Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission


BACKGROUND

Although induction chemotherapy results in remission in many older patients with acute myeloid leukemia (AML), relapse is common and overall survival is poor.

METHODS

We conducted a phase 3, randomized, double-blind, placebo-controlled trial of the oral formulation of azacitidine (CC-486, a hypomethylating agent that is not bioequivalent to injectable azacitidine), as maintenance therapy in patients with AML who were in first remission after intensive chemotherapy. Patients who were 55 years of age or older, were in complete remission with or without complete blood count recovery, and were not candidates for hematopoietic stem-cell transplantation were randomly assigned to receive CC-486 (300 mg) or placebo once daily for 14 days per 28-day cycle. The primary end point was overall survival. Secondary end points included relapse-free survival and health-related quality of life.

RESULTS

A total of 472 patients underwent randomization; 238 were assigned to the CC-486 group and 234 were assigned to the placebo group. The median age was 68 years (range, 55 to 86). Median overall survival from the time of randomization was significantly longer with CC-486 than with placebo (24.7 months and 14.8 months, respectively; P<0.001). Median relapse-free survival was also significantly longer with CC-486 than with placebo (10.2 months and 4.8 months, respectively; P<0.001). Benefits of CC-486 with respect to overall and relapse-free survival were shown in most subgroups defined according to baseline characteristics. The most common adverse events in both groups were grade 1 or 2 gastrointestinal events. Common grade 3 or 4 adverse events were neutropenia (in 41% of patients in the CC-486 group and 24% of patients in the placebo group) and thrombocytopenia (in 22% and 21%, respectively). Overall health-related quality of life was preserved during CC-486 treatment.

CONCLUSIONS

CC-486 maintenance therapy was associated with significantly longer overall and relapse-free survival than placebo among older patients with AML who were in remission after chemotherapy. Side effects were mainly gastrointestinal symptoms and neutropenia. Quality-of-life measures were maintained throughout treatment. (Supported by Celgene; QUAZAR AML-001 ClinicalTrials.gov number, NCT01757535.)
Acutely myeloid leukemia (AML) is an aggressive disease that predominantly affects older people. Although complete remission is achieved with standard induction chemotherapy in 40 to 60% of patients older than 60 years of age who have AML, most patients (80 to 90%) eventually have a relapse. Clonal evolution, epigenetic reprogramming leading to aberrant DNA methylation, and persistence of leukemia-initiating cells despite chemotherapy are thought to contribute to disease recurrence.5-8

Longer durations of first remission are associated with better survival outcomes. Therefore, preventing early AML relapse with postremission therapy is an important goal. Although hematopoietic stem-cell transplantation (HSCT) after induction chemotherapy is potentially curative, this option is not feasible for many older patients.10

For patients who are not candidates for HSCT, effective AML maintenance therapies are needed that can reduce the risk of relapse and prolong overall survival without causing undue adverse effects or compromising health-related quality of life.4 Although some studies have shown improvements in disease-free survival, no maintenance therapy has so far been shown to significantly prolong overall survival among patients with AML after standard intensive chemotherapy.11-13 Consequently, maintenance therapy is not a widely established practice in the treatment of AML.

Until recently, no therapy was approved in the United States for use in patients with AML in remission after chemotherapy. Histamine dihydrochloride–interleukin-2 combination therapy is approved for use as maintenance therapy in the European Union on the basis of studies showing improvements in disease-free survival.19 Although midostaurin is approved for use as maintenance therapy in the European Union for patients with FLT3-mutant AML,20 the specific contribution of maintenance therapy is confounded by the use of midostaurin during induction and consolidation.21 Hypomethylating agents are recommended by the National Comprehensive Cancer Network (NCCN) as maintenance therapy for older patients with AML on the basis of studies showing benefits with respect to disease-free survival but not overall survival.22 Similarly, maintenance approaches that involve cytotoxic chemotherapy have been found to improve disease-free survival.23

Oral azacitidine, known as CC-486, is a hypomethylating agent that can be administered in extended dosing schedules (for 14 or 21 days per 28-day treatment cycle) to sustain therapeutic activity.24 The pharmacokinetic and pharmacodynamic profiles of CC-486 are distinct from those of injectable azacitidine,24,25 and early studies showed that a response to CC-486 was achieved in some patients who had clinical resistance to injectable hypomethylating agents.26

Here, we report results from the international, phase 3, double-blind, placebo-controlled QUAZAR AML-001 trial, in which CC-486 was evaluated as maintenance therapy in patients 55 years of age or older with AML in first remission after induction chemotherapy, with or without consolidation chemotherapy, who were not candidates for HSCT at trial entry.

