



original reports

Phase III, Randomized, Placebo-Controlled Trial of CC-486 (Oral Azacitidine) in Patients With Lower-Risk Myelodysplastic Syndromes

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abstract

PURPOSE Treatment options are limited for patients with lower-risk myelodysplastic syndromes (LR-MDS). This phase III, placebo-controlled trial evaluated CC-486 (oral azacitidine), a hypomethylating agent, in patients with International Prognostic Scoring System LR-MDS and RBC transfusion–dependent anemia and thrombocytopenia.

METHODS Patients were randomly assigned 1:1 to CC-486 300-mg or placebo for 21 days/28-day cycle. The primary end point was RBC transfusion independence (TI).

RESULTS Two hundred sixteen patients received CC-486 (n = 107) or placebo (n = 109). The median age was 74 years, median platelet count was $25 \times 10^9/L$, and absolute neutrophil count was $1.3 \times 10^9/L$. In the CC-486 and placebo arms, 31% and 11% of patients, respectively, achieved RBC-TI ($P = .0002$), with median durations of 11.1 and 5.0 months. Reductions of ≥ 4 RBC units were attained by 42.1% and 30.6% of patients, respectively, with median durations of 10.0 and 2.3 months, and more CC-486 patients had ≥ 1.5 g/dL hemoglobin increases from baseline (23.4% v 4.6%). Platelet hematologic improvement rate was higher with CC-486 (24.3% v 6.5%). Underpowered interim overall survival analysis showed no difference between CC-486 and placebo (median, 17.3 v 16.2 months; $P = .96$). Low-grade GI events were the most common adverse events in both arms. In the CC-486 and placebo arms, 90% and 73% of patients experienced a grade 3-4 adverse event. Overall death rate was similar between arms, but there was an imbalance in deaths during the first 56 days (CC-486, n = 16; placebo, n = 6), most related to infections; the median pretreatment absolute neutrophil count for the 16 CC-486 patients was $0.57 \times 10^9/L$.

CONCLUSION CC-486 significantly improved RBC-TI rate and induced durable bilineage improvements in patients with LR-MDS and high-risk disease features. More early deaths occurred in the CC-486 arm, most related to infections in patients with significant pretreatment neutropenia. Further evaluation of CC-486 in MDS is needed.

J Clin Oncol 39:1426-1436. © 2021 by American Society of Clinical Oncology

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ASSOCIATED CONTENT

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on February 7, 2021 and published at ascopubs.org/journal/jco on March 25, 2021; DOI <https://doi.org/10.1200/JCO.20.02619>

INTRODUCTION

Myelodysplastic syndromes (MDS) encompass a heterogeneous group of hematologic disorders characterized by bone marrow dysplasia and peripheral blood cytopenias.¹ The International Prognostic Scoring System (IPSS) stratifies patients into four risk groups based on cytogenetic features, number of cytopenias, and blast percentage²; Low and Intermediate-1 risks are considered lower-risk MDS (LR-MDS), and Intermediate-2 and High risks are considered higher-risk MDS.

Anemia is the most frequent clinical finding in MDS. RBC transfusion dependence (TD) is associated with decreased overall survival (OS) and health-related

quality of life (HRQoL) and increased risk of transformation to acute myeloid leukemia (AML).^{3,4} Thrombocytopenia has especially poor prognostic implications for patients with LR-MDS and is among the strongest predictors of decreased OS across all IPSS MDS risk categories.^{5,6}

Supportive care measures have traditionally been the mainstay of LR-MDS therapy, including RBC and platelet transfusions, erythropoiesis stimulating agents, and hematopoietic growth factors such as granulocyte CSF.⁷ Thrombopoietin receptor agonists are under investigation for treatment of MDS-related thrombocytopenia, although these agents are not yet

CONTEXT

Key Objective

Myelodysplastic syndromes (MDS) are a diverse group of hematologic disorders with a range of prognoses. Within the International Prognostic Scoring System lower-risk MDS population exists a subgroup of patients with high-risk disease features including multiple cytopenias. The AZA-MDS-003 study was a randomized, placebo-controlled phase III trial of CC-486, an oral hypomethylating agent, in patients with International Prognostic Scoring System lower-risk MDS with transfusion-dependent anemia and thrombocytopenia.

Knowledge Generated

CC-486 was associated with a significantly higher rate of RBC transfusion independence versus placebo and with improvements in hemoglobin and platelet counts over time. The most common adverse events were GI and hematologic events. Although overall death rate was similar between treatment arms, more early deaths occurred in the CC-486 arm, most related to infections in patients with significant pretreatment neutropenia.

Relevance

Further evaluation of CC-486 in patients with MDS is needed, including rational identification of patients most likely to benefit from the drug.

recommended for routine use.^{8,9} Injectable hypomethylating agents (HMAs) may address anemia and thrombocytopenia in patients with MDS,^{10,11} and lusparcept, an erythroid maturation agent, was recently approved for treatment of anemia for patients with LR-MDS with ring sideroblasts. Within the LR-MDS population exists a subgroup of patients with poor prognosis and high-risk disease features, including RBC–transfusion dependent (RBC-TD) anemia and thrombocytopenia, who require therapeutic agents that address both anemia and thrombocytopenia.

