Oral azacitidine preserves favorable level of fatigue and health-related quality of life for patients with acute myeloid leukemia in remission: results from the phase 3, placebo-controlled QUAZAR AML-001 trial

by Gail J. Roboz, Hartmut Döhner, Christopher Pocock, Hervé Dombret, Farhad Ravandi, Jun Ho Jang, Dominik Selleslag, Jiří Mayer, Uwe M. Martens, Jane Liesveld, Teresa Bernal, Ming Chung Wang, Peiwen Yu, Ling Shi, Shien Guo, Ignazia La Torre, Barry Skikne, Qian Dong, Julia Braverman, Salem Abi Nehme, C. L. Beach, and Andrew H. Wei

Received: May 7, 2021.
Accepted: September 15, 2021.


Publisher's Disclaimer.
E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval; the final version of the manuscript will then appear in a regular issue of the journal. All legal disclaimers that apply to the journal also pertain to this production process.
Oral azacitidine preserves favorable level of fatigue and health-related quality of life for patients with acute myeloid leukemia in remission: results from the phase 3, placebo-controlled QUAZAR AML-001 trial

Gail J. Roboz¹,²; Hartmut Döhner³; Christopher Pocock⁴; Hervé Dombret⁵; Farhad Ravandi⁶; Jun Ho Jang⁷; Dominik Selleslag⁸; Jiří Mayer⁹; Uwe M. Martens¹⁰; Jany Liesveld¹¹; Teresa Bemal¹²; Ming Chung Wang¹³; Peiwen Yu¹⁴; Ling Shi¹⁴; Shien Guo¹⁴; Ignazia La Torre¹⁵; Barry Skikne¹⁶;¹⁷; Qian Dong¹⁶; Julia Braverman¹⁶; Salem Abi Nehme¹⁵; C. L. Beach¹⁶; and Andrew H. Wei¹⁸

¹Weill Cornell Medical College, New York, NY; ²New York Presbyterian Hospital, New York, NY; ³Ulms University Hospital, Ulm, Germany; ⁴Kent & Canterbury Hospital, Canterbury, United Kingdom; ⁵Hôpital Saint-Louis, Assistance Publique – Hôpitaux de Paris (AP-HP) and Institut de Recherche Saint-Louis, Université de Paris, Paris, France; ⁶The University of Texas MD Anderson Cancer Center, Houston, TX; ⁷Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; ⁸AZ Sint-Jan Brugge-Oostende AV, Bruges, Belgium; ⁹University Hospital Brno, Brno, Czech Republic; ¹⁰SLK-Kliniken GmbH, MOLIT Institute for Personalized Medicine, Heilbronn, Germany; ¹¹Wilmut Cancer Institute, University of Rochester, New York, NY; ¹²Hospital Universitario Central de Asturias, Oviedo, Spain; ¹³Chang Gung Medical Foundation, Kaohsiung, Taiwan; ¹⁴Evidera, Waltham, MA; ¹⁵Celgene, a Bristol-Myers Squibb Company, Boudry, Switzerland; ¹⁶Bristol Myers Squibb, Princeton, NJ; ¹⁷University of Kansas Medical Center, Kansas City, KS; ¹⁸The Alfred Hospital and Monash University, Melbourne, Australia

Corresponding Author:
Gail J. Roboz, M.D.
Director, Clinical and Translational Leukemia Programs
Professor of Medicine
Weill Cornell Medical College
The New York Presbyterian Hospital
525 East 68th Street
New York, NY 10021
O: (646) 962-2700
F: (646) 962-0115
gar2001@med.cornell.edu

Acknowledgments: This study was sponsored and funded by Celgene, a Bristol-Myers Squibb Company. Editorial support on an early draft of the manuscript was provided by Sheila Truten and Brian Kaiser from Medical Communication Company, Inc. (Wynnewood, PA, USA), funded by Bristol Myers Squibb and in accordance with Good Publication Practice guidelines.

Author Contributions: The sponsors collected and analyzed data in conjunction with all authors. The lead author wrote the initial draft of the manuscript. All authors revised the manuscript and approved the final version for submission.