## METHODS

### Trial Design

We conducted this trial at 148 sites in 23 countries. The sponsor provided the drug and placebo and designed the trial in collaboration with the authors and an independent steering committee and with advice from regulatory agencies, in accordance with principles of the Declaration of Helsinki. The sponsor collected and analyzed the data and participated with the authors in its interpretation. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org. A professional writer paid by the sponsor assisted with preparation of the submitted manuscript. All the authors participated in revising the manuscript for submission and are fully responsible for its content. The protocol was approved by an institutional review board or ethics committee at each participating site. All the patients provided informed written consent. An independent data and safety monitoring committee assessed trial conduct and safety outcomes.

To be eligible for participation in the trial, patients had to be at least 55 years of age and to have newly diagnosed de novo AML (i.e., AML without an antecedent hematologic disorder) or secondary AML and intermediate- or poor-risk
cytogenetic characteristics at diagnosis (defined according to National Comprehensive Cancer Network 2011 guidelines) (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Patients were excluded if they were considered to be candidates for HSCT at the time of screening (there were no trial-specified criteria associated with transplantation eligibility). At screening, patients had to have an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 to 3 (scores range from 0 to 5, with higher scores indicating greater disability) and had to have recovered from induction chemotherapy with adequate marrow function (i.e., absolute neutrophil count ≥0.5×10⁹ per liter and platelet count ≥20×10⁹ per liter). The full list of inclusion and exclusion criteria is provided in the Supplementary Appendix. All patients had to have undergone induction chemotherapy, with or without consolidation therapy, before screening. Chemotherapy regimens were selected at the discretion of the treating physician.

Patients had to be in first complete remission or complete remission with incomplete blood count recovery within 4 months (±7 days) before randomization. Patients were randomly assigned in a 1:1 ratio to receive CC-486 (300 mg) or placebo, administered once daily on days 1 through 14 of repeated 28-day cycles. Assessment of remission status on the basis of bone marrow and peripheral blood examination was performed every 3 cycles during the first 24 cycles, at cycles 30 and 36, and as clinically indicated. Patients who were identified as having AML relapse with 5 to 15% blasts in blood or bone marrow during receipt of CC-486 or placebo could have their dosing regimen increased to 21 days per cycle at the discretion of the treating investigator. Administration of CC-486 or placebo continued until more than 15% blasts were present or unacceptable adverse effects occurred. All the patients could receive supportive care according to local practice.

END POINTS

The primary end point was overall survival, defined as the time from randomization to death from any cause. All patients were followed until death, withdrawal of consent, or loss to follow-up. The key secondary end point was relapse-free survival — the time from randomization to relapse or death, whichever occurred first. Additionally, secondary end points included measures of safety and of the effect of CC-486 and placebo on health-related quality of life, assessed as changes from baseline in scores on the patient-reported Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale and three-level version of the European Quality of Life—5 Dimensions (EQ-5D-3L) questionnaires.

Central review of bone marrow and peripheral blood was conducted by a hematopathologist who was unaware of the treatment assignments. Complete remission with or without complete blood count recovery and AML relapse were defined according to International Working Group 2003 response criteria for AML. The presence of measurable residual disease at trial entry was assessed centrally by means of flow cytometry, with the use of a leukemia-associated immunophenotype (LAIP)—based “different-from-normal” method with a 0.1% threshold for measurable residual disease positivity. Safety was assessed among patients who received at least one dose of CC-486 or placebo. Adverse events were monitored through 28 days after the last dose. Prophylactic therapy for gastrointestinal or hematologic adverse events was permitted at the discretion of the treating investigator. AML relapse was not considered an adverse event for the purposes of the safety analysis.

STATISTICAL ANALYSIS

Detailed statistical methods are described in the Supplementary Appendix. Under the assumption of a median overall survival of 16.0 months in the placebo group and 22.9 months in the CC-486 group, a trial duration of 60 months, a 5% dropout rate, and 330 deaths, enrollment of approximately 460 patients (230 per group) would provide 90% power to detect a hazard ratio of 0.70 and to show a significant difference in overall survival between the treatment groups. Sample-size calculations were based on a one-sided alpha of 0.025.

Overall and relapse-free survival were estimated with the use of the Kaplan–Meier method, and survival distributions were compared with a stratified log-rank test. Overall survival and then relapse-free survival were tested with the use of a sequential gate-keeping approach. The assumption of proportional hazards was tested with a
time-dependent Cox model with interaction terms of treatment and time and with a P value of 0.006. The proportional hazards assumption appeared to be violated, as indicated by the significant treatment-by-time interaction; thus, hazard ratios are not provided. Confidence intervals for survival estimates at 6 months, 1 year, and 2 years were calculated with Greenwood’s variance formula. No adjustments for multiplicity were made for other end points, and the resulting point estimates and 95% confidence intervals should not be used to infer treatment effects. We performed univariate analyses of overall and relapse-free survival in subgroups defined on the basis of clinically relevant baseline characteristics. Statistical methods relating to assessments of health-related quality of life are described in the Supplementary Appendix.

RESULTS

PATIENTS

From May 2013 through October 2017, a total of 472 patients were randomly assigned to receive either CC-486 (238 patients) or placebo (234 patients) (Fig. 1). Most patients (47 of 83) who were ineligible after screening had exceeded the acceptable 4-month period from attainment of remission to randomization. Three patients (2 in the CC-486 group and 1 in the placebo group) did not receive CC-486 or placebo and were excluded from safety analyses.

At data cutoff (July 15, 2019), 193 patients (81%) had discontinued CC-486 and 208 patients (89%) had discontinued placebo. The median time to discontinuation was 11.4 months (95% confidence interval [CI], 9.8 to 13.6) in the CC-486 group and 6.1 months (95% CI, 5.1 to 7.4) in the placebo group. AML relapse led to discontinuation of the trial regimen in 143 patients (60%) in the CC-486 group and 180 patients (77%) in the placebo group.

Baseline characteristics were generally balanced between the groups (Table 1, and Table S1). The median age in the overall trial population was 68 years (range, 55 to 86), and most patients had de novo AML (91%) and intermediate-risk cytogenetic characteristics (86%). All patients received induction with cytarabine-based regimens, in combination with an anthracycline or similar agent, before enrollment. In all, 80% of the patients (186 [78%] in the CC-486 group and 192 [82%] in the placebo group) received at least one course of consolidation chemotherapy before trial entry, with 45% of all patients receiving one consolidation cycle and 31% receiving two consolidation cycles. The most common agents used for consolidation were cytarabine (in 377 of 378 patients), idarubicin (in 95 of 378), and daunorubicin (in 37 of 378). Among the patients who did not receive consolidation therapy, 25% initially received two cycles of induction chemotherapy. Thus, approximately 85% of patients who had received...
two or more cycles of chemotherapy before enrollment.

The median time from complete remission to randomization was 85.0 days. At randomization, 5 patients (2%) in the CC-486 group and 11 (5%) in the placebo group were no longer in remission.

**OVERALL SURVIVAL**

At a median follow-up of 41.2 months, the median overall survival from the time of randomization was significantly longer in the CC-486 group than in the placebo group (24.7 months vs. 14.8 months; P<0.001) (Fig. 2A). The esti-
mated percentages of patients surviving at 1 year were 72.8% in the CC-486 group and 55.8% in the placebo group (difference, 17.0 percentage points; 95% CI, 8.4 to 25.6), and the corresponding percentages at 2 years were 50.6% and 37.1% (difference, 13.5 percentage points; 95% CI, 4.5 to 22.5).

The results for overall survival at 2 years from the time of randomization favored CC-486 in most subgroups based on disease characteristics at baseline (Fig. 3). An overall survival benefit was observed with CC-486 regardless of whether patients had received any consolidation therapy, had been in complete remission after induction chemotherapy, or had had persistent measurable residual disease at randomization.

**RELAPSE-FREE SURVIVAL**

Relapse-free survival was significantly longer with CC-486 than with placebo (P<0.001). Median relapse-free survival from the time of randomization was 10.2 months with CC-486, as compared with 4.8 months with placebo (Fig. 2B). The estimated percentages of patients with relapse-free survival at 6 months were 67.4% in the CC-486 group and 45.2% in the placebo group (difference, 22.2 percentage points; 95% CI, 13.2 to 31.2), and the corresponding estimates at 1 year
Figure 3. Univariate Analyses of Overall Survival at 2 Years in Patient Subgroups Defined on the Basis of Clinically Relevant Baseline Characteristics.

Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. CMML denotes chronic myelomonocytic leukemia, MDS myelodysplastic syndrome, MRD measurable residual disease, and WHO World Health Organization.
were 44.9% and 27.4% (difference, 17.5 percentage points; 95% CI, 8.5 to 26.4). The estimated time to onset of AML relapse is summarized in Table S2. Relapse-free survival at 1 year was generally higher with CC-486 than with placebo in patient subgroups defined on the basis of clinically relevant baseline characteristics (Fig. S2).

HEALTH-RELATED QUALITY OF LIFE
At baseline, patients reported relatively low levels of fatigue and physical impairment, and the FACTIT Fatigue Scale and EQ-5D-3L scores were similar in the two treatment groups. No meaningful differences in FACTIT Fatigue scores were noted between the groups across postbaseline visits (Fig. S3A). Similarly, EQ-5D-3L health utility index scores were similar in the two treatment groups at all visits except at cycles 22 and 23, when scores were numerically higher in the placebo group than in the CC-486 group (Fig. S3B). Mixed-effects models with repeated measures, which controlled for baseline health-related quality-of-life scores and other preselected covariates, showed no clinically meaningful differences in least-squares mean changes from baseline between the treatment groups at any visit, a finding that supported the noninferiority of CC-486 relative to placebo for health-related quality of life.

SAFETY
The median duration of receipt of CC-486 was 12 cycles (range, 1 to 80), and the median duration of receipt of placebo was 6 cycles (range, 1 to 73). In both groups, the most common adverse events that occurred during the period between the first dose and 28 days after the last dose of CC-486 or placebo were gastrointestinal events, including nausea, vomiting, and diarrhea (Table 2), which occurred more frequently with CC-486. CC-486–induced nausea and vomiting occurred mainly during cycles 1 and 2 (Table S3) and were less common during subsequent cycles after incorporation of antiemetic agents. The most common hematologic adverse events were neutropenia (in 44% of the patients in the CC-486 group and 26% of the patients in the placebo group), thrombocytopenia (in 33% and 27%), and anemia (in 20% and 18%) (Table 2). The percentages of patients with hematologic adverse events within each treatment group were generally consistent over time up to cycle 12 (Table S4). The most common serious adverse events were infections, which were reported in 17% of patients in the CC-486 group and 8% of patients in the placebo group (Table S5).

Adverse events led to dosing interruptions for 43% of the patients in the CC-486 group and 17% of the patients in the placebo group (Table S6) and led to dose reductions in 16% and 3% of the patients, respectively (Table S7). Neutropenia was the most common adverse event leading to dose modifications in both groups. Adverse events led to discontinuation of the trial regimen in 13% of the patients in the CC-486 group and 4% of the patients in the placebo group (Table S8). The most common adverse events leading to discontinuation of CC-486 were gastrointestinal events, which were infrequent (5% of the patients in the CC-486 group and <1% of the patients in the placebo group). Three patients (1%) in each group discontinued the trial regimen because of a hematologic adverse event.

Adverse events led to death in nine patients (4%) in the CC-486 group: two died from sepsis, two from cerebral hemorrhage, one from both sepsis and multiorgan failure, and one each from intracranial hemorrhage, cardiogenic shock, aspiration pneumonia, and suicide. In the placebo group, adverse events led to death in four patients (2%): two died from multiorgan failure, one from cerebral hemorrhage, and one from general health deterioration.

ESCALATED DOsing
On identification of AML relapse with 5 to 15% blasts, 91 patients (51 [21%] in the CC-486 group and 40 [17%] in the placebo group) were assigned by their treating investigator to receive an escalated 21-day dosing schedule. The median time to escalated dosing was 9.2 months (range, 1.0 to 52.7) in the CC-486 group and 6.0 months (range, 0.5 to 19.3) in the placebo group. Patients received a median of two escalated dosing cycles in both the CC-486 group (range, 1 to 45) and the placebo group (range, 1 to 16); 43% of the patients in the CC-486 group received more than three escalated dosing cycles, as compared with 18% of the patients in the placebo group. Median overall survival from the time of randomization among these 91 patients was 22.8 months in the CC-486 group and 14.6 months in the placebo group. Among the 78 patients who had central confirmation of at least 5% blasts in
their bone marrow on or before the first day of 21-day dosing, 10 of 43 patients (23%) in the CC-486 group and 4 of 35 patients (11%) in the placebo group had restoration of complete remission status while receiving the escalated dosing regimen. Hematologic events were the most common adverse events first reported during escalated dosing (Table S9).

**Subsequent Therapy**

Most patients (307 [65%]) received at least one course of subsequent treatment after discontinuation of the trial regimen, including 137 patients (58%) in the CC-486 group and 170 patients (73%) in the placebo group. Among the patients who had AML relapse during the trial, 96% of those in the CC-486 group and 94% of those in the placebo group received subsequent therapy. One third of the patients (33%) received an intensive chemotherapy regimen as salvage therapy (Table S10). Fifteen patients (6%) in the CC-486 group proceeded to HSCT: 6 remained in first remission at the time of HSCT, and 9 had a relapse. In the placebo group, 32 patients

---

**Table 2. Adverse Events That Occurred in at Least 10% of Patients in Either Group.**

<table>
<thead>
<tr>
<th>Event</th>
<th>CC-486 (N=236)</th>
<th>Placebo (N=233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>231 (98)</td>
<td>225 (97)</td>
</tr>
<tr>
<td>Nausea</td>
<td>153 (65)</td>
<td>147 (63)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>141 (60)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>119 (50)</td>
<td>50 (21)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>105 (44)</td>
<td>44 (19)</td>
</tr>
<tr>
<td>Constipation</td>
<td>91 (39)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>79 (33)</td>
<td>66 (28)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>70 (30)</td>
<td>45 (19)</td>
</tr>
<tr>
<td>Anemia</td>
<td>48 (20)</td>
<td>42 (18)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>44 (19)</td>
<td>13 (6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>36 (15)</td>
<td>44 (19)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>32 (14)</td>
<td>24 (10)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>31 (13)</td>
<td>16 (7)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>31 (13)</td>
<td>32 (14)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>30 (13)</td>
<td>15 (6)</td>
</tr>
<tr>
<td>Cough</td>
<td>29 (12)</td>
<td>39 (17)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>28 (12)</td>
<td>18 (8)</td>
</tr>
<tr>
<td>Back pain</td>
<td>28 (12)</td>
<td>23 (10)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>25 (11)</td>
<td>19 (8)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>25 (11)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>25 (11)</td>
<td>21 (9)</td>
</tr>
<tr>
<td>Headache</td>
<td>23 (10)</td>
<td>26 (11)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>21 (9)</td>
<td>24 (10)</td>
</tr>
</tbody>
</table>

*Adverse events were evaluated from the date of the first dose of CC-486 or placebo through 28 days after the last dose. Events were coded according to preferred terms from the Medical Dictionary of Regulatory Activities, version 22, and were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Patients are counted only once for multiple events within each preferred term.
(14%) underwent HSCT, all of whom had had a relapse.

**DISCUSSION**

CC-486 maintenance therapy provided a significant prolongation of both overall and relapse-free survival among older patients with AML who were in remission after intensive chemotherapy with or without consolidation therapy. The results for overall and relapse-free survival favored CC-486 in most subgroups based on age, sex, cytogenetic risk, initial response to induction chemotherapy, receipt of consolidation therapy, or measurable residual disease status at trial entry.

Median relapse-free survival in the CC-486 group was more than twice that in the placebo group, which probably explains the superior overall survival with CC-486. In this trial, the median time from complete remission to randomization was approximately 3 months, and both overall and relapse-free survival were measured from the time of randomization, whereas other studies have measured survival from the time of induction or soon after attainment of complete remission. In addition, the frequency of bone marrow evaluation in this trial (required every 3 months) facilitated the recognition of early, subclinical relapse. Thus, cross-study comparisons of time-to-event estimates should be made with caution.

A formidable challenge to effective maintenance therapy in AML is the genomic and epigenomic complexity of the disease. As compared with targeted therapies, epigenetic reprogramming with hypomethylating agents may offer broad antileukemic activity in a disease that has substantial biologic heterogeneity. The antitumor activity of hypomethylating agents is thought to include reactivation of silenced tumor suppressor genes through DNA hypomethylation and the induction of cytotoxicity-mediated DNA damage and apoptosis. Although parenteral azacitidine and CC-486 have the same active ingredient, they are not bio-equivalent and cannot be used interchangeably. The significant clinical benefits of CC-486 in delaying relapse and prolonging survival may reflect the pharmacodynamic effect of extending drug exposure and sustaining epigenetic regulation over the course of the treatment cycle.

Maintenance therapy with injectable azacitidine has been investigated in other trials, including the U.K. National Cancer Research Institute AML16 trial, involving patients with AML or high-risk myelodysplastic syndromes. Although there are important differences between that trial and our trial, maintenance therapy with injectable azacitidine in that trial did not provide a survival benefit over no maintenance therapy among patients who had received one previous consolidation cycle or in those who had measurable residual disease after induction chemotherapy. In contrast, benefits with respect to both relapse-free survival and overall survival were shown with CC-486 in this trial, regardless of receipt of consolidation therapy or the presence of measurable residual disease at randomization. The convenience of oral CC-486 dosing may also improve adherence and promote longer-term treatment than is practical with injectable agents.

Treatment-related adverse effects have been a deterrent to the use of maintenance therapy in patients with AML. In our trial, CC-486 was associated with an adverse-event profile similar to that of injectable azacitidine, and health-related quality of life was preserved. Nausea, vomiting, and diarrhea were the most frequent adverse events with CC-486, but the frequency of these events decreased after the first two treatment cycles, perhaps aided by implementation of antiemetics, antidiarrheals, and dose modifications. Treatment discontinuation due to these events was infrequent. Neutropenia is a known side effect of hypomethylating therapy; dosing modifications and the use of granulocyte colony-stimulating factor (G-CSF) may be useful to consider, as clinically indicated. Few patients (approximately 1%) discontinued CC-486 because of hematologic adverse events.

Determining which molecular characteristics may influence outcomes of maintenance therapy could be useful for identifying patients who are likely to derive the most benefit from this approach. Although assessment of molecular abnormalities was not required for this trial, correlative samples were obtained for potential future analysis.

Despite demonstrable survival advantages with CC-486 maintenance therapy, the risk of eventual relapse and death from AML remains prob-
lematric. Whether CC-486 may benefit patients with AML when it is used in other clinical contexts requires further investigation. Results from an open-label phase 2 study suggest that CC-486 may provide effective maintenance therapy after HSCT, but larger, controlled trials are needed.

In this trial, CC-486 maintenance therapy prolonged overall and relapse-free survival among patients with AML who were in remission after intensive chemotherapy. Side effects were mainly gastrointestinal adverse events, which were controllable with antiemetics and anti-diarrheal agents, and neutropenia, which was managed with hematopoietic growth factors and CC-486 dose modifications. Discontinuation of CC-486 therapy owing to adverse events was uncommon. Quality of life was maintained during treatment.

Supported by Celgene (a wholly owned subsidiary of Bristol Myers Squibb).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients, families, coinvestigators, and all personnel who participated in this trial; and Sheila Truten, Brian Kaiser, and Kelly Ditmore (of Medical Communication Company) for editorial and writing assistance with an early draft of the manuscript, funded by the sponsor.

APPENDIX

The authors’ full names and academic degrees are as follows: Andrew H. Wei, M.B., B.S., Ph.D., Hartmut Döhner, M.D., Christopher Pocock, M.B., B.S., Pau Montesinos, M.D., Ph.D., Boris Afanasyev, M.D., D.Sci., Hervé Dombret, M.D., Farhad Ravandi, M.D., Hamid Sayar, M.D., Jun-Ho Jung, M.D., Ph.D., Kimmo Poroikka, M.D., Dominik Selleslag, M.D., Irwindeep Sandhu, M.D., Mehmet Turgut, M.D., Valentina Gai, M.D., Ph.D., Vishal Ofan, M.D., Merih Kizil Çakar, M.D., Aida Botelho de Sousa, M.D., Justyna Rybka, M.D., Ph.D., Chiara Frairia, M.D., Lorenzo Borin, M.D., Germana Beltrami, M.D., Jaroslav Cermák, M.D., Ph.D., Gert J. Ossenkoppele, M.D., Ph.D., Ignazia La Torre, M.D., Barry Skikne, M.D., Keshava Kumar, Ph.D., Ph.D., Qian Dong, Dr. Ph.D., C.L. Beach, Pharm.D., and Gail J. Roboz, M.D.

The authors’ affiliations are as follows: the Department of Clinical Haematology, Alfred Hospital, and the Australian Centre for Blood Diseases, Monash University, Melbourne, VIC, Australia (A.H.W.); the Department of Internal Medicine III, Ulm University Hospital, Ulm, Germany (H. Döhner); Kent and Canterbury Hospital, Canterbury, United Kingdom (C.P.); Centro de Investigación Biomédica en Red de Cáncer, Instituto Carlos III, Madrid, and Hospital Universitari i Politècnic La Fe, Valencia — both in Spain (P.M.); Raisa Gorbacheva Memorial Research Institute for Pediatric Oncology, Hematology, and Transplantation, Pavlov First Saint Petersburg State Medical University, St. Petersburg, Russia (B.A.); the Department of Haematology, Hôpital Saint-Louis, Assistance Publique–Hôpitaux de Paris, and Institut de Recherche Saint-Louis, Université de Paris, Paris (H. Dombret); the Department of Leukemia, University of Texas M.D. Anderson Cancer Center, Houston (F.R.); Indiana University Cancer Center, Indianapolis (H.S.); Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea (J.H.I.); Hospital District of Helsinki and Uusimaa (HUS) Comprehensive Cancer Center, Hematology Research Unit Helsinki and ICAN Digital Precision Cancer Center Medicine Flagship, University of Helsinki, Helsinki (K.P.); AZ Saint-Jan Brugge-Oostende AV, Bruges, Belgium (D.S.); University of Alberta Hospital, Edmonton, Canada (I.S.); Ondokuz Mayis University, Samsun (M.T.), and Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara (M.K.C.) — both in Turkey; Antonio e Biagio e Cesare Arrigo Hospital, Alessandria (V.G.), Città della Salute e della Scienza, Turin (C.F.), Ospedale San Gerardo Monza, Monza (L.B.), and Ospedale Policlinico San Martino, Genoa (G.B.) — all in Italy; Rambam Medical Center and Faculty of Medicine Technion, Haifa, Israel (Y.O.); Hospital dos Capuchos, Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal (A.B.S.); Wrocław Medical University, Wrocław, Poland (J.R.); Ustav Hematologje a Krenvi Transfuzie, Prague, Czech Republic (J.C.); Amsterdam University Medical Center, Location VUMC (Vrije Universiteit Medical Center), Amsterdam (G.J.O.); Celgene (Bristol Myers Squibb), Boudry, Switzerland (I.L.T.); Bristol Myers Squibb, Princeton, NJ (B.S., K.K., Q.D., C.L.B.); University of Kansas Medical Center, Kansas City (B.S.); and Weill Cornell Medicine and New York Presbyterian Hospital, New York (G.J.R.).

REFERENCES


Copyright © 2020 Massachusetts Medical Society.