CC-486 is an oral HMA that has been evaluated in patients with hematologic malignancies.¹²⁻¹⁶ CC-486 (ONUREG; azacitidine tablets) was recently approved in the United States for continuous treatment of adult patients with AML in first remission following induction chemotherapy, who are not able to complete curative therapy (eg, transplant).¹⁶ CC-486 has a unique pharmacokinetic or pharmacodynamic profile from injectable azacitidine, and the two are not bioequivalent. CC-486 allows for extended dosing schedules over each treatment cycle to sustain drug exposure. Longer HMA dosing regimens have been associated with higher response rates compared with shorter schedules,¹⁷⁻¹⁹ and extended CC-486 dosing has shown more prolonged hypomethylation compared with a 7-day schedule.^{14,20}

Reported here are outcomes from a randomized, placebo-controlled, phase III trial of CC-486 in patients with IPSS-defined LR-MDS, with RBC-TD anemia and thrombocytopenia at study entry.

METHODS

Trial Design

This trial (ClinicalTrials.gov identifier: [NCT01566695](https://clinicaltrials.gov/ct2/show/study/NCT01566695)) enrolled patients at 101 sites in 20 countries between April 2013 and February 2018. The sponsor designed the trial in

collaboration with an independent steering committee and with advice from regulatory agencies. The Protocol (online only) was approved at each participating site. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The sponsor supplied study drug and contributed to data collection and analysis. The authors are responsible for all content in this report. The corresponding author had full access to study data and had final responsibility for the decision to submit for publication.

The study comprised an initial screening phase, a double-blind treatment period, and a survival follow-up period (Data Supplement, online only). Eligible patients were age ≥ 18 years, with IPSS-defined² LR-MDS (the Revised IPSS [IPSS-R]²¹ was not available when this study was designed), Eastern Cooperative Oncology Group performance status score ≤ 2 , RBC-TD anemia, and thrombocytopenia. RBC-TD was defined according to International Working Group (IWG) 2006 criteria²² as an average requirement of ≥ 2 RBC units per 28 days for ≥ 56 days, with no transfusion-free period of ≥ 28 consecutive days during the 56 days before random assignment. Thrombocytopenia was defined as two platelet counts $\leq 75 \times 10^9/L$, measured ≥ 21 days apart. Full eligibility criteria are provided in the Data Supplement.

Patients were randomly assigned 1:1 to CC-486 300-mg or placebo, administered once daily for 21 days per 28-day treatment cycle. All patients could receive best supportive care as needed. Erythropoiesis stimulating agents and other growth factors were not allowed. All patients signed informed consent following institutional guidelines.

Procedures and Assessments

Clinical laboratory assessments are reported per central review. Disease status and treatment response were assessed centrally at the end of cycle 6; patients who achieved a response or showed no evidence of disease

progression could continue receiving randomized treatment.

End Points

The primary end point was rate of RBC transfusion independence (TI) lasting ≥ 56 consecutive days, per IWG 2006 criteria.²² The primary end point was assessed after all patients had completed 12 months of treatment or discontinued study drug. The key secondary end point was OS, defined as the time from random assignment to death (or last follow-up). Other end points included time to and duration of RBC-TI, rate and duration of ≥ 84 -day RBC-TI, rate and duration of platelet-TI (≥ 56 days), hematologic improvement (HI) in the erythroid (HI-E) and platelet (HI-P) lineages, morphologic response among patients with $> 5\%$ blasts at baseline and with ≥ 1 postbaseline assessment (IWG 2006 criteria²²), and AML progression (WHO 2008 criteria²³). The Functional Assessment of Cancer Therapy-Anemia (FACT-An)²⁴ questionnaire was used to measure effects of treatment on patient-reported HRQoL related to anemia and fatigue. The primary HRQoL end points were changes from baseline in the Functional Well-Being (FWB) domain and the Trial Outcome Index (TOI).

All patients were evaluated for treatment-emergent adverse events (TEAEs) from first dose through 28 days following last dose. Study drug dosing could be interrupted, delayed, or modified to ameliorate TEAEs (Data Supplement).

Statistical Analyses

The prospectively planned sample size was 386 patients, which would provide 80% power to determine a treatment effect on OS after approximately 250 deaths. However, in January 2018, the Data Monitoring Committee recommended halting study enrollment because of safety concerns related to an excess of early mortality in the CC-486 arm. In consultation with the US Food and Drug Administration, a partial clinical hold was placed on the study. In July 2018, the clinical hold was lifted; however, given historically slow recruitment, the sponsor decided not to reopen enrollment. The number of patients randomly assigned at the time of clinical hold ($N = 216$) provided only approximately 72% power to detect a difference in OS between arms at a significance level of 0.05 with 205 deaths but remained sufficient to detect a difference in RBC-TI with approximately 99% power. At data cutoff (January 25, 2019), 140 deaths had occurred.

RBC-TI rates were compared between arms using a stratified Mantel-Haenszel chi-squared test with a two-sided alpha of .05. Durations of RBC-TI and platelet-TI, time to AML progression, and OS from time of randomization were estimated using Kaplan-Meier methods, and OS was compared between treatment groups by stratified log-rank test. No adjustments for multiplicity were made for

other secondary end points, and the associated P values should not be used to infer treatment effects.

RESULTS

Patients

In all, 499 patients were screened for participation, but 283 (56.7%) failed screening, most commonly because of unconfirmed LR-MDS ($n = 180$) and not meeting protocol-defined criteria for thrombocytopenia or RBC-TD anemia ($n = 76$). Twenty-four patients died during the screening period, most often because of infections ($n = 7$) or MDS progression ($n = 6$).

