




Extended dosing with CC-486 (oral azacitidine) in patients with myeloid malignancies

Michael R. Savona¹  | Kathryn Kolibaba^{2,3} | Paul Conkling^{2,4} | Edwin C. Kingsley^{2,5} | Carlos Becerra^{2,6} | John C. Morris⁷ | Robert M. Rifkin^{2,8} | Eric Laille⁹ | Amy Kellerman⁹ | Stacey M. Ukrainskyj⁹ | Qian Dong⁹ | Barry S. Skikne⁹

¹Vanderbilt-Ingram Cancer Center, Nashville, Tennessee

²US Oncology Research, Woodlands, Texas

³Northwest Cancer Specialists, Vancouver, Western Australia

⁴Virginia Oncology Associates, Norfolk, Virginia

⁵Comprehensive Cancer Centers of Nevada, Las Vegas, Nevada

⁶Texas Oncology, PA (North), Sammons Cancer Center, Dallas, Texas

⁷University of Cincinnati Cancer Institute, Cincinnati, Ohio

⁸Rocky Mountain Cancer Centers, Denver, Colorado

⁹Celgene Corporation, Summit, New Jersey

Correspondence

Michael R. Savona, Division of Hematology/Oncology, Vanderbilt University Medical Center, 2220 Pierce Ave, 777 PRB, Nashville, TN 37232-6307.

Email: michael.savona@vanderbilt.edu

Funding information

Celgene Corporation

Abstract

CC-486 (oral azacitidine) is an epigenetic modifier in clinical development for treatment of hematological cancers. This study of extended CC-486 dosing included patients with myelodysplastic syndromes (MDSs), chronic myelomonocytic leukemia (CMML), or acute myeloid leukemia (AML). After a pharmacokinetic assessment period, 31 patients (MDS $n = 18$, CMML $n = 4$, and AML $n = 9$) entered a clinical phase in which they received CC-486 300 mg once-daily for 21 days of repeated 28-day cycles. Median age was 71 years (range: 53-93); 42% of patients were aged ≥ 75 years. A total of 5 patients with AML (63%) had prior MDS. Median number of CC-486 treatment cycles was 4 (range: 1-32). The most common treatment-emergent adverse events (TEAEs) were gastrointestinal (84% of patients) and hematologic (81%). Most common grade 3-4 TEAEs were neutropenia ($n = 13$, 42%) and anemia ($n = 9$, 29%). Ten patients experienced grade 4 neutropenia. Infrequently, CC-486 dose was interrupted or reduced due to gastrointestinal ($n = 5$, 16%) or hematologic ($n = 6$, 19%) TEAEs. Overall response rate (complete remission [CR], CR with incomplete hematological recovery [CRi], partial remission [PR], marrow CR) in the MDS/CMML subgroups was 32% and in the AML subgroup (CR/CRi/PR) was 22%. Red blood cell transfusion independence rates in the MDS/CMML and AML subgroups were 33% and 25%, respectively, and 2 MDS/CMML patients attained hematologic improvement as a best response on-study. No baseline gene mutation was predictive of response/nonresponse. CC-486 allows flexible dosing and schedules to improve tolerability or response. Neutropenia in early treatment cycles deserves scrutiny and may warrant initiation of prophylactic antibiotics.

KEY POINTS

The safety profile of oral CC-486 was comparable to that of injectable azacitidine; most adverse events were hematological and gastrointestinal.

Extended (21-day/cycle) CC-486 dosing induced responses in patients with hematological malignancies, many of whom had prior DNMTi failure.

1 | INTRODUCTION

Azacitidine is an epigenetic modifier and DNA methyltransferase inhibitor (DNMTi).¹⁻³ Hypermethylation of epigenetic regions of DNA and consequent alterations in expression of genes associated with normal cell cycling, apoptosis, and tumor suppression, are implicated in the pathogenesis of myelodysplastic syndromes (MDSs) and acute myeloid leukemia (AML).⁴ Azacitidine mechanisms of action have not been fully elucidated, but it is thought to reduce DNA methylation

upon incorporation into DNA, alter protein expression upon incorporation into RNA, and exert direct cytotoxic effects on abnormal hematopoietic cells in bone marrow.¹⁻³

Parenteral azacitidine has been extensively evaluated in patients with MDS, chronic myelomonocytic leukemia (CMML), and AML in large randomized clinical trials,⁵⁻⁷ in regional registry studies,⁸⁻¹³ and in numerous smaller retrospective analyses of patients treated in community practice.^{14,15} These studies show azacitidine reduces cytopenias in select lower-risk MDS and prolongs overall survival (OS) in

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2018 The Authors. *American Journal of Hematology* published by Wiley Periodicals, Inc.

higher-risk MDS and AML,^{5-7,16} may be effective maintenance therapy after induction chemotherapy (IC) or allogeneic hematopoietic stem cell transplant (alloHSCT),¹⁷⁻²⁰ and can induce responses in patients with relapsed/refractory disease.^{12,21} Importantly, the study of azacitidine has revealed nuances of treatment with DNMTi therapy not seen with the use of traditional chemotherapy. These include improved OS, which can occur in the absence of a complete remission (CR),^{7,8,22} a need to treat with as many as 6 treatment cycles prior to achieving maximal response, and hematologic toxicities seen during early treatment tend to decrease if patients can remain on treatment.^{7,8,23}