Competing Interests: G.J.R. reports Consultancy or Advisory Board or Data and Safety Monitoring Committee: AbbVie, Actinium, Agios, Amphivena, Amgen, Argenx, Array Biopharma, Astex, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Celltrion, Daiichi Sankyo, Eisai, Epizyme, GlaxoSmithKline, Helsinn, Janssen, Jasper Therapeutics, Jazz, Mesoblast, MEI Pharma (IDMC Chair),
Novartis, Orsenix, Otsuka, Pfizer, Roche/Genentech, Sandoz, Takeda (IRC Chair), Trovagene; Research
Support: Cellectis. **H. Döhner** reports personal fees from Abbvie, Agios, Astellas, Astex Pharmaceuticals,
Helsinn, Janssen, Oxford Biomedicals, and Roche; grants and personal fees from Amgen, Celgene, Jazz
Pharmaceuticals, and Novartis; and grants from AROG Pharmaceuticals, Bristol Myers Squibb, Pfizer, and
Sunesis. **H. Dombret** reports grants and personal fees from Celgene, Amgen, Incyte, Novartis, Jazz
Pharmaceuticals, Daiichi Sankyo, Servier, and Astellas; and personal fees from Pfizer, Cellectis, Menarini,
Otsuka, AbbVie, Janssen, Shire-Baxalta, Celyad, Agios, and Immunogen. **F. R.** reports honoraria and
consulting fees from Bristol Myers Squibb and Celgene; and Research funding from Bristol Myers Squibb.
**D.S.** reports honoraria from Novartis, Celgene, Amgen, Janssen-Cilag, AbbVie, Alexion, GSK, MSD, Pfizer,
Sanofi, Takeda, Incyte, and Teva; consultancy for Novartis, Celgene, Amgen, Janssen-Cilag, AbbVie,
Alexion, GSK, MSD, Pfizer, Sanofi, Takeda, Incyte, and Teva; and speakers’ bureau participation for
Novartis, Celgene, Amgen, MSD, Takeda, and Teva. **J.M.** reports research funding from Celgene. **U.M.M.**
reports consultancy for Bristol Myers Squibb, Merck, Amgen, Roche, and Celgene; and travel
accommodations/expenses from Bristol Myers Squibb, Amgen, Pierre-Fabre, and Celgene. **J.L.** reports
participation in DSMB for Onconova. **P.Y., L.S.,** and **S.G.** are employed by Evidera. **B.S.** is employed by
Bristol Myers Squibb. **I.L.T., Q.D., J.B., S.A.N.,** and **C.I.B.** are employed at and have equity ownership in
Bristol Myers Squibb. **A.H.W.** reports study-related fees and personal fees from Celgene; royalties
from Walter and Eliza Hall Institute of Medical Research; grants from the Medical Research Future
Fund; grants and personal fees from Servier, AbbVie, Novartis, Celgene, Astra Zeneca, and Janssen;
and personal fees from Astellas, Pfizer, Macrogenics, and Amgen. **C.P., J.H.J., T.B.,** and **M.C.W.** report
no conflicts.

**Running head (limit 50 characters, including spaces)**: *HRQol with Oral Azacitidine for AML Maintenance
Word count (limit 1500): 1499

**References (limit 15):** 13

**Tables and figures (limit 3):** 1 table + 2 figures

**Supplementary material (limit 3 tables/figures):** 2 tables + 1 figure

**Trial registration:** ClinicalTrials.gov NCT01757535

**Data sharing statement:** BMS policy on data sharing may be found at
Despite relatively high remission rates with intensive chemotherapy (IC), most patients with acute myeloid leukemia (AML) will relapse, and overall survival (OS) in relapsed AML is dismal. In the phase 3, placebo-controlled QUAZAR AML-001 trial, oral azacitidine (Oral-AZA [CC-486]) showed to significantly prolong OS vs. placebo ($P=0.0009$; median 24.7 vs. 14.8 months from randomization) and relapse-free survival (RFS) ($P=0.0001$; 10.2 vs. 4.8 months) as maintenance therapy for patients with AML in first remission after IC, and was associated with a manageable safety profile. Health-related quality of life (HRQoL) and fatigue generally improve over time for patients with AML in remission; an ideal maintenance treatment should prolong survival without compromising HRQoL.

The impact of Oral-AZA on patient-reported fatigue and HRQoL, a key secondary endpoint in QUAZAR AML-001, was assessed using the self-administered Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale and EuroQol EQ-5D-3L instruments. We hypothesized that Oral-AZA treatment would not meaningfully worsen fatigue or overall HRQoL from baseline, and that mean changes from baseline in fatigue and HRQoL scores in the Oral-AZA arm would be comparable (ie, noninferior) to those in the placebo arm.

Topline HRQoL outcomes of this study are described briefly elsewhere. At study entry, patients reported generally favorable levels of fatigue and overall HRQoL. Mean FACIT-Fatigue and EQ-5D-3L health utility index (HUI) scores remained similar to baseline over time during Oral-AZA treatment, with similar changes between the Oral-AZA and placebo arms. We describe previously unreported HRQoL results from QUAZAR AML-001, including longitudinal analyses using linear mixed-effect models for repeated measures (MMRM), outcomes in patient subgroups defined by prognostic baseline characteristics, and rates of clinically meaningful deterioration in HRQoL scores.
QUAZAR AML-001 was a randomized, double-blind, placebo-controlled phase 3 trial. Study design and endpoints are reported in detail elsewhere. Briefly, patients aged ≥55 years, with intermediate- or poor-risk cytogenetics at diagnosis, ECOG PS ≤3, and ineligible for transplant, were randomized to Oral-AZA 300-mg or placebo once-daily for 14 days/28-day cycle within 4 months after achieving first CR or CR with incomplete hematologic recovery (CRI) with IC (induction ± consolidation). Patients who relapsed on-study with 5-15% blasts could receive an escalated 21-days/cycle dosing schedule at the discretion of the treating investigator.

The FACIT-Fatigue Scale is a 13-item questionnaire that measures an individual's level of fatigue during daily activities over the previous week. The EQ-5D-3L is a generic instrument that includes a descriptive questionnaire that assesses impairment across 5 dimensions (mobility, self-care, pain/discomfort, usual activities, anxiety/depression) at 3 severity levels (none, moderate, severe), and a visual analogue scale (VAS) that asks patients to rate their perceived HRQoL from 0-100. Higher scores indicate lower fatigue (FACIT-Fatigue) and better health state (EQ-5D-3L). Both instruments were completed on day 1 of each cycle and end-of-treatment (EOT). HRQoL-evaluable patients had non-missing assessments at baseline and ≥1 post-baseline visit.

To interpret changes from baseline, we used predefined thresholds for clinically meaningful changes within/between treatment arms (ie, minimally important differences [MIDs]) and at the individual level (ie, responder definitions [RDs]). Thresholds used to define clinically meaningful improvement and deterioration from baseline, respectively, were score changes of +3/–3 on the FACIT-Fatigue Scale; +0.08/–0.10 on the EQ-5D-3L HUI; and +11/–11 on the EQ-5D VAS.

MMRM models were performed to confirm the hypothesized noninferiority of Oral-AZA and placebo; these models used an unstructured covariance matrix and included the intercept and visit as random effects, and treatment arm, randomization stratification factors, baseline HRQoL score, visit,
baseline-by-visit interaction, and treatment-group-by-visit interaction as fixed effects. The dependent variable was change in HRQoL score from baseline. Noninferiority of Oral-AZA vs. placebo was demonstrated if the lower bound of the 2-sided 95% confidence interval (95%CI) of the between-group difference in the overall least-squares (LS) mean change from baseline was greater than the MID for deterioration at each assessment.5,10

Empirical cumulative distribution frequency (eCDF) curves were generated showing FACIT-Fatigue score changes from baseline for individual patients within each treatment arm at cycles 3, 6, 12, and 24, using the predefined RDs for clinically meaningful improvement and deterioration (+3/–3 points). Time to confirmed deterioration was assessed for each patient from the time of randomization until the first of ≥2 consecutive visits with a change from baseline surpassing the RD for clinically meaningful deterioration, or until death. Time to confirmed deterioration was estimated using Kaplan-Meier product-limit methods and compared between treatment arms using a stratified Cox proportional hazards regression model with treatment group and baseline score as covariates.