Overall, 216 patients were randomly assigned to receive CC-486 ($n = 107$) or placebo ($n = 109$) (Fig 1). At data cutoff, all patients had completed 12 months of treatment or had discontinued treatment. Baseline characteristics were generally well-balanced between treatment groups (Table 1), except that a higher proportion of patients in the placebo arm had $> 5\%$ blasts (28.4% v 15.9% in the CC-486 arm). The median age was 74 years (range, 30-89), 70.8% of patients had refractory cytopenia with multilineage dysplasia MDS, and all but one patient had IPSS Intermediate-1 risk disease. Post hoc assessment showed that 28.3% of patients had IPSS-R–defined²¹ high- or very high-risk MDS. Median RBC transfusion requirement was 6.7 units/56 days (range, 2.6-20.0). The most common gene mutations were *ASXL1* (33.2%) and *TET2* (21.5%).

Efficacy

Significantly more patients in the CC-486 arm than in the placebo arm achieved RBC-TI for ≥ 56 consecutive days (30.8% v 11.1%, respectively; odds ratio [OR], 3.6 [95% CI, 1.7 to 7.4]; $P = .0002$). In univariate analysis, RBC-TI rates appeared to consistently favor CC-486 across subgroups defined by prognostic baseline characteristics (Data Supplement). Multivariate analysis confirmed the significant treatment effect of CC-486 on RBC-TI after controlling for prognostic baseline characteristics ($P = .0002$) (Data Supplement). No clear associations were observed between baseline gene mutations and achievement of RBC-TI (Data Supplement).

The median time to RBC-TI was 2.4 months in the CC-486 arm and 2.0 months in the placebo arm, and estimated median RBC-TI durations were 11.1 and 5.0 months, respectively ($P = .42$) (Fig 2A). Similar to 56-day RBC-TI rates, the rate of RBC-TI lasting ≥ 84 days was higher in the CC-486 arm (28.0%) than in the placebo arm (5.6%) (OR, 6.6 [95% CI, 2.6 to 16.7]; $P < .0001$).

An HI-E response was attained by 46 patients (43.0%) in the CC-486 arm and 34 patients (31.5%) in the placebo arm (OR, 1.6 [95% CI, 0.9 to 2.9]; $P = .12$). Twenty-five patients (23.4%) in the CC-486 arm and 5 (4.6%) in the placebo arm had a ≥ 1.5 g/dL increase in hemoglobin concentration from baseline (OR, 6.3 [95% CI, 2.3 to 17.1];