CC-486 is an oral formulation of azacitidine in clinical development for treatment of hematological malignancies. A phase 1 dose-escalation study evaluated treatment outcomes for patients with MDS, CMML, or AML who, after receiving an initial cycle of standard subcutaneous (SC) azacitidine dosing (75 mg/m²/day for 7 days of a 28-day cycle), received CC-486 doses of 180-600 mg/day for 7 consecutive days per cycle thereafter.²⁴ Pharmacodynamic evaluation of 7-day administration of SC azacitidine and oral CC-486 showed both treatments resulted in greatest respective reductions in global methylation (per Infinium Human Methylation27 BeadArray assay; Illumina, San Diego, CA) near mid-cycle, after which, methylation levels began to rise to approximately pretreatment levels.^{24,25} As some of the benefit of parenteral azacitidine is thought to be from global hypomethylation, it is reasonable to consider that prolongation of hypomethylation may be beneficial. This is logistically difficult for parenteral administration, and one potential advantage of an oral formulation of azacitidine is that it may be administered more easily over a prolonged period. Indeed, extending dosing of CC-486 to 14 or 21 days per 28-day cycle was shown to significantly reduce methylation of highly methylated gene loci from pretreatment levels and hypomethylation was sustained over the entire treatment cycle.^{25,26} Moreover, sustained hypomethylation with CC-486 can be achieved with lower azacitidine exposure.²⁶ Cumulative azacitidine exposures per cycle with 300 mg daily 14- and 21-day CC-486 regimens provide 38% and 57% of exposure with injectable azacitidine 75 mg/m²/day for 7 days per 28-day cycle.²⁶

This 2-part, multicenter, open-label, phase 1 trial was conducted to assess the effect of food on the pharmacokinetics (PKs) of CC-486 (part 1) and gastric pH modulation on CC-486 PK parameters (part 2). Following the PK phase, patients could enroll into the clinical phase of the study in which the safety and efficacy of extended CC-486 dosing were evaluated. Results of the PK phase, which showed that food or concomitant use of a proton-pump inhibitor did not meaningfully alter CC-486 and are reported elsewhere.²⁷ Reported here are the safety, tolerability, and hematologic responses for all patients with MDS, CMML, or AML who enrolled in the study extension and received extended dosing with CC-486300 mg.

2 | METHODS

2.1 | Patients

Patients ages 18 years and older with a diagnosis of MDS, CMML, or AML according to the World Health Organization (WHO) classification system,²⁸ based on bone marrow aspirate and biopsy performed

within 30 days before starting CC-486, could participate. Patients must have had an Eastern Cooperative Oncology Group performance status score of 0-2 and life expectancy of at least 3 months. Patients were excluded if they had acute promyelocytic leukemia or had received standard or investigational cancer therapies within 21 days before starting CC-486 treatment. Previous treatment with azacitidine or decitabine was allowed except for within 21 days of beginning CC-486. Concurrent use of erythropoiesis-stimulating agents and other red blood cell (RBC) hematopoietic growth factors was disallowed unless the patient was on a stable dose for at least 4 weeks before starting CC-486. All procedures pertaining to study conduct, evaluation, and documentation were in accordance with the International Conference on Harmonization Guideline E6, and complied with the ethical principles outlined in the Declaration of Helsinki. The study protocol was approved by all relevant Institutional Review Boards or Independent Ethics Committees before study initiation. All patients provided written, informed consent before participating. Authors had access to all study data. This study is registered at ClinicalTrials.gov (NCT01519011).

2.2 | Treatment

Patients in the clinical extension phase of this study received CC-486300 mg QD for 21 days of repeated 28-day cycles, and could remain on-treatment for as long as they benefitted from therapy. Use of antiemetic medication 30 min before CC-486 ingestion was recommended. Rates of dose modification (ie, doses that were interrupted, reduced, or discontinued) due to hematological or gastrointestinal adverse events (AEs) were recorded.

2.3 | Analysis populations

The safety evaluable population included patients who received at least 1 dose of CC-486, and the efficacy evaluable population comprised patients who received at least 1 dose of CC-486 and who had at least 1 post-baseline efficacy assessment performed in the clinical phase of the study.

2.4 | Endpoints

The primary goal was to evaluate the safety and tolerability of extended dosing with CC-486. Safety and tolerability were assessed by type, frequency, and severity of treatment-emergent adverse events (TEAEs), defined as any AEs reported on or after the date of the first CC-486 dose in the clinical phase of the study until 28 days after the last CC-486 dose. TEAEs were coded by the Medical Dictionary for Regulatory Activities version 18.0 and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. A secondary endpoint of the study was overall response rate (ORR) based on investigator-reported hematologic responses. Efficacy endpoints are reported for patients with MDS or CMML together due to the small number of patients with CMML in the study, and separately for AML. For patients with MDS or CMML, ORR comprised CR, partial remission (PR) and marrow CR (mCR), per modified IWG 2006 response criteria for MDS.²⁹ ORR for