The FACIT-Fatigue-evaluable population comprised 225/238 patients (94.5%) randomized to Oral-AZA and 219/234 patients (93.6%) randomized to placebo, and the EQ-5D-3L–evaluatable population included 225 and 217 patients, respectively. Baseline demographic and disease characteristics of HRQoL-evaluable patients were balanced between treatment arms (Supplementary Table 1). FACIT-Fatigue and EQ-5D-3L compliance rates were ≥95% in both treatment arms at baseline and remained high (>85%) across postbaseline visits except at EOT (~65%), suggesting that HRQoL endpoints were unlikely to be confounded by missing data. Patient-reported FACIT-Fatigue, EQ-5D-3L HUI, and EQ-5D VAS scores were comparable between treatment groups at baseline and similar to reference values from general populations in the United States (FACIT-Fatigue) and Germany (EQ-5D-3L) (Supplementary Table 2).2,11,12 Median treatment durations for HRQoL-evaluable patients were 12 cycles and 7 cycles in the Oral-AZA and placebo arms, respectively.
As reported previously, there were no clinically meaningful differences in observed mean changes from baseline FACIT-Fatigue or EQ-5D-3L HUI scores within treatment arms, or between the Oral-AZA and placebo arms, at any postbaseline visit.\textsuperscript{2} Longitudinal MMRM analyses confirmed the noninferiority of Oral-AZA effects on fatigue and overall HRQoL relative to placebo, as the lower bounds of the 95% CIs for between-group differences in LS mean changes from baseline did not exceed the predefined MIDs for worsening on any instrument (Table 1).

In subgroup analyses, observed mean HRQoL scores generally remained similar to baseline over time within each arm. Mean changes in FACIT-Fatigue, EQ-5D-3L HUI, and EQ-5D VAS scores were comparable between treatment arms within patient subgroups defined by cytogenetic risk at diagnosis (intermediate/poor), response after induction (CR/CRi), receipt of consolidation chemotherapy (yes/no), ECOG PS score (0-1/2-3), age (&lt;65/65-74/≥75 years), and HRQoL domain score (&lt;25 th/25 th-74 th/≥75 th percentile). Overall, 45 HRQoL-evaluable patients experienced relapse with 5-15% blasts and received Oral-AZA for 21 days/cycle. Escalated Oral-AZA dosing was not associated with clinically meaningful differences in changes from baseline in mean FACIT-Fatigue, EQ-5D-3L HUI, or EQ-5D VAS scores at any visit compared with 14-day Oral-AZA dosing.

eCDF curves detailing individual FACIT-Fatigue changes from baseline in the Oral-AZA and placebo arms at cycles 3, 6, 12, and 24 generally overlapped, with similar proportions of patients reporting clinically meaningful improvement or deterioration at each visit (Figure 1). Proportions of patients with clinically meaningful deterioration for each measure were low in both treatment arms, and rates were similar between arms on each instrument at almost all post-baseline visits (Supplementary Figure 1); deterioration rates were significantly higher in the Oral-AZA arm at cycle 19 (EQ-5D VAS) and cycle 29 (FACIT-Fatigue), but these may have occurred by chance as these analyses did not include any adjustments for multiple testing. Times to confirmed deterioration were similar between the Oral-AZA and placebo arms on each instrument (Figure 2). Estimated median times to confirmed deterioration
were 41 weeks for Oral-AZA and 44 weeks for placebo on the FACIT-Fatigue (HR 1.06 [95%CI 0.80-1.40]);
200 and 164 weeks, respectively, on the EQ-5D-3L HUI (0.91 [0.62-1.34]); and not reached vs. 136 weeks
on the EQ-5D VAS (0.86 [0.61-1.22]). Similar findings were observed when censoring patients at the time
of death.