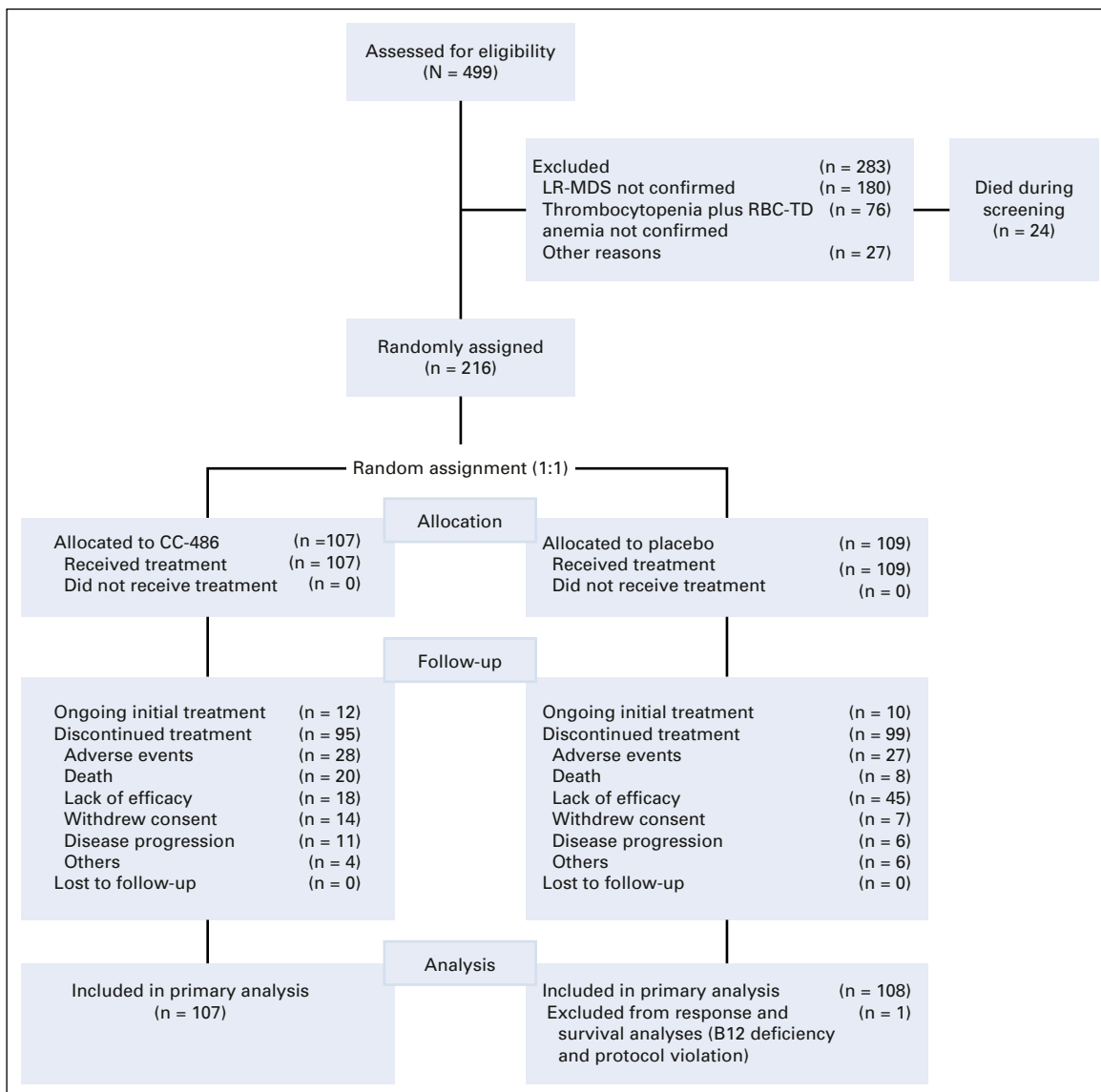


FIG 1. Patient disposition. Data cutoff: January 25, 2019. LR-MDS, lower-risk myelodysplastic syndromes; RBC-TD, RBC-transfusion dependent.

$P < .0001$). Forty-five patients (42.1%) in the CC-486 arm and 33 (30.6%) in the placebo arm achieved RBC transfusion reductions of ≥ 4 units/56 days (OR, 1.7 [95% CI, 0.9 to 2.9]; $P = .12$). RBC transfusion reductions were sustained for the median of 10.0 months with CC-486 and 2.3 months with placebo (Fig 2B); 29 patients (27.1%) in the CC-486 arm sustained these transfusion reductions for ≥ 16 weeks, compared with only six patients (5.6%) in the placebo arm.

Among 75 patients who were platelet-TD at baseline, five of 30 (16.7%) in the CC-486 arm and five of 35 (14.3%) in the placebo arm attained platelet-TI and sustained for the median of 12.1 months (95% CI, 8.3 to not estimable) and 4.4 months (2.3 to not estimable), respectively. However, HI-P rate was higher in the CC-486 arm than in the placebo

arm: 24.3% versus 6.5%, respectively (OR, 4.6 [95% CI, 1.9 to 11.2]; $P = .0003$).

Within the CC-486 arm, 25 patients (23.3%) achieved both HI-E and HI-P (ie, bilineage response) (Data Supplement). Patients in the CC-486 arm showed early and sustained improvement in mean hemoglobin levels and platelet counts on study (Fig 3).

Few patients ($n = 37$; 17%) were eligible to achieve an IWG-defined morphologic response (ie, had $\geq 5\%$ blasts at baseline). Of 13 eligible patients in the CC-486 arm, one achieved complete remission (CR), no patient achieved partial remission, and three achieved marrow CR. Among 24 eligible patients in the placebo arm, no patient achieved CR or partial remission and one patient attained marrow CR.

TABLE 1. Baseline Demographic and Disease Characteristics

Characteristic	CC-486 (n = 107)	Placebo (n = 109)	Total (N = 216)
Age, years, median (range)	74.0 (30-89)	73.0 (44-88)	74.0 (30-89)
Age ≥ 65 years, n (%)	91 (85.0)	95 (87.2)	186 (86.1)
Sex, n (%)			
Male	79 (73.8)	79 (72.5)	158 (73.1)
Female	28 (26.2)	30 (27.5)	58 (26.9)
WHO 2008 MDS classification, n (%)			
RCMD	80 (74.8)	73 (67.0)	153 (70.8)
RAEB-1	17 (15.9)	29 (26.6)	46 (21.3)
RA	4 (3.7)	3 (2.8)	7 (3.2)
RARS	3 (2.8)	2 (1.8)	5 (2.3)
MDS-U	2 (1.9)	2 (1.8)	4 (1.9)
RT	1 (0.9) ^a	0 (0.0)	1 (0.5)
IPSS risk, n (%)			
Low	0 (0.0)	0 (0.0)	0 (0.0)
Intermediate-1	106 (99.1)	109 (100)	215 (99.5)
Intermediate-2	1 (0.9)	0 (0.0)	1 (0.5)
High	0 (0.0)	0 (0.0)	0 (0.0)
IPSS-R risk, n (%)			
Very low (≤ 1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Low (> 1.5-3)	24 (22.4)	21 (19.3)	45 (20.8)
Intermediate (> 3-4.5)	51 (47.7)	48 (44.0)	99 (45.8)
High (> 4.5-6)	27 (25.2)	33 (30.3)	60 (27.8)
Very high (> 6)	1 (0.9)	0 (0.0)	1 (0.5)
Missing	4 (3.7)	7 (6.4)	11 (5.1)
IPSS cytogenetic risk, n (%)			
Good	87 (81.3)	90 (82.6)	177 (81.9)
Intermediate	17 (15.9)	14 (12.8)	31 (14.4)
Missing ^b	3 (2.8)	5 (4.6)	8 (3.7)
IPSS-R cytogenetic risk, n (%)			
Very good	2 (1.9)	3 (2.8)	5 (2.3)
Good	86 (80.4)	89 (81.7)	175 (81.0)
Intermediate	16 (15.0)	11 (10.1)	27 (12.5)
Missing ^b	3 (2.8)	6 (5.5)	9 (4.2)
Gene mutations, ^c n (%)	n = 102	n = 102	n = 204
<i>ASXL1</i>	29 (28.4)	39 (38.2)	68 (33.3)
<i>TET2</i>	21 (20.6)	23 (22.5)	44 (21.6)
<i>RUNX1</i>	10 (9.8)	23 (22.5)	33 (16.2)
<i>U2AF1</i>	18 (17.6)	15 (14.7)	33 (16.2)
<i>SRSF2</i>	14 (13.7)	16 (15.7)	30 (14.7)
<i>DNMT3A</i>	10 (9.8)	15 (14.7)	25 (12.3)
Months since MDS diagnosis, median (range)	18.9 (0.9-153)	16.1 (0.4-381)	17.5 (0.4-381)
Platelet transfusion-dependent, ^d n (%)	30 (28.0)	35 (32.1)	65 (30.1)
RBC transfusion requirement per 28 days, ^e units, median (range)	3.3 (1.3-10.0)	3.3 (1.3-9.5)	3.3 (1.3-10.0)