TABLE 1 Patient characteristics at baseline

Characteristic	MDS (n = 18)	CMML (n = 4)	AML (n = 9)	Total (N = 31)
Age (years), median (range)	74.5 (55, 90)	68.0 (59, 85)	70.0 (53, 93)	71.0 (53, 93)
Age ≥ 75 years, n (%)	9 (50)	1 (25)	3 (33)	13 (42)
Male gender, n (%)	13 (72)	4 (100)	5 (56)	22 (71)
WHO classification, n (%)				
MDS-RA	4 (22)	4 (13)
MDS-RAEB-1	2 (11)	2 (7)
MDS-RAEB-2	6 (33)	6 (19)
MDS-RARS	1 (5)	1 (3)
MDS-RCMD	4 (22)	4 (13)
MDS-Missing	1 (5)	1 (3)
CMML-1	...	4 (100)	...	4(13)
AML not otherwise specified	3 (33)	3 (10)
AML-MRC	6 (67)	6 (19)
Months since diagnosis, median (range)	15.9 (-0.4, 118.1)	13.5 (2.5, 26.8)	3.1 (-0.1, 19.7)	
Prior MDS, n (%)				
Yes	NA	NA	5 (56)	
Primary	4 (44)	
Secondary	1 (11)	
No	4 (44)	
Prior injectable DNMTi use, n (%)	6 (33)	2 (50)	6 (67)	14 (45)
Bone marrow blasts (%), median (range)	5.0 (0, 10)	2.5 (0, 5)	25.0 (20.0, 40.0)	9.0 (0.0, 40.0)
Peripheral blood blasts (%)	0 (0, 10)	0.5 (0, 5)	11.5 (0, 62)	0.5 (0, 62)
IPSS risk, n (%) (MDS patients only)				
Low	4 (21)	
Intermediate-1	6 (37)	
Intermediate-2	5 (26)	
High	0	
Missing	3 (16)	
Cytogenetic risk status, n (%)				
Good	12 (67)	3 (75)	0	21 (68)
Intermediate	1 (6)	0	6 (67)	1 (3)
Poor	3 (17)	0	2 (22)	4 (13)
Missing	2 (11)	1 (25)	1 (11)	5 (16)
ECOG PS score, n (%)				
Grade 0	5 (28)	1 (25)	1 (11)	7 (23)
Grade 1	12 (67)	3 (75)	6 (67)	21 (68)
Grade 2	1 (6)	0	2 (22)	3 (10)
Baseline transfusion dependence, n (%)				
RBC TD	5 (28)	1	5 (56)	11 (35)
Platelet TD	0	0	3 (33)	3 (16)
Hgb (g/dL), median (range)	9.1 (7.2, 12.9)	11.0 (7.1, 14.6)	8.5 (7.1, 11.7)	9.0 (7.1, 14.6)
Platelets (10 ⁹ /L), median (range)	70.0 (15, 283)	171.0 (54, 365)	33.0 (3, 435)	66.0 (3, 435)
ANC (10 ⁹ /L), median (range)	1.5 (0, 8.6)	12.2 (4.2, 56.0)	0.5 (0, 18.6)	1.5 (0, 56.0)
WBC (10 ⁹ /L), median (range)	3.7 (0.8, 13.9)	22.4 (7.5, 73.1)	9.0 (1.3, 129.0)	4.5 (0.8, 129.0)

Abbreviations: AML, acute myeloid leukemia; AML-MRC, AML with myelodysplasia-related changes; ANC, absolute neutrophil count; CMML, chronic myelomonocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; Hgb, hemoglobin; DNMTi, DNA methyltransferase inhibitor; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; TD, transfusion-dependent; WBC, white blood cell; WHO, World Health Organization.

patients with AML included CR, CR with incomplete hematologic recovery (CRi), and PR per IWG 2003 response criteria for AML.³⁰ Hematologic improvement (HI) in the erythroid (HI-E), platelet (HI-P), or neutrophil (HI-N) lineages, (per the IWG 2006 criteria for MDS²⁹) and

RBC or platelet transfusion independence (TI) in patients who were transfusion-dependent at baseline, are also reported. Baseline transfusion dependence was defined as receipt of ≥4 RBC units or ≥ 2 platelet transfusions within the 84 days before the first CC-486 dose, with no

TABLE 2 CC-486 exposure and dose modifications

Characteristic	MDS (n = 18)	CMML (n = 4)	AML (n = 9)	Total (N = 31)
Number of CC-486 treatment cycles, median (range)	5.0 (1-32)	4.0 (2-17)	1.0 (1-9)	4.0 (1-32)
>6 CC-486 treatment cycles initiated, n (%)	7 (39)	1 (25)	1 (11)	9 (29)
Average cycle length (days), mean [SD]	32.8 [8.1]	26.4 [5.0]	24.6 [11.6]	29.6 [9.5]
Dose interruption/reduction due to gastrointestinal TEAEs, n (%) ^a	3 (17)	0	2 (22)	5 (16)
Dose interruption/reduction due to hematologic TEAEs, n (%) ^a	5 (28)	0	1 (11)	6 (19)

Abbreviations: AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndromes; TEAE, treatment-emergent adverse event.

^a Dose interrupted, reduced, or discontinued.

consecutive transfusion-free interval of ≥ 42 days. TI was defined as having received no RBC or platelet transfusion for 84 consecutive days during treatment. As this was a phase 1 study, OS was not a prospective endpoint.

ORR is also reported for the subgroup of patients who had previously been treated with injectable DNMTi. To limit this analysis to only patients with recent DNMTi experience, ORR was analyzed only for patients who had received ≥ 2 cycles of an injectable DNMTi within the 1 year before receiving CC-486, or who received 1 cycle of an DNMTi that was stopped due to intolerance within 4 months before receiving of CC-486 treatment.

2.5 | Mutational analyses

The Illumina TruSight Myeloid Panel (Illumina, San Diego, CA) was used to identify mutations in the coding region of 54 relevant genes involved in AML and MDS (Supporting Information Table S1). The assay targets 15 full exomes and exonic hotspots in 39 additional genes. Sequencing data (500x coverage per sample) were obtained on the Illumina MiSeq genome sequencing platform. Variant allele frequencies were calculated as a fraction of the mutated allele reads over total reads (mutated allele + wild type allele) in each sample.