While improving survival is the primary goal of AML treatment, systematic evaluation of the
impact of treatment on HRQoL is essential because prolonged survival may be less meaningful if
accompanied by drug-related HRQoL decrements. To our knowledge, QUAZAR AML-001 is the first
placebo-controlled study to prospectively investigate the impact of long-term maintenance therapy on
HRQoL for patients with AML in remission post-IC. At study entry, these older patients (median age 68
years\(^2\)) reported generally favorable levels of fatigue and overall HRQoL that were comparable to levels
in general populations.\(^{11,12}\) Mean FACIT-Fatigue and EQ-5D-3L scores during Oral-AZA treatment
remained at or above baseline levels at almost all post-baseline assessments, and longitudinal MMRM
analyses confirmed the noninferiority of Oral-AZA relative to placebo for preserving HRQoL. These
HRQoL data are also consistent with the reported manageable safety profile and acceptable tolerability
of Oral-AZA in QUAZAR AML-001.\(^2\)

A potential limitation of this study was that HRQoL assessments were conducted on day 1 of
each 28-day treatment cycle, allowing for 14 days of recovery after each 14-day dosing period.
Additionally, patients in both arms had to undergo routine hospital visits, testing, and marrow
collections, which could potentially negatively affect HRQoL outcomes compared with an “observation-
only” approach during AML remission.

Oral azacitidine administration offers a number of potential benefits, including optimal
convenience for patients, no injection-site reactions, fewer clinic visits and lower associated costs, and
treatment flexibility for long-term use. Findings from QUAZAR AML-001 show that Oral-AZA significantly
improves OS and RFS without compromising fatigue or overall HRQoL for patients with AML in remission.
References
1. Brandwein JM, Saini L, Geddes MN, et al. Outcomes of patients with relapsed or refractory acute


with intensive chemotherapy for acute myeloid leukemia improve over time independent of age. J Geriatr

function over three years in adult survivors of acute myeloid leukemia after intensive chemotherapy.

5. Gerlinger C, Schmelter T. Determining the non-inferiority margin for patient reported outcomes.

the clinical significance of health-related quality of life (HrQOL) improvements in anaemic cancer patients

7. Kvam AK, Fayers PM, Wisloff F. responsiveness and minimal important score differences in
quality-of-life questionnaires: a comparison of the EORTC QLQ-C30 cancer-specific questionnaire to the
2011;87(4):330-337.

8. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and

9. Ashbeck EL, Bell ML. Single time point comparisons in longitudinal randomized controlled trials:


Cancer Stat Facts: Leukemia - Acute Myeloid Leukemia (AML). [cited March 1, 2021]; Available from:
Table 1. Mixed-effect models for repeated measures (MMRM) analyses: Overall least-squares (LS) mean changes from baseline within in each arm, between-group differences in overall LS mean changes, and prespecified minimally important differences (MIDs) for each assessment

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Overall LS mean [95%CI] change from baseline</th>
<th>Difference in overall LS mean change, Oral-AZA vs. placebo, mean [95%CI]*</th>
<th>Prespecified MID for clinically meaningful worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral-AZA</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACIT-Fatigue scale</td>
<td>–0.60 [–2.19, 0.99]</td>
<td>–0.89 [–2.37, 0.59]</td>
<td>–3</td>
</tr>
<tr>
<td>EQ-5D-3L health utility index</td>
<td>–0.01 [–0.03, 0.01]</td>
<td>–0.01 [–0.03, 0.01]</td>
<td>–0.10</td>
</tr>
<tr>
<td>EQ-5D visual analogue scale</td>
<td>2.64 [–0.59, 5.86]</td>
<td>–0.95 [–4.38, 2.47]</td>
<td>–11</td>
</tr>
<tr>
<td></td>
<td>3.59 [0.01, 7.17]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*MMRM analyses confirmed the noninferiority of Oral-AZA effects on fatigue and overall HRQoL vs. placebo, as the lower bounds of the 95% CIs for between-group differences in LS mean changes from baseline did not exceed the predefined MIDs for worsening on any assessment.

95%CI, 95% confidence interval; AZA, azacitidine; FACIT, Functional Assessment of Chronic Illness Therapy; LS, least-squares; MID, minimally important difference.
Figure Legends

Figure 1. Empirical cumulative distribution frequency (eCDF) curves of observed changes from baseline on FACIT-Fatigue scores for individual patients in the oral azacitidine and placebo arms at cycles 3, 6, 12 and 24.

Figure 2. Kaplan-Meier estimated times to confirmed deterioration from baseline. (A) FACIT-Fatigue scale. (B) EQ-5D-3L health utility index. (C) EQ-5D visual analogue scale scores.
A positive change score indicates an improvement from baseline. A change from baseline of ≥ 3 points was used to define clinically meaningful improvement and worsening. Odds ratios, 95% confidence intervals, and P values were estimated using Cochran-Mantel-Haenszel tests, stratified by randomization stratification factors.