(continued on following page)

TABLE 1. Baseline Demographic and Disease Characteristics (continued)

Characteristic	CC-486 (n = 107)	Placebo (n = 109)	Total (N = 216)
> 4 units, n (%)	36 (33.6)	34 (31.2)	70 (32.4)
ECOG-PS score, n (%)			
0-1	91 (85.0)	94 (86.2)	185 (85.6)
2	16 (15.0)	15 (13.8)	31 (14.4)
Hemoglobin, g/dL, median (range)	8.3 (5.4-10.9)	8.1 (5.7-10.1)	8.1 (5.4-10.9)
Platelets, 10 ⁹ /L, median (range)	24 (566)	25 (573)	25 (573)
Platelet count < 20 × 10 ⁹ /L, n (%)	44 (41.1)	48 (44.0)	92 (42.6)
ANC, 10 ⁹ /L, median (range)	1.36 (0.07-25.2)	1.28 (0.06-20.5)	1.31 (0.06-25.2)
Absolute lymphocyte count, n (%)			
< 0.5 × 10 ⁹ /L	20 (18.7)	11 (10.1)	31 (14.4)
≥ 0.5 × 10 ⁹ /L	87 (81.3)	97 (89.0)	184 (85.2)
Bone marrow blasts, median (range)	3.0 (0.0-9.0)	3.5 (0.0-9.0)	3.0 (0.0-9.0)
< 5% blasts, n (%)	89 (83.2)	78 (71.6)	167 (77.3)
≥ 5% blasts, n (%)	17 (15.9)	31 (28.4)	48 (22.2)
Derived transferrin saturation, median (range)	85.9 (66.3-91.0)	88.0 (64.4-91.3)	87.0 (65.4-91.1)
Ferritin category, n (%)			
< 1,000 μg/L	38 (35.5)	38 (34.9)	76 (35.2)
≥ 1,000 μg/L	69 (64.5)	71 (65.1)	140 (64.8)

Abbreviations: ANC, absolute neutrophil count; ECOG-PS, Eastern Cooperative Oncology Group performance status; IPSS, International Prognostic Scoring System; IPSS-R, Revised IPSS; MDS, myelodysplastic syndromes; MDS-U, MDS-unclassified; RA, refractory anemia; RAEB, RA with excess blasts; RARS, RA with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RT, refractory thrombocytopenia.

^aThis patient was classified by treating investigator as MDS-RT on the case report form. Because all patients were RBC transfusion-dependent at baseline, this patient likely had MDS-RCMD.

^bIn cases where it was not possible to obtain a karyotype, a fluorescence in situ hybridization panel was employed to determine cytogenetic assignment and IPSS risk classification.

^cMutations reported in > 10% of patients with available next-generation sequencing (NGS) data.

^dPatients were considered platelet transfusion-dependent at baseline if they had received ≥ 2 platelet transfusions within the 56 days before random assignment (inclusive) and had no consecutive 28-day period during which no platelet transfusions were administered. Transfusions had to be given within 21 days of random assignment.

^eThe average of RBC transfusion units per 28 days is derived using transfusion records for the 84 days (original Protocol, Protocol amendment 1) or 56 days (Protocol amendment 2) before random assignment (inclusive).

Baseline FACT-An FWB and TOI scores were similar between arms and lower (worse) than reference values from a general population.²⁵ During treatment, FACT-An FWB scores generally improved from baseline over time in both arms and TOI scores trended toward improvement only in the CC-486 arm. No significant between-group differences in changes from baseline FWB or TOI scores were reported. HRQoL outcomes will be reported in full detail elsewhere.

Overall Survival

At data cutoff, 140 patients (CC-486, n = 69; placebo, n = 71) had died (April 2013 to January 2019). Thirty-nine deaths (CC-486, n = 25; placebo, n = 14) occurred during treatment (ie, from first dose through 28 days after last dose), and 101 (CC-486, n = 44; placebo, n = 57)

occurred during post-treatment follow-up (most attributed to disease progression).