2.6 | Statistical analysis

Demographic, safety, efficacy, and mutational outcomes are reported descriptively.

3 | RESULTS

3.1 | Patient disposition

The study was conducted between February 9, 2012 and May 12, 2015. Of 36 patients screened, 31 patients received CC-486 during the clinical phase of the study and comprise the safety and efficacy cohort for these analyses (Supporting Information

TABLE 3 Occurrence of gastrointestinal and hematologic TEAEs (any grade, any cause) by cycle of onset

	Cycles 1-2 (N = 31) n (%)	Cycles 3-4 (N = 19) n (%)	Cycles 5-6 (N = 13) n (%)
Gastrointestinal TEAEs	26 (84)	7 (37)	6 (46)
Diarrhea	17 (55)	2 (11)	0
Nausea	9 (29)	3 (16)	1 (8)
Vomiting	11 (36)	1 (5)	1 (8)
Constipation	10 (32)	0	2 (15)
Abdominal pain ^a	5 (15)	1 (5)	0
Hematologic TEAEs	21 (68)	10 (53)	3 (23)
Neutropenia	13 (42)	0	0
Anemia	12 (39)	0	0
Thrombocytopenia	9 (29)	1 (5)	0
Febrile neutropenia	4 (13)	0	0

^a Preferred terms "abdominal pain" and "upper abdominal pain".

Figure S1). In total 18 patients (58%) had a diagnosis of MDS, 4 patients (13%) had CMML, and 9 patients (29%) had AML (Table 1). The most common reasons for study discontinuation were TEAEs ($n = 12$, 36%) and disease progression ($n = 11$, 36%) (Supporting Information Figure S1).

The patients had a median age of 71 years [range 53-93], and 42% of patients were aged 75 years or older. The most common subtype of MDS was refractory anemia with excess blasts-2 (RAEB-2; 33%), and the majority of AML included myelodysplasia-related changes (AML-MRC; 67%). All patients with CMML had WHO-defined CMML-1 with $< 10\%$ blasts. Among AML patients, 5 (56%) had previously had a diagnosis of MDS. In all, 14 patients (45%) had received prior therapy with an injectable DNMTi.

As a group, the median number of CC-486 treatment cycles received was 4 (range 1-32) (Table 2). Mean [SD] CC-486 treatment cycle length for all patients was 29.6 [9.5] days. In total 23 patients (74%) had no CC-486 dose modification during the study. In total 8 patients (26%) had one or more dose modifications: 6 patients had 1 dose modification, 1 patient had 2 dose modifications, and 1 patient had 3 dose modifications. The most common ($n = 5$ patients) were

TABLE 4 Most frequent ($\geq 10\%$) treatment-related TEAEs

Preferred term	MDS (n = 18) n (%)	CMML (n = 4) n (%)	AML (n = 9) n (%)	Total (N = 31) n (%)
Diarrhea	10 (56)	4 (100)	5 (56)	19 (61)
Nausea	6 (33)	3 (75)	5 (56)	14 (45)
Vomiting	7 (39)	1 (25)	4 (44)	12 (39)
Neutropenia	10 (56)	0	1 (11)	10 (32)
Decreased appetite	5 (28)	1 (25)	3 (33)	9 (29)
Anemia	7 (39)	0	1 (11)	8 (26)
Fatigue	5 (28)	0	3 (33)	8 (26)
Constipation	4 (22)	1 (25)	1 (11)	6 (19)
Febrile neutropenia	3 (17)	0	1 (11)	4 (12)

Abbreviations: AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndromes; TEAE, treatment-emergent adverse event.

TABLE 5 Gastrointestinal and hematologic TEAEs

	MDS n (%) (n = 18)	CMML (n = 4)	AML (n = 9)	Total (N = 31)
Most common ^a gastrointestinal TEAEs (any grade)				
Diarrhea	10 (56)	4 (100)	5 (56)	19 (61)
Nausea	6 (33)	3 (75)	5 (56)	14 (45)
Vomiting	8 (44)	1 (25)	4 (44)	13 (42)
Constipation	6 (33)	2 (50)	2 (22)	10 (32)
Abdominal pain	2 (11)	1 (25)	1 (11)	4 (13)
Dyspepsia	3 (17)	0	0	3 (10)
Grades 3–4 gastrointestinal TEAEs				
Diarrhea	1 (6)	1 (25)	0	2 (7)
Vomiting	0	0	2 (25)	2 (7)
Abdominal pain	0	1 (25)	0	1 (3)
Constipation	1 (6)	0	0	1 (3)
Upper GI hemorrhage	0	0	1 (13)	1 (3)
Most common ^a hematologic TEAEs (any grade)				
Anemia	10 (56)	1 (25)	3 (33)	14 (45)
Neutropenia	11 (61)	1 (25)	2 (22)	14 (45)
Thrombocytopenia	7 (39)	0	3 (33)	10 (32)
Febrile neutropenia	3 (17)	0	1 (11)	4 (13)
Grades 3–4 hematologic TEAEs				
Neutropenia	10 (56)	1 (25)	2 (22)	13 (42)
Anemia	7 (39)	1 (25)	1 (11)	9 (29)
Thrombocytopenia	4 (22)	0	3 (33)	7 (23)
Febrile neutropenia	3 (17)	0	1 (11)	4 (13)

Abbreviations: AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndromes; TEAE, treatment-emergent adverse event.