95%CI, 95% confidence interval; AZA, azacitidine; FACIT, Functional Assessment of Chronic Illness Therapy; OR, odds ratio; RD, responder definition.
Figure 2.

A. FACIT-Fatigue Scale

- Oral AZA
- Placebo

Proportion of patients without deterioration vs. time to clinically meaningful deterioration, weeks.

HR 1.06 [95% CI 0.80, 1.40]

P = 0.6984

No. at risk:
- Oral AZA: 225, 90, 53, 37, 23, 13, 7, 5, 5, 4, 2, 0
- Placebo: 217, 65, 28, 17, 13, 6, 4, 3, 2, 1, 0

B. EQ-5D-3L Health Utility Index

Proportion of patients without deterioration vs. time to clinically meaningful deterioration, weeks.

HR 0.91 [95% CI 0.62, 1.34]

P = 0.6330

No. at risk:
- Oral AZA: 225, 127, 79, 57, 36, 18, 12, 9, 6, 5, 3, 0
- Placebo: 217, 82, 42, 28, 22, 12, 8, 5, 3, 2, 0

C. EQ-5D Visual Analogue Scale

Proportion of patients without deterioration vs. time to clinically meaningful deterioration, weeks.

HR 0.86 [95% CI 0.61, 1.22]

P = 0.4019

No. at risk:
- Oral AZA: 225, 120, 74, 58, 37, 21, 12, 9, 7, 6, 3, 0
- Placebo: 217, 73, 41, 26, 20, 13, 9, 6, 4, 2, 0

Time to definitive deterioration was defined as time from randomization to clinically meaningful deterioration sustained for ≥ 2 consecutive assessment visits.

AZA, azacitidine; CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; HR, hazard ratio.
Supplementary Table 1. Baseline demographic and disease characteristics in the health-related quality of life (HRQoL) evaluable population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Oral Azacitidine N = 225</th>
<th>Placebo N = 219</th>
<th>All Patients N = 444</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (min, max)</td>
<td>68 (55, 86)</td>
<td>68 (55, 82)</td>
<td>68 (55, 86)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>114 (50.7)</td>
<td>101 (46.1)</td>
<td>215 (48.4)</td>
</tr>
<tr>
<td>Male</td>
<td>111 (49.3)</td>
<td>118 (53.9)</td>
<td>229 (51.6)</td>
</tr>
<tr>
<td>WHO AML classification, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent genetic abnormalities</td>
<td>37 (16.4)</td>
<td>43 (19.6)</td>
<td>80 (18.0)</td>
</tr>
<tr>
<td>Myelodysplasia-related changes</td>
<td>47 (20.9)</td>
<td>38 (17.4)</td>
<td>85 (19.1)</td>
</tr>
<tr>
<td>Therapy-related</td>
<td>2 (0.9)</td>
<td>0 (0.0)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Not otherwise specified</td>
<td>139 (61.8)</td>
<td>137 (62.6)</td>
<td>276 (62.2)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>1 (0.5)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>AML type, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary (de novo)</td>
<td>201 (89.3)</td>
<td>204 (93.2)</td>
<td>405 (91.2)</td>
</tr>
<tr>
<td>Secondary</td>
<td>24 (10.7)</td>
<td>15 (6.8)</td>
<td>39 (8.8)</td>
</tr>
<tr>
<td>Cytogenetic risk status at induction, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>195 (86.7)</td>
<td>192 (87.7)</td>
<td>387 (87.2)</td>
</tr>
<tr>
<td>Poor</td>
<td>30 (13.3)</td>
<td>27 (12.3)</td>
<td>57 (12.8)</td>
</tr>
<tr>
<td>ECOG PS score, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>112 (49.8)</td>
<td>109 (49.8)</td>
<td>221 (49.8)</td>
</tr>
<tr>
<td>1</td>
<td>95 (42.2)</td>
<td>95 (43.4)</td>
<td>190 (42.8)</td>
</tr>
<tr>
<td>2-3</td>
<td>18 (8.0)</td>
<td>15 (6.8)</td>
<td>33 (7.4)</td>
</tr>
<tr>
<td>MRD-positive at randomization, n (%)</td>
<td>99 (44.0)</td>
<td>109 (49.8)</td>
<td>208 (46.8)</td>
</tr>
<tr>
<td>Bone marrow blasts, %, median (min, max)</td>
<td>2.0 (0.0, 5.0)</td>
<td>2.0 (0.0, 6.5)</td>
<td>2.0 (0.0, 6.5)</td>
</tr>
<tr>
<td>Consolidation therapy after IC, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>178 (79.1)</td>
<td>180 (82.2)</td>
<td>358 (80.6)</td>
</tr>
<tr>
<td>1 cycle</td>
<td>108 (60.7)</td>
<td>96 (53.3)</td>
<td>204 (57.0)</td>
</tr>
<tr>
<td>2 cycles</td>
<td>65 (36.5)</td>
<td>71 (39.4)</td>
<td>136 (38.0)</td>
</tr>
<tr>
<td>3 cycles</td>
<td>5 (2.8)</td>
<td>13 (7.2)</td>
<td>18 (5.0)</td>
</tr>
<tr>
<td>No</td>
<td>47 (20.9)</td>
<td>39 (17.8)</td>
<td>86 (19.4)</td>
</tr>
<tr>
<td>Response following induction, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>176 (78.2)</td>
<td>185 (84.5)</td>
<td>361 (81.3)</td>
</tr>
<tr>
<td>CRi</td>
<td>49 (21.8)</td>
<td>34 (15.5)</td>
<td>83 (18.7)</td>
</tr>
<tr>
<td>Time from diagnosis to randomization, months, median (min, max)</td>
<td>4.2 (1.5, 9.2)</td>
<td>4.2 (1.4, 10.9)</td>
<td>4.2 (1.4, 10.9)</td>
</tr>
<tr>
<td>Time from start of induction to randomization, months, median (min, max)</td>
<td>4.0 (1.4, 8.8)</td>
<td>4.0 (1.3, 15.1)</td>
<td>4.0 (1.3, 15.1)</td>
</tr>
</tbody>
</table>