In interim survival analysis (median follow-up 13.3 months), the estimated median OS was 17.3 months in the CC-486 arm and 16.2 months in the placebo arm (hazard ratio, 0.99 [95% CI, 0.70 to 1.40]; *P* = .96) (Data Supplement). There were no significant OS differences between treatment arms among patient subgroups defined by baseline characteristics. Rate of AML progression in the CC-486 arm (7.5% [n = 8]) was approximately one half of that in the placebo arm (16.7% [n = 18]) (HR, 0.40 [95% CI, 0.16 to 0.97]; *P* = .04). In the CC-486 arm, three patients progressed to AML on study and five progressed after discontinuing treatment. Estimated median time to AML progression was not reached in either arm in interim analysis; among patients who did progress, the median time to progression was 17.9 months

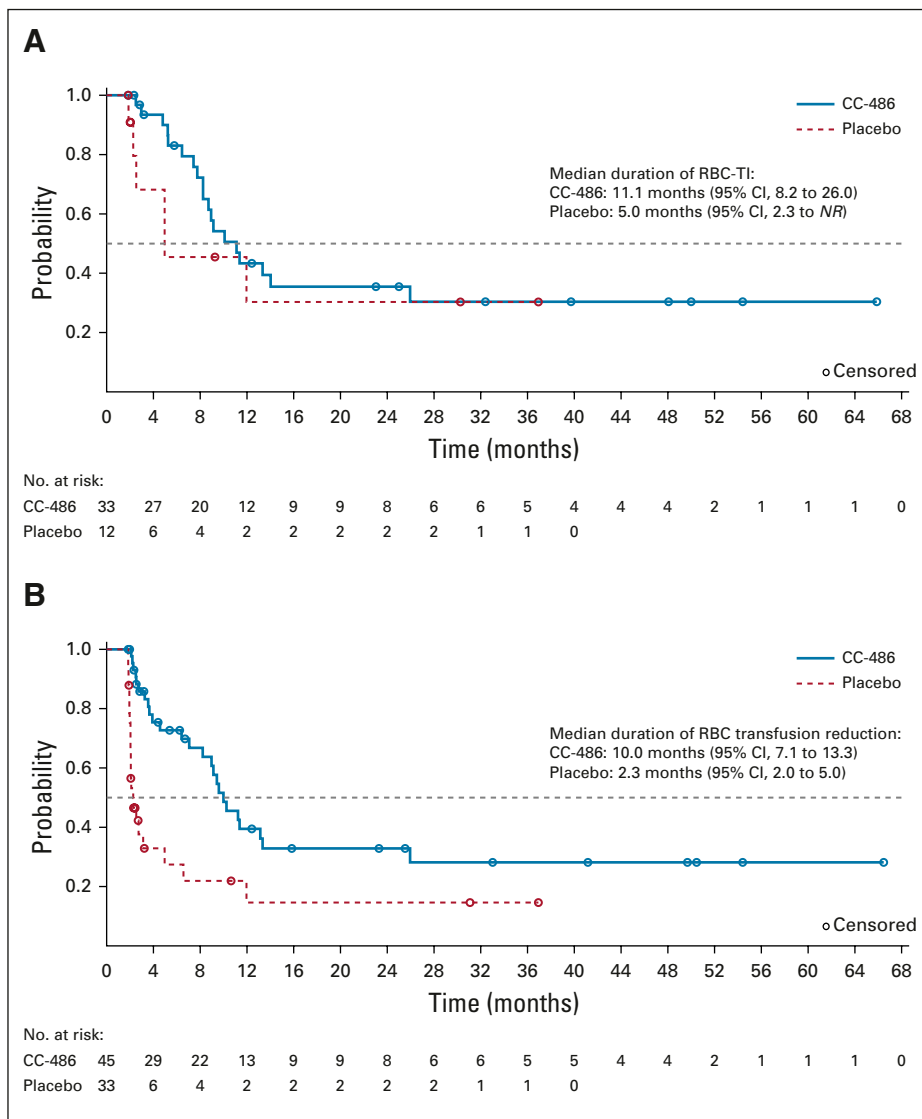


FIG 2. Kaplan-Meier estimated durations of (A) RBC transfusion independence and (B) RBC transfusion reductions (≥ 4 units). Data cutoff: January 25, 2019. NR, not reached; RBC-TI, RBC transfusion independence.

(range, 0.8-32.9) in the CC-486 arm and 9.9 months (1.0-35.2) in the placebo arm.

Safety

Patients received a median of 5 (range, 1-70) CC-486 cycles and 6 (1-69) placebo cycles. In the CC-486 arm, the median adherence to CC-486 was 97% and the median cycle length was 28 days.

During the treatment period, all patients treated with CC-486 experienced ≥ 1 TEAE (any grade), as did all but one patient (99.1%) who received placebo. Most patients (89.7% in the CC-486 arm and 73.4% in the placebo arm) experienced a grade 3-4 TEAE. GI and hematologic events were the most common TEAEs in both arms but occurred more frequently in the CC-486 arm (Data Supplement). GI

TEAEs were mostly grade 1-2 in severity; grade 3-4 events were uncommon and occurred primarily during early treatment cycles. Grade 3-4 neutropenia, thrombocytopenia, and febrile neutropenia were reported more frequently in the CC-486 arm (Table 2); incidence of these events was generally higher during early treatment cycles (Data Supplement). Grade 3-4 infections were reported in 46 CC-486 patients (43.0%) and 30 placebo patients (27.5%).