^a Occurring in $\geq 10\%$ of all patients.

dose reductions from 300 to 200 mg QD (1 patient subsequently returned to the 300 mg QD dose).

3.2 | Safety

The most common TEAEs were gastrointestinal (84%) and hematologic (81%) in nature, with the majority of events occurring during the first 2 treatment cycles (Table 3). The most frequent TEAEs (any cause) were diarrhea (61%), and anemia, neutropenia, and nausea (45% each) (Supporting Information Table S2). Except for fatigue, all treatment-related TEAEs occurring in $\geq 10\%$ of patients, at any point within the study, were gastrointestinal or hematological (Table 4).

Seven grade 3 gastrointestinal TEAEs were reported in 6 patients (19%) (Table 5); no grade 4 gastrointestinal TEAEs occurred on-study.

TABLE 6 Hematologic response

	MDS+CMML ^a Total (N = 22)	Prior HMA (n = 8)	Tx-naïve (n = 14)	AML total (N = 9)	Prior HMA (n = 6)	Tx-naïve (n = 3)
ORR, ^b n (%)	7 (32)	0	7 (50)	2 (22)	1 (17)	1 (33)
CR	4 (18)	0	4 (29)	1 (11)	1 (17)	0
CRi/mCR	0	0	0	0	0	0
PR	3 (14)	0	3 (21)	1 (11)	0	1 (33)
TI, n/N (%)						
RBC TI	2/6 (33)	NA	2/6 (33)	1/4 (25)	1/3 (33)	0/1
Platelet TI	0/0	NA	NA	1/2 (50)	1/2 (50)	NA

Abbreviations: CR, complete remission; CRi, CR with incomplete hematologic recovery; NA, not applicable; PR, partial remission, RBC, red blood cell; TI, transfusion independence.

^a Investigator reported responses were available for only 3 of 4 CMML patients.

^b CR + PR + mCR for patients with MDS/CMML; CR + CRi + PR for patients with AML.

Grade 3-4 hematologic TEAEs were reported for 19 patients, including 10 patients who experienced grade 4 neutropenia (Table 5).

Treatment-related grade 3-4 TEAEs were reported for 20 patients (65%; MDS n = 14, CMML n = 1, AML n = 5); those occurring in 2 or more patients were neutropenia (n = 11), anemia (n = 5), thrombocytopenia (n = 4), febrile neutropenia (n = 4), and pneumonia (n = 3). All treatment-related grade 4 TEAEs reported on-study were hematological. A total of 13 CC-486-related serious TEAEs were reported for 9 patients (29%): febrile neutropenia (n = 4), pneumonia (n = 3), and (n = 1 each) hemolytic anemia, atrial fibrillation, supraventricular tachycardia, upper gastrointestinal hemorrhage, peritonsillar abscess, and septic shock.

Dose modifications due to gastrointestinal TEAEs were reported for 5 patients (16%) or due to hematologic TEAEs for 6 patients (19%) (Table 2). Three patients (10%) experienced 1 or more TEAE that led to CC-486 dose reduction (neutropenia, nausea and vomiting, and WBC decrease). CC-486 dose interruptions were reported for 11 patients (36%). TEAEs leading to discontinuation of CC-486 (n = 10, 32.3%) were thrombocytopenia and fatigue (n = 2 each), febrile neutropenia, disseminated intravascular coagulation, diarrhea, pneumonia, sepsis, and decreased appetite (n = 1 each).

Six patients died during the clinical phase of the study or within 28 days after their last CC-486 dose; 2 of the deaths were considered possibly related to study drug (septic shock, hemolytic anemia).

3.3 | Efficacy

ORR for patients with MDS and CMML was 32%, including 4 patients who attained CR and 3 patients who had PR (Table 6). ORR for patients with AML was 22% (1 CR and 1 PR). Two patients, 1 with MDS and 1 with CMML had IWG-2006 defined HI as a best response on-study (HI-E and HI-N, respectively). Of 6 patients with MDS or CMML who were RBC transfusion-dependent at baseline, 2 attained RBC TI on-study, with TI durations of 340 and 470 days. No MDS or CMML patient was platelet transfusion-dependent at baseline. In total 1 of 4 patients with AML who were RBC transfusion-dependent at baseline attained RBC-TI for a duration of 147 days, and of 2 AML patients who were platelet transfusion-dependent at baseline 1 achieved platelet-TI sustained for 158 days.

In all, 14 patients (45%) had received prior injectable DNMTi therapy before receiving CC-486, including 6 patients with AML and 8 patients with MDS/CMML. Of the 6 patients with AML, 4 had

- A 67-year old female with IPSS Intermediate-2 risk MDS that had transformed to AML by time of study entry
- Refractory to or relapsed during prior HMA treatment intervals
- CC-486 300mg QD x 21 days per cycle