The HRQoL-evaluable population was based on baseline completion of the FACIT-Fatigue Scale.
AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete blood count recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, induction chemotherapy; MRD, measurable residual disease; WHO, World Health Organization.
### Supplementary Table 2. Baseline FACIT-Fatigue and EQ-5D-3L scores in QUAZAR AML-001 and historical reference values from general populations

<table>
<thead>
<tr>
<th>HRQoL Assessment</th>
<th>Oral Azacitidine</th>
<th>Placebo</th>
<th>All Patients</th>
<th>Reference value from general population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean [SD]</td>
<td>Mean [SD]</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>FACIT-Fatigue scale</td>
<td>40.8 [8.6]</td>
<td>40.7 [8.3]</td>
<td>40.8 [8.4]</td>
<td>43.2*</td>
</tr>
<tr>
<td>EQ-5D-3L health utility index</td>
<td>0.80 [0.10]</td>
<td>0.79 [0.14]</td>
<td>0.80 [0.12]</td>
<td>0.76†</td>
</tr>
<tr>
<td>EQ-5D visual analogue scale</td>
<td>74.6 [17.4]</td>
<td>75.4 [16.2]</td>
<td>75.0 [16.8]</td>
<td>75.1†</td>
</tr>
</tbody>
</table>

*Reference value from a general population in Germany (N = 2,426); data were re-weighted with age distributions by gender from the study population.

†Reference value from a general population aged 65-74 years in the United States (N = 38,678).

FACIT, Functional Assessment of Chronic Illness Therapy; HRQoL, health-related quality of life; SD, standard deviation.


Supplementary Figure 1. Proportions of patients in the Oral-AZA and placebo treatment arms that experienced clinically meaningful deterioration on the A) FACIT-Fatigue scale; B) EQ-5D-3L Health Utility Index score; and C) EQ-5D Visual Analog Scale.

Data are reported from day 1 of each treatment cycle.

*Indicates a statistically significant \( P < 0.05 \) difference between treatment arms.

AZA, azacitidine; FACIT, Functional Assessment of Chronic Illness Therapy; No., number.