Thirty-one patients (29.0%) required ≥ 1 CC-486 dose reduction because of a TEAE, most commonly related to neutropenia (14.0%), thrombocytopenia (4.7%), diarrhea (3.7%), and febrile neutropenia (2.8%). Thirty-two patients (29.9%) in the CC-486 arm and 31 patients (28.4%) in the placebo arm permanently discontinued study drug because of a TEAE. The most common TEAEs requiring

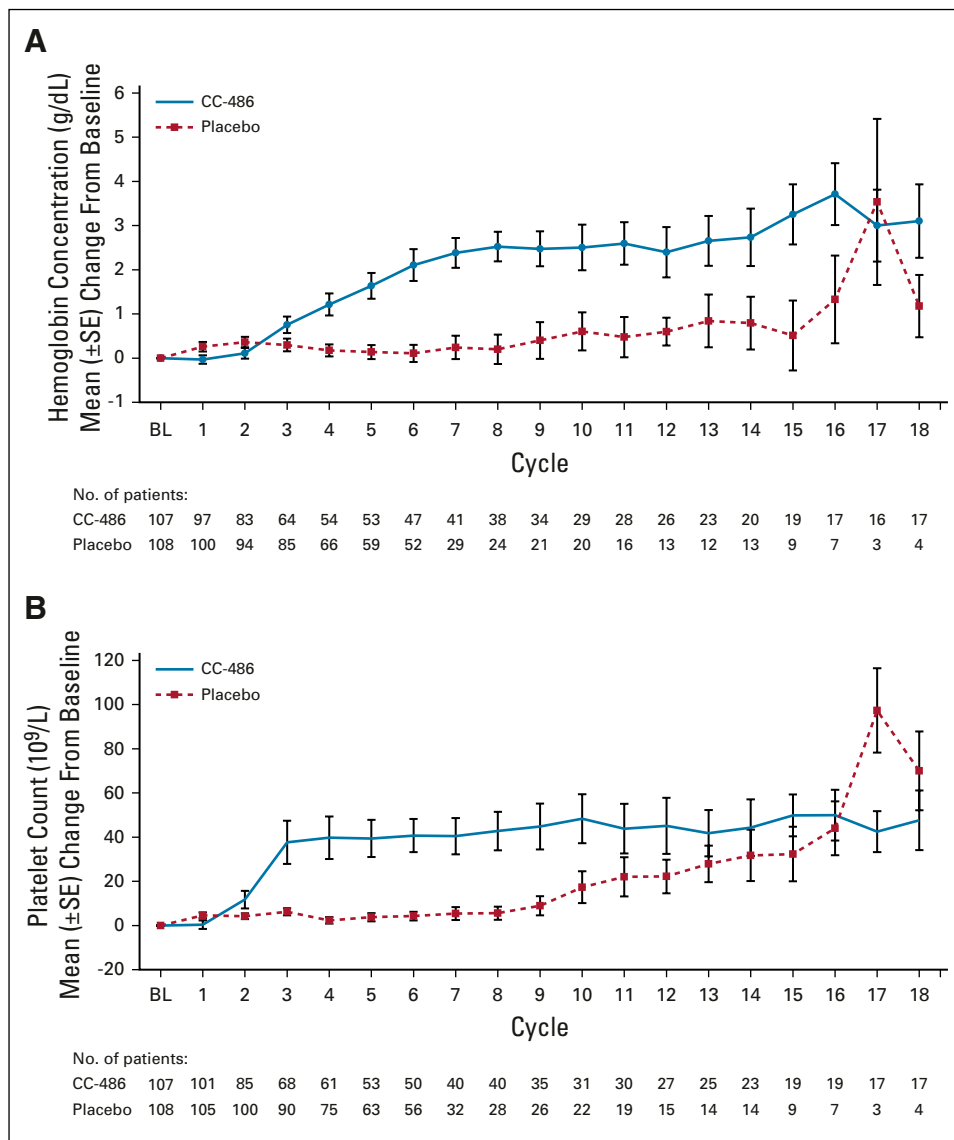


FIG 3. Mean (\pm SE) changes from baseline in (A) hemoglobin concentrations and (B) platelet counts. BL, baseline; SE, standard error.

discontinuation of CC-486 were nausea (3.7%), febrile neutropenia (2.8%), and sepsis (2.8%) (Data Supplement).

Infections were the most common TEAEs leading to death (CC-486, $n = 10$; placebo, $n = 4$). There was an imbalance in early deaths between treatment arms, with 16 in the CC-486 arm and six in the placebo arm occurring between study days 1 and 56. Post hoc analyses showed that the 16 patients in the CC-486 arm who died early were severely neutropenic and thrombocytopenic at baseline, with a median absolute neutrophil count (ANC) of $0.57 \times 10^9/L$ and a platelet count of $15.5 \times 10^9/L$; for the six patients in the placebo arm, the median ANC was $2.31 \times 10^9/L$ and the platelet count was $22.0 \times 10^9/L$ at baseline. The most common reason for early death in the CC-486 arm was infection (primarily bacterial).

DISCUSSION

The primary end point of this phase III study was met: CC-486 was associated with a significantly higher rate of RBC-TI compared with placebo. The estimated median duration of RBC-TI was 11.1 months with CC-486, compared with 5.0 months with placebo, and the median duration of RBC transfusion reduction of ≥ 4 units was substantially longer with CC-486 (10.0 v 2.3 months, respectively). The durability of these responses is consistent with the observed increases in hemoglobin levels during CC-486 treatment. RBC-TD is associated with transformation to AML⁴; consistent with higher rates of RBC-TI, the rate of AML progression in the CC-486 arm was one half of that in the placebo arm.

TABLE 2. Grade 3-4 Treatment-Emergent Adverse Events Reported in $\geq 10\%$ of Patients Randomly Assigned to CC-486

Preferred Term	CC-486 (n = 107)	Placebo (n = 109)
	n (%)	
≥ 1 Grade 3-4 TEAE	96 (89.7)	80 (73.4)
Neutropenia	50 (46.7)	13 (11.9)
Thrombocytopenia	31 (29.0)	17 (15.6)
Febrile neutropenia	30 (28.0)	11 (10.1)
Anemia	20 (18.7)	18 (16.5)
Pneumonia	13 (12.1)	10 (9.2)

NOTE. TEAEs include any adverse events that started on or after the date of first dose and within 28 days after the date of last dose. TEAEs were coded using Medical Dictionary for Regulatory Activities version 21.0 and graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. A patient is counted only once for multiple events of the same preferred term.

Abbreviation: TEAE, treatment-emergent adverse event.

The HI-E rate in the placebo arm (31.5%) was substantially higher than what has been reported for placebo in other LR-MDS trials.²⁶⁻²⁸ The HI-E responses reported in the placebo arm were driven by 30.6% of patients who sustained RBC transfusion reductions for ≥ 8 weeks (transfusions were administered at physician discretion), and hemoglobin increases of ≥ 1.5 g/dL were infrequent; thus, transfusion reductions did not necessarily reflect meaningful improvements in hemoglobin levels, highlighting a limitation of the IWG 2006 HI-E criteria.²² Moreover, the median duration of transfusion reductions was shorter with placebo than with CC-486. The 2018 IWG MDS response criteria,²⁹ which were not available when this study was designed, require a 16-week transfusion-reduction duration for an HI-E response; had those criteria been in place (our study did not require a 16-week screening period), the HI-E rate would have been substantially lower.

Almost one half (43%) of all patients in our study had baseline platelet counts of $< 20 \times 10^9/L$. Although platelet-TI rate was not significantly different between treatment arms, patients in the CC-486 arm experienced sustained platelet count increases over time, and patients were > 4 times more likely to achieve HI-P. Notably, nearly one fourth of patients treated with CC-486 achieved both HI-E and HI-P.

Patients in this study represent a particularly unfavorable subgroup of the IPSS Intermediate-1 risk LR-MDS population. Indeed, 28% of these patients would have had high- or very high-risk MDS at study entry by IPSS-R classification. The genetic landscape of this lower-risk study population at baseline was enriched with adverse-

risk mutations, also suggestive of a higher-risk phenotype.³⁰⁻³³ There were also a high number of deaths during screening (n = 24), mainly because of infections or disease progression. During the first 56 days on study, a higher rate of early death was observed in the CC-486 arm than in the placebo arm, most related to infections. The propensity to develop fatal infections early in the study could be partly attributed to poor prognostic baseline characteristics of these mostly older patients (median age 74 years), but this does not explain the imbalance between treatment arms (except for the notable difference in baseline ANC) and a causal relationship between CC-486 and these early deaths cannot be excluded. Given the unfavorable prognostic features of patients in this study, there might have been a subgroup of patients who were more sensitive to the myelosuppressive effects of CC-486, inducing an ANC reduction during early treatment that could have rendered already significantly neutropenic patients more prone to fatal infections. Currently, the ONUREG prescribing information does not recommend using CC-486 for MDS outside of a clinical trial.¹⁶

At data cutoff, underpowered interim OS analysis showed no survival benefit for patients receiving CC-486. The relatively poor OS seen in both arms of this trial also speaks to the severity of illness in this population.²

Hematologic and GI TEAEs were the most frequently observed toxicities with CC-486. These events occurred most often during cycles 1-2, after which they were less frequent, suggesting a lack of cumulative toxicity. The majority of GI TEAEs were mild or moderate in severity. Grade 3-4 hematological TEAEs and infections occurred more frequently in the CC-486 arm. Similarly, more patients in the CC-486 arm had TEAEs leading to a dose reduction, but similar proportions of patients in each arm discontinued treatment because of a TEAE, suggesting that CC-486 dose modifications allowed some patients to continue treatment with better tolerance.

These results demonstrate that CC-486 can provide clinically meaningful reductions in RBC transfusion burden and ameliorate thrombocytopenia in patients with LR-MDS with symptomatic disease and refractory cytopenias. A higher rate of early deaths occurred in the CC-486 arm, most related to infections in patients with significant pretreatment neutropenia. Ongoing molecular and HRQoL analyses may provide additional context for these clinical outcomes. Further evaluation of CC-486 in patients with MDS is needed and may help identify patients who may benefit from this therapy.

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Sheila Truten and Brian Kaiser from Medical Communication Company, Inc (Wynnewood, PA), funded by Bristol-Myers Squibb Company and in accordance with Good Publication Practice guidelines.

CLINICAL TRIAL INFORMATION

NCT01566695

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO.20.02619>.

DATA SHARING STATEMENT

See Bristol-Myers Squibb Company policy on data sharing at <https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html>.

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PRIOR PRESENTATION

Presented in abstract form at the 25th EHA Annual Congress (June 11–21, 2020; Virtual).

SUPPORT

Supported by Celgene Corporation, a Bristol-Myers Squibb company. Editorial support on an early draft of the manuscript was provided by

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Phase III, Randomized, Placebo-Controlled Trial of CC-486 (Oral Azacitidine) in Patients With Lower-Risk Myelodysplastic Syndromes**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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No other potential conflicts of interest were reported.