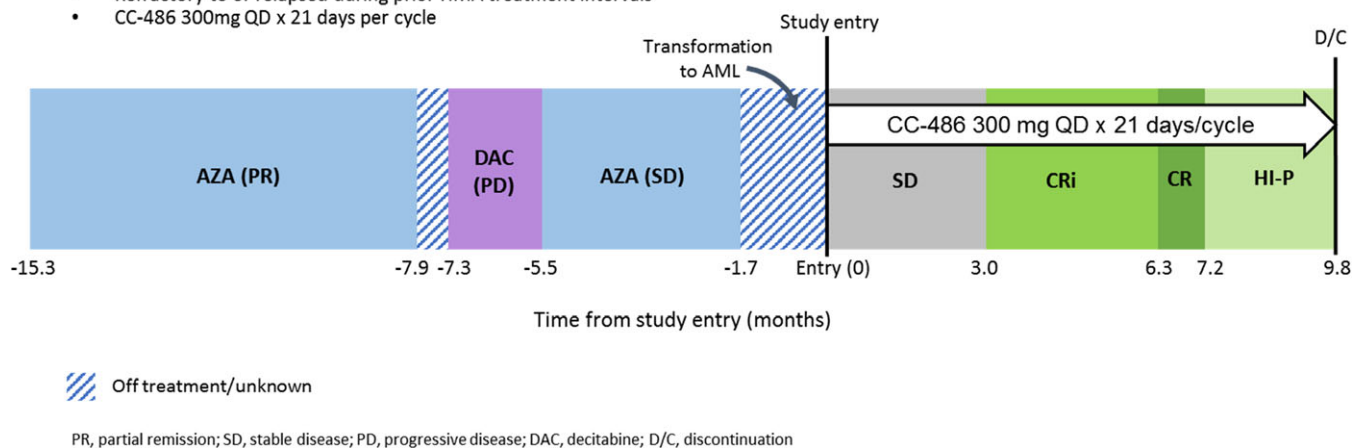


FIGURE 1 A patient who received injectable hypomethylating agents before study entry and attained complete remission during CC-486 treatment

relapsed and 2 were refractory to prior DNMTi treatment. Of the 8 patients with MDS/CMML, 3 had relapsed and 5 were refractory to prior DNMTi treatment. ORR for all patients who had received prior DNMTi therapy was 14%, including 1 patient with AML who attained CR and 1 patient with MDS who attained HI-E. The patient who attained CR was a 67-year-old female with AML secondary to MDS had received injectable decitabine and azacitidine prior to study entry (Figure 1). The patient had trisomy 8 karyotype and a *TET2* mutation (L1721 W) at study entry that remained throughout the course of CC-486 treatment.

Pre and posttreatment blood samples for mutational testing were available for 21 patients. In this subgroup, investigator-reported responses included 5 CRs (4 MDS patients and 1 AML patient) and 4 PRs (1 MDS, 2 CMML, and 1 AML). No emerging trends in number or type of mutations appeared to distinguish responders from non-responders. Variant allele frequencies changed little over the course of treatment from pre-treatment values in responders and non-responders alike. Infrequent gains or losses of mutations were not retained for all cycles. The small number of patients with longitudinal mutation data limited the ability to detect correlations between mutational status and/or changes with response. As shown in Supporting Information Table S3 normal karyotype and IPSS good- or intermediate-risk cytogenetics appeared to have greater influence on the likelihood of response than mutational profile.

4 | DISCUSSION

Since approval for treatment for MDS in 2004,³¹ parenteral azacitidine has been shown to induce remissions and HI in a range of settings, from first-line treatment of higher-risk MDS, CMML and AML to maintenance therapy after alloHSCT.^{5-7,12,19,20,32-34} CC-486, is an oral drug formulation of azacitidine. Oral administration of CC-486 is not pharmacokinetically equivalent to parenteral azacitidine, and thus can induce alternate demethylated regions in the genome.²⁴ This is thought to account for responses in both azacitidine naïve and azacitidine failure patients.^{24,26} In addition, there is considerable flexibility in

dosing and schedule with an oral DNMTi, so understanding the safety profile and pharmacodynamics of CC-486 in various treatment regimens may provide new treatment strategies for patients with myeloid malignancies.

The safety profile of CC-486 300 mg QD for 21 days per 28-day cycle is consistent with the known safety profile of injectable azacitidine.³⁵ The proportions of patients with anemia, neutropenia, and thrombocytopenia in the current study were 45%, 45%, and 32%, respectively. Comparably, cytopenias were reported for 51%, 66%, and 70%, respectively, in patients with higher-risk MDS receiving parenteral azacitidine in the phase 3 AZA-001 trial.³⁵ It is possible that lower azacitidine exposure over a longer period with CC-486 may attenuate drug-induced cytopenias often seen during early treatment. Gastrointestinal side effects appear to be more common with the oral formulation than the injectable formulation of azacitidine. For example, proportions of patients experiencing diarrhea or vomiting in this study (61% and 39%, respectively) are higher than those reported for patients in the AZA-001 trial (22% and 27%).³⁵ It is unclear if this is a function of changes in the microbiome in the gut leading to gastrointestinal AEs,³⁶ or, perhaps the local effects of oral cytotoxic therapy which may cause irritation to the gastrointestinal mucosa.

As reported for SC azacitidine,³⁵ the frequency of TEAEs with CC-486 tended to decrease as treatment cycles continued. Most patients in this study (>80%) did not require dose modifications (reducing, delaying, or discontinuing dosing) due to AEs; however, prolonging the dosing cycle to slightly longer than 28 days or decreasing CC-486 dose even temporarily may help patients who experience hematological or gastrointestinal toxicity. As with parenterally administered DNMTis, neutropenia seen in this patient population may warrant initiation of prophylactic antibiotics. Management strategies for gastrointestinal AEs employed for patients who have received injectable azacitidine include prophylactic use of antiemetics and symptomatic treatment with laxatives or antidiarrheal agents, and these should also be employed with CC-486.³⁵ Further prophylaxis against gastrointestinal toxicity may be warranted. As concomitant use of a proton pump inhibitor (PPI) showed no clinically meaningful effect on CC-486 PK parameters—including the area under the concentration-

time curve and C_{max} of CC-486—coadministration with a PPI would not interfere with CC-486 drug levels. Likewise, as PK parameters were shown to be comparable under fed and fasted conditions, diet changes may assist in the management of gastrointestinal toxicities.²⁷

The kinetics of demethylation observed when CC-486 dosing is extended for more than 7 days provides an additional facet to DNMTi therapy²⁵; delaying or preventing DNA remethylation with continuous demethylation provided from prolonged dosing of CC-486 may account for sustained HI, and recovery of response in patients for whom parenteral DNMTi have failed. In total 7 patients with MDS or CMML and 2 patients with AML receiving CC-486 monotherapy in this study attained CR or PR, including, importantly, patients for whom previous DNMTi therapy had failed. While multiple studies have shown injectable azacitidine can improve OS in higher-risk MDS and AML without requiring CR^{5,7-9,37}; the effect of CC-486 on OS has not yet been reported and was not captured in this phase 1 study, but is under investigation in an ongoing phase 3 trial of CC-486 in patients with MDS (NCT01566695).

Attaining CR with treatment remains elusive with lower-intensity therapies for MDS and AML. Thus, there is strong rationale for the concomitant use of drugs with different molecular targets. Oral DNMTi therapy could potentially be used in combination treatment regimens with other novel agents for synergy.

Outcomes of the current study suggest CC-486 can induce responses in patients with MDS, CMML, or AML who have relapsed or are refractory to prior treatments, those who have AML transformed from MDS, and those who had previously failed injectable DNMTi treatment. The influence of mutations on the likelihood of response could not be established due to the limited number of patients. The safety and tolerability of CC-486 are consistent with the well-established safety profile of parenteral azacitidine, and similar strategies can be used to manage CC-486-related AEs. Confirmation of the clinical effects of CC-486 monotherapy and mutational analyses in patients with hematologic malignancies are expected from 2 ongoing multicenter, placebo-controlled, randomized, phase 3 clinical trials: a study in patients with lower-risk MDS who are RBC transfusion dependent and thrombocytopenic (platelet count $\leq 75 \times 10^9/L$) (ClinicalTrials.gov NCT01566695), and as maintenance therapy in patients with AML who attain a first CR with induction chemotherapy (ClinicalTrials.gov NCT01757535).

ACKNOWLEDGMENTS

Editorial support was provided by Sheila Truten and Kelly Dittmore (Medical Communication Company, Inc.; Wynnewood, PA), funded by Celgene Corporation.

CONFLICT OF INTEREST

Astex, Incyte, Karyopharm, Sunesis, Takeda, TG Therapeutics, consultancy and research funding, Karyopharm equity; Celgene DSMB, Gilead DSMB (Michael R. Savona), Advisory board participation for Amgen, Celgene, Takeda (Robert M. Rifkin), and EL, AK, SMU, QD,

BSS are employed by Celgene Corporation (Eric Laille, Amy Kellerman, Stacey M. Ukrainskyj, Qian Dong, Barry S. Skikne).

ORCID

Michael R. Savona  <http://orcid.org/0000-0003-3763-5504>

REFERENCES

- Jones PA. Altering gene expression with 5-azacytidine. *Cell*. 1985;40:485-486.
- Jones PA. Effects of 5-azacytidine and its 2'-deoxyderivative on cell differentiation and DNA methylation. *Pharmacology and Therapeutics*. 1985;28:17-27.
- Jones PA, Taylor SM, Wilson VL. Inhibition of DNA methylation by 5-azacytidine. *Recent Results Cancer Res*. 1983;84:202-211.
- Estey EH. Epigenetics in clinical practice: the examples of azacitidine and decitabine in myelodysplasia and acute myeloid leukemia. *Leukemia*. 2013;27:1803-1812.
- Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol*. 2009;10:223-232.
- Lyons RM, Cosgriff TM, Modi SS, et al. Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. *J Clin Oncol*. 2009;27:1850-1856.
- Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood*. 2015;126:291-299.
- Pleyer L, Burgstaller S, Girschikofsky M, et al. Azacitidine in 302 patients with WHO-defined acute myeloid leukemia: results from the Austrian Azacitidine registry of the AGMT-study group. *Ann Hematol*. 2014;93:1825-1838.
- Itzykson R, Thepot S, Quesnel B, et al. Prognostic factors for response and overall survival in 282 patients with higher-risk myelodysplastic syndromes treated with azacitidine. *Blood*. 2011;117:403-411.
- Ramos F, Thepot S, Pleyer L, et al. Azacitidine frontline therapy for unfit acute myeloid leukemia patients: clinical use and outcome prediction. *Leuk Res*. 2015;39:296-306.
- Maurillo L, Venditti A, Spagnoli A, et al. Azacitidine for the treatment of patients with acute myeloid leukemia: report of 82 patients enrolled in an Italian compassionate program. *Cancer*. 2012;118:1014-1022.
- Itzykson R, Thepot S, Berthon C, et al. Azacitidine for the treatment of relapsed and refractory AML in older patients. *Leuk Res*. 2015;39:124-130.
- Grinblatt DL, Sekeres MA, Komrokji RS, Swern AS, Sullivan KA, Narang M. Patients with myelodysplastic syndromes treated with azacitidine in clinical practice: the AVIDA registry. *Leuk Lymphoma*. 2015;56:887-895.
- Sudan N, Rossetti JM, Shaddock RK, et al. Treatment of acute myelogenous leukemia with outpatient azacitidine. *Cancer*. 2006;107:1839-1843.
- Sadashiv SK, Hilton C, Khan C, et al. Efficacy and tolerability of treatment with azacitidine for 5 days in elderly patients with acute myeloid leukemia. *Cancer Med*. 2014;3:1570-1578.
- Borthakur G, Dombret H, Schafhausen P, et al. A phase I study of danusertib (PHA-739358) in adult patients with accelerated or blastic phase chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia resistant or intolerant to imatinib and/or other second generation c-ABL therapy. *Haematologica*. 2015;100:898-904.
- Gerds AT, Gooley TA, Estey EH, Appelbaum FR, Deeg HJ, Scott BL. Pre-transplant therapy with Azacitidine versus induction chemotherapy and post-transplant outcome in patients with MDS. *Biol Blood Marrow Transplant*. 2012;18:1211-1218.
- Grovdal M, Karimi M, Khan R, et al. Maintenance treatment with azacitidine for patients with high-risk myelodysplastic syndromes (MDS) or acute myeloid leukaemia following MDS in complete remission after induction chemotherapy. *Br J Haematol*. 2010;150:293-302.
- Griffin PT, Komrokji RS, De Castro CM, et al. A multicenter, phase II study of maintenance azacitidine in older patients with acute myeloid

- leukemia in complete remission after induction chemotherapy. *Am J Hematol*. 2015;90:796-799.
20. de Lima M, Giral S, Thall PF, et al. Maintenance therapy with low-dose azacitidine after allogeneic hematopoietic stem cell transplantation for recurrent acute myelogenous leukemia or myelodysplastic syndrome: a dose and schedule finding study. *Cancer*. 2010;116:5420-5431.
 21. Ivanoff S, Gruson B, Chantepie SP, et al. 5-Azacitidine treatment for relapsed or refractory acute myeloid leukemia after intensive chemotherapy. *Am J Hematol*. 2013;88:601-605.
 22. Gore SD, Fenaux P, Santini V, et al. A multivariate analysis of the relationship between response and survival among patients with higher-risk myelodysplastic syndromes treated within azacitidine or conventional care regimens in the randomized AZA-001 trial. *Haematologica*. 2013;98:1067-1072.
 23. Seymour JF, Fenaux P, Silverman LR, et al. Effects of azacitidine compared with conventional care regimens in elderly (>=75 years) patients with higher-risk myelodysplastic syndromes. *Crit Rev Oncol Hematol*. 2010;76:218-227.
 24. Garcia-Manero G, Gore SD, Cogle C, et al. Phase I study of oral azacitidine in myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia. *J Clin Oncol*. 2011;29:2521-2527.
 25. Laille E, Shi T, Garcia-Manero G, et al. Pharmacokinetics and pharmacodynamics with extended dosing of CC-486 in patients with hematologic malignancies. *PLoS One*. 2015;10:e0135520.
 26. Garcia-Manero G, Gore SD, Kambhampati S, et al. Efficacy and safety of extended dosing schedules of CC-486 (oral azacitidine) in patients with lower-risk myelodysplastic syndromes. *Leukemia*. 2016;30:889-896.
 27. Laille E, Savona MR, Scott BL, Boyd TE, Dong Q, Skikne B. Pharmacokinetics of different formulations of oral azacitidine (CC-486) and the effect of food and modified gastric pH on pharmacokinetics in subjects with hematologic malignancies. *J Clin Pharmacol*. 2014;54:630-639.
 28. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*. 2009;114:937-951.
 29. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the international working group (IWG) response criteria in myelodysplasia. *Blood*. 2006;108:419-425.
 30. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. *J Clin Oncol*. 2003;21:4642-4649.
 31. Kaminskas E, Farrell AT, Wang YC, Sridhara R, Pazdur R. FDA drug approval summary: azacitidine (5-azacytidine, Vidaza) for injectable suspension. *Oncologist*. 2005;10:176-182.
 32. Powers HR, Bachar M, Savage N, et al. Azacitidine as salvage therapy for acute myeloid leukemia in a severely ill patient. *Hematol Rep*. 2014;6:5516.
 33. Gerds AT, Gooley TA, Estey EH, et al. Pre-transplant therapy with Azacitidine versus induction chemotherapy and post-transplant outcome in patients with MDS. *Biol Blood Marrow Transplant*. 2012;8:1211-1218.
 34. Damaj G, Duhamel A, Robin M, et al. Impact of azacitidine before allogeneic stem-cell transplantation for myelodysplastic syndromes: a study by the Societe Francaise de Greffe de Moelle et de Therapie-Cellulaire and the Groupe-francophone des Myelodysplasies. *J Clin Oncol*. 2012;30:4533-4540.
 35. Santini V, Fenaux P, Mufti GJ, et al. Management and supportive care measures for adverse events in patients with myelodysplastic syndromes treated with azacitidine. *Eur J Haematol*. 2010;85:130-138.
 36. Toucheffeu Y, Montassier E, Nieman K, et al. Systematic review: the role of the gut microbiota in chemotherapy- or radiation-induced gastrointestinal mucositis - current evidence and potential clinical applications. *Aliment Pharmacol Ther*. 2014;40:409-421.
 37. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol*. 2010;28:562-569.

SUPPORTING INFORMATION

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

How to cite this article: Savona MR, Kolibaba K, Conkling P, et al. Extended dosing with CC-486 (oral azacitidine) in patients with myeloid malignancies. *Am J Hematol*. 2018;93:1199-1206. <https://doi.org/10.1002/ajh.25216>