed data and wrote the paper. AA, GA-A, JI, UP, PK, PS, RM, DM, QB, AO, JJ and ES performed research and wrote the paper.*

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**Data-sharing statement**

*Qualified researchers can request access to patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report forms, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of trial participants. All data sharing will be contingent on institutional approval.*

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