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CC-486 Maintenance after Stem Cell Transplantation in Patients with Acute Myeloid Leukemia or Myelodysplastic Syndromes

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A B S T R A C T

Relapse is the main cause of treatment failure after allogeneic stem cell transplant (alloSCT) in acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). Injectable azacitidine can improve post-transplant outcomes but presents challenges with exposure and compliance. Oral CC-486 allows extended dosing to prolong azacitidine activity. We investigated use of CC-486 maintenance therapy after alloSCT.

Adults with MDS or AML in morphologic complete remission at CC-486 initiation (42 to 84 days after alloSCT) were included. Patients received 1 of 4 CC-486 dosing schedules per 28-day cycle for up to 12 cycles. Endpoints included safety, pharmacokinetics, graft-versus-host disease (GVHD) incidence, relapse/progression rate, and survival.

Of 30 patients, 7 received CC-486 once daily for 7 days per cycle (200 mg, n = 3; 300 mg, n = 4) and 23 for 14 days per cycle (150 mg, n = 4; 200 mg, n = 19 [expansion cohort]). Grades 3 to 4 adverse events were infrequent and occurred with similar frequency across regimens. Standard concomitant medications did not alter CC-486 pharmacokinetic parameters. Three patients (10%) experienced grade III acute GVHD and 9 experienced chronic GVHD. Of 28 evaluable patients, 6 (21%) relapsed or had progressive disease: 3 of 7 patients (43%) who had received 7-day dosing and 3 of 23 (13%) who had received 14-day dosing. Transplant-related mortality was 3%. At 19 months of follow-up, median overall survival was not reached. Estimated 1-year survival rates were 86% and 81% in the 7-day and 14-day dosing cohorts, respectively.

CC-486 maintenance was generally well tolerated, with low rates of relapse, disease progression, and GVHD. CC-486 maintenance may permit epigenetic manipulation of the alloreactive response postallograft. Findings require confirmation in randomized trials. (ClinicalTrials.gov NCT01835587.)

INTRODUCTION

Allogeneic stem cell transplantation (alloSCT) is a potentially curative therapeutic option for patients with myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML). Disease relapse occurs in 35% to 45% of patients after alloSCT and is the most frequent cause of treatment failure and mortality [1-4]. Moreover, relapse after alloSCT is associated with poor prognosis despite salvage chemotherapy, donor lymphocyte infusions, and/or second transplants [4].

Duration of remission is a key determinant of patient outcomes after alloSCT [5]. A longer interval from transplant to relapse is associated with reduced risk of death [5]. Therefore, maximizing the duration of remission is an important treatment goal [6], and novel therapeutic strategies are needed to provide long-term disease control and extend remission in the post-transplant setting.

Acute and chronic graft-versus-host disease (GVHD) are major causes of non-relapse mortality after alloSCT [7]. Post-transplant maintenance therapy should be well tolerated, with acceptable myelotoxicity and limited drug−drug interactions,

and should reduce the incidence or severity of GVHD without impeding graft-versus-leukemia effects [8].

The DNA methyltransferase inhibitor, azacitidine, is a well-established treatment option for higher-risk MDS and AML [9-11], shown to increase expression of epigenetically silenced leukemia antigens and to induce a CD8^{+} T cell response to tumor antigens post-transplant, potentially augmenting a graft-versus-leukemia effect [12-14]. Studies further suggest azacitidine may accelