

CORRESPONDENCE

Long-term survival with oral azacitidine for patients with acute myeloid leukemia in first remission after chemotherapy: Updated results from the randomized, placebo-controlled, phase 3 QUAZAR AML-001 trial

To the Editor:

Despite recent therapeutic advances, outcomes remain poor for older patients with acute myeloid leukemia (AML). For patients in the USA diagnosed with AML between 2010–2017, the 5-year overall survival (OS) rate was 22% for patients aged 60–69 years, and only 5% for those aged ≥ 70 years.¹ Survival outcomes are influenced by patient- and disease-related factors, including age, comorbidities, cytogenetic abnormalities, gene mutations, and persistence of leukemic cells after intensive chemotherapy (IC) (i.e., measurable residual disease [MRD]).^{2,3} For patients with AML in remission, hematopoietic stem cell transplantation (HSCT) is often the only potentially curative option, but many patients are not candidates for HSCT due to advanced age, poor performance status, comorbidities, patient preference, or favorable AML European Leukemia Net risk, particularly in younger patients. Thus, there is a need for effective maintenance therapies to prolong survival among HSCT-ineligible patients in complete remission.

In the randomized, double-blind, phase 3 QUAZAR AML-001 trial, oral azacitidine (Oral-AZA) significantly prolonged OS and relapse-free survival (RFS) versus placebo in patients ≥ 55 years with AML in first remission after IC who were not HSCT candidates.⁴ At the July 2019 primary data cutoff, with a median follow-up time of 41.2 months, approximately one-quarter of all patients were alive and in survival follow-up. Here, we present updated OS outcomes (data cutoff March 2022) with the median follow-up time now 55.5 months and investigate clinical and biological variables predictive of long-term survival, defined here as survival ≥ 3 years from randomization, in patients treated with Oral-AZA or placebo.

The study design was described in detail in Wei et al.⁴ Briefly, patients aged ≥ 55 years with intermediate- or poor-risk cytogenetics at diagnosis who achieved first complete remission (CR) or CR with incomplete blood count recovery (CRI) with IC, were randomized 1:1 to receive Oral-AZA 300-mg or placebo once-daily for 14 days in repeated 28-day cycles. Patients in the Oral-AZA arm could continue treatment in an optional open-label extension phase after trial

unblinding (Figure S1). The primary endpoint was OS, defined as the time from randomization until death. Patients who withdrew consent or were lost to follow-up were then censored for OS. OS was estimated by Kaplan–Meier methods and compared between treatment groups by stratified log-rank test. *NPM1* and *FLT3* gene mutations^(mut) were assessed locally at diagnosis for most patients; post-IC MRD status was assessed centrally at study screening by multiparameter flow cytometry.^{5,6} During study therapy, surveillance bone marrow monitoring for hematologic remission and MRD status was performed every 3 cycles from cycles 3–24, then every 6 cycles or as clinically indicated. For patients MRD+ at baseline ($\geq 0.1\%$), MRD response was defined as achieving MRD negativity ($< 0.1\%$) at ≥ 2 consecutive assessments during study.

In all, 472 patients were randomized to Oral-AZA ($n = 238$) or placebo ($n = 234$). At diagnosis, 86% of patients had intermediate-risk cytogenetics, 29% had *NPM1*^{mut}, and 14% had *FLT3*^{mut} (Table S1).^{4–6} Median age was 68 (range 55–86) years and 47% of patients were MRD+ at screening.

Median OS at the primary data cutoff (median follow-up 41.2 months) was 24.7 versus 14.8 months with Oral-AZA versus placebo, respectively ($p < .001$); estimated 2-year survival rates were 50.6% versus 37.1% (difference [Δ] +13.5%; 95% confidence interval [CI], +4.5% to +22.5%).⁴ Over one-fourth of randomized patients (26.5%) were being followed for survival and censored for OS, including 71 patients still receiving Oral-AZA ($n = 45$) or placebo ($n = 26$) (Figure S2). After unblinding, 39 (16%) patients continued receiving Oral-AZA in an optional extension phase and 6 patients discontinued (3 withdrew consent, 2 relapsed, and 1 died). Patients still receiving placebo at unblinding had treatment discontinued and were followed for OS. After the primary data cutoff, patients not receiving active therapy (including patients who discontinued Oral-AZA during the extension phase) were followed for OS for up to 12 months.

At the updated March 2022 cutoff, median study follow-up was 55.5 months and 25 (11%) patients were receiving Oral-AZA maintenance in the extension phase (Figure S2). Overall, 54 (23%) patients in

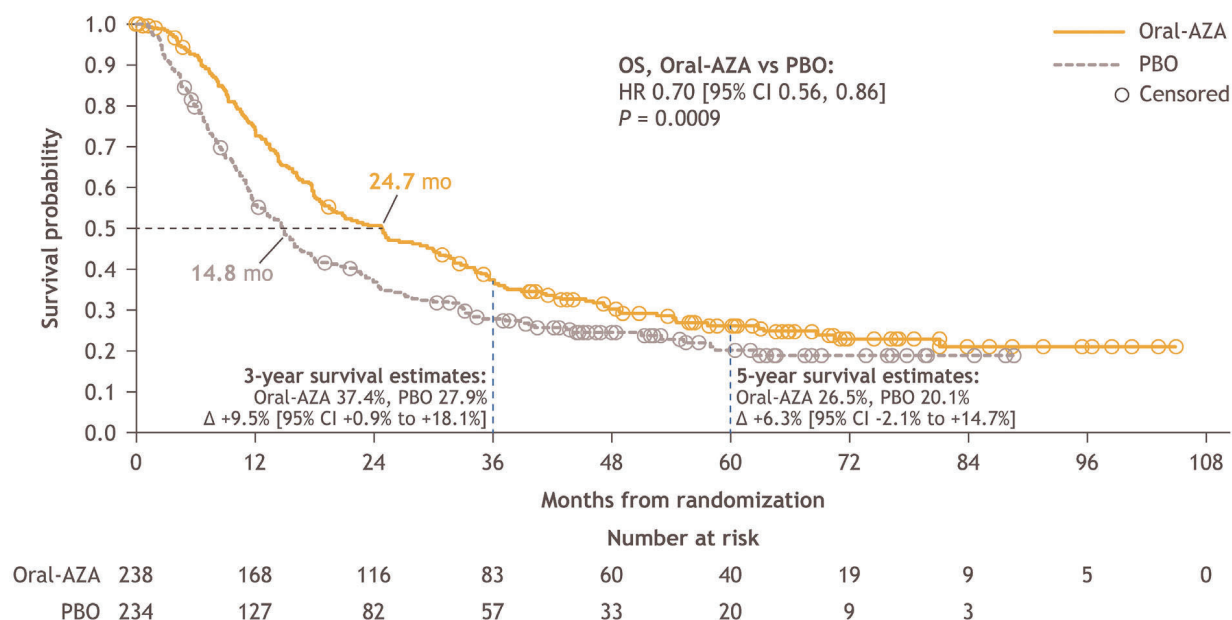


FIGURE 1 Kaplan-Meier estimated overall survival by treatment arm as of March 2022. CI, confidence interval; HR, hazard ratio; mo, months; Oral-AZA, oral azacitidine; OS, overall survival; PBO, placebo.

the Oral-AZA arm had received ≥ 36 treatment cycles (~ 3 years), and 34 (14%) had received ≥ 60 cycles. Median OS in each arm at the updated cutoff remained unchanged from the primary analysis, but the Kaplan-Meier curves for Oral-AZA and placebo remained separated through ~ 80 months from randomization (Figure 1). Estimated 3-year survival rates in the Oral-AZA and placebo arms were 37.4% and 27.9%, respectively ($\Delta +9.5\%$ with Oral-AZA [95%CI +0.9% to +18.1%]); 5-year survival rates were 26.5% versus 20.1% ($\Delta +6.3\%$ [95%CI -2.1% to +14.7%]).

To assess clinical and biological variables predictive of long-term survival, patients were separated into two subgroups: the “Long-term Survivors” (LTS) cohort comprised patients known to have survived ≥ 3 years from randomization, whereas the “Non-LTS” cohort included patients who died, were lost to follow-up, or withdrew consent before 3 years. The LTS cohort comprised 30% (140/472) of all patients, including 35% (83/238) and 24% (57/234) of patients in the Oral-AZA and placebo arms, respectively. Compared with the Non-LTS group, patients in the LTS cohort were more likely to have intermediate-risk cytogenetics (95% vs. 82%, respectively) and *NPM1*^{mut} (45% vs. 22%) at diagnosis, and less likely to be MRD+ at screening (34% vs. 53%) (Table S2). Use of consolidation chemotherapy and number of consolidation cycles were generally similar between the LTS and Non-LTS cohorts. Baseline demographic and disease characteristics were largely balanced between treatment arms within each LTS-defined cohort. Patients in the Oral-AZA arm who were LTS received a median of 47 treatment cycles, compared with 8 cycles in the Non-LTS cohort. In the placebo arm, patients in the LTS cohort and the Non-LTS cohort received a median of 34 cycles and 5 cycles, respectively.

In post-hoc univariate analyses, intermediate-risk cytogenetics and *NPM1*^{mut} at diagnosis were each significantly correlated with long-term (≥ 3 years from randomization) survival within each treatment arm

(Figure S3). No significant relationship was found between prior consolidation and long-term survival within either arm. In the placebo arm, there was a trend for greater long-term survival in patients who received 2–3 prior consolidation cycles versus no consolidation but this association was not significant after adjusting for multiple testing ($p = .161$). As may be expected, longer randomized treatment duration was significantly associated with long-term survival in both arms. Baseline MRD— status was positively associated with long-term survival in the placebo arm but not the Oral-AZA arm (Figure S3). Overall, 37% (38/103) of baseline MRD+ patients in the Oral-AZA arm achieved MRD response (i.e., conversion from MRD+ at baseline to MRD–), compared with 19% (22/116) of patients in the placebo arm (odds ratio 2.50 [95%CI 1.35–4.61]).⁶ MRD response on study was significantly associated with superior long-term survival in both arms. While acknowledging the potential for lead-time bias by including MRD response in these survival analyses (i.e., longer survival may have allowed for more time to achieve MRD response), most (Oral-AZA, 76% [29/38]; placebo, 95% [21/22]) MRD responses occurred ≤ 6 months from randomization,⁶ whereas long-term survival required that a patient survive ≥ 3 years from randomization. Fifteen patients (6%) in the Oral-AZA arm underwent HSCT within 3 years from randomization, including 6 who discontinued treatment while in first remission to receive HSCT, compared with 32 (14%) in the placebo arm (all of whom had relapsed); in univariate analyses, subsequent HSCT was significantly associated with long-term survival only in the placebo arm (Figure S3).

A post-hoc multivariable logistic regression analysis was performed to identify baseline characteristics independently associated with long-term survival and assess the independent treatment effect of Oral-AZA when adjusting for other covariates. The model included randomized treatment arm (Oral-AZA vs. placebo), *NPM1* status (*NPM1*^{mut} vs. *NPM1*^{wt}) at diagnosis, cytogenetic risk (poor

vs. intermediate) at diagnosis, MRD status (MRD+ vs. MRD-) at screening, and absolute neutrophil count (continuous variable) at screening. After controlling for other covariates, Oral-AZA remained significantly and independently predictive of long-term survival, as were *NPM1*^{mut}, intermediate-risk cytogenetics, and baseline MRD-status at screening (Table S3).

These updated data demonstrate the long-term survival benefit of Oral-AZA for patients in first remission after IC. With additional survival follow-up, Oral-AZA showed sustained OS improvement versus placebo for over 5 years from randomization, and improved absolute 3- and 5-year OS rates versus placebo by 9.5% and 6.3%, respectively. Nearly one-fourth (23%) of patients randomized to Oral-AZA received ≥ 36 cycles (~ 3 years) of treatment, with 11% (25/238) of patients still receiving Oral-AZA at the updated cutoff, supporting the feasibility and tolerability of long-term maintenance therapy with Oral-AZA. As expected, intermediate cytogenetic risk status (vs. poor) and presence of *NPM1*^{mut} (vs. *NPM1*^{wt}) at diagnosis were each significantly associated with long-term survival (≥ 3 years from randomization) in both univariate and multivariable analyses. While significant in the overall population in multivariate analysis, baseline MRD- status was only significantly predictive of superior long-term survival within the placebo arm in univariate analyses, suggesting that Oral-AZA may increase the likelihood of long-term survival by partially mitigating the adverse prognostic effect of post-IC MRD positivity, as evidenced by the two-fold higher rate of conversion from MRD positive to negative status during Oral-AZA therapy. For patients MRD+ at screening, achievement of MRD- status on study was significantly correlated with long-term survival in both arms. When controlling for key prognostic pretreatment covariates, Oral-AZA remained significantly predictive of long-term survival compared with placebo. In conclusion, these updated findings demonstrate the feasibility and sustained long-term clinical benefit of Oral-AZA maintenance, now with over 4 years of median follow-up time for patients in remission after chemotherapy. Patients with AML completing intensive induction and consolidation therapy should therefore be strongly considered for Oral-AZA maintenance, particularly those for whom HSCT may not be feasible or initially indicated, including patients with favorable risk *NPM1* mutated disease.

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CONFLICT OF INTEREST STATEMENT

AHW has served on advisory boards for AbbVie, Agios, Amgen, Celgene/Bristol Myers Squibb, Gilead, Janssen, MacroGenics, Novartis, Pfizer, Roche, and Servier; has received research funding to his institution from AbbVie, Amgen, AstraZeneca, Celgene/Bristol Myers Squibb, Novartis, and Servier; has served on a speakers bureau for AbbVie, Celgene, and Novartis; and is eligible for royalty payments from the Walter and Eliza Hall Institute of Medical

Research related to venetoclax. HDö has served in a consultancy position for AbbVie, Agios, Amgen, Astellas, Berlin-Chemie, Bristol Myers Squibb, Daiichi Sankyo, Gilead, Janssen, Jazz Pharmaceuticals, Novartis, Servier, and Syndax; reports receiving research funding from AbbVie, Agios, Amgen, Astellas, Bristol Myers Squibb, Jazz Pharmaceuticals, Kronos Bio, Novartis, and Pfizer; and reports receiving honoraria from AbbVie, Agios, Amgen, Astellas, AstraZeneca, Berlin-Chemie, Bristol Myers Squibb, Daiichi Sankyo, Gilead, Janssen, Jazz Pharmaceuticals, Novartis, Servier, and Syndax. HS has served on advisory committees for Bristol Myers Squibb. FR reports receiving research funding from Amgen, Astellas, Astex/Taiho, Biomea Fusion, Celgene/Bristol Myers Squibb, Prelude, Syros, and Xencor; and honoraria from AbbVie, Astellas, AstraZeneca, Celgene/Bristol Myers Squibb, Novartis, and Syros. PM has served in a consultancy position for Menarini/Stemline, Gilead, Otsuka, Kura Oncology, AbbVie, Bristol Myers Squibb, Novartis, Jazz Pharmaceuticals, BeiGene, Astellas, Pfizer, Incyte, Takeda, Ryvu, and Nerviano; reports receiving research funding from AbbVie, Bristol Myers Squibb, Jazz Pharmaceuticals, Menarini/Stemline, Novartis, Pfizer, and Takeda; and has served on a speakers bureau for AbbVie, Astellas, Bristol Myers Squibb, Gilead, Jazz Pharmaceuticals, and Pfizer. HDo reports receiving honoraria from Incyte and Servier. DS reports receiving grants or contracts, honoraria, consulting fees, and travel support from AbbVie, Bristol Myers Squibb, Novartis, and Pfizer; and has served in a leadership role for the Belgian College for Reimbursement of Orphan Drugs. BS reports prior employment with Celgene/Bristol Myers Squibb. CLB reports prior employment and stock ownership with Bristol Myers Squibb. TP and GZ report employment and stock ownership with Bristol Myers Squibb. AR and DM report employment, stock ownership, and patents with Bristol Myers Squibb. MU and WLS report employment with Bristol Myers Squibb. GJR reports receiving research support from Janssen and has served in an advisory position for AbbVie, Agios, Amgen, Astellas, AstraZeneca, Bluebird Bio, Blueprint Medicines, Bristol Myers Squibb, Catamaran, Celgene, Glaxo SmithKline, Helsinn, Janssen, Jasper Therapeutics, Jazz Pharmaceuticals, Mesoblast, Novartis, Pfizer, Roche, Syndax, and Takeda (IRC Chair).

DATA AVAILABILITY STATEMENT

BMS policy on data sharing may be found at <https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html>.

PATIENT CONSENT STATEMENT

All patients provided informed written consent. An independent data monitoring committee assessed study conduct and safety outcomes.

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REFERENCES

1. Sasaki K, Ravandi F, Kadia TM, et al. De novo acute myeloid leukemia: a population-based study of outcome in the United States based on the surveillance, epidemiology, and end results (SEER) database, 1980 to 2017. *Cancer*. 2021;127(12):2049-2061.
2. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022;140(12):1345-1377.
3. Ravandi F, Walter RB, Freeman SD. Evaluating measurable residual disease in acute myeloid leukemia. *Blood Adv*. 2018;2(11):1356-1366.
4. Wei AH, Döhner H, Pocock C, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. *N Engl J Med*. 2020;383(26):2526-2637.
5. Döhner H, Wei AH, Roboz GJ, et al. Prognostic impact of *NPM1* and *FLT3* mutations in patients with AML in first remission treated with oral azacitidine. *Blood*. 2022;140(15):1674-1685.
6. Roboz GJ, Ravandi F, Wei AH, et al. Oral azacitidine prolongs survival of patients with AML in remission independent of measurable residual disease status. *Blood*. 2022;139(14):2145-2155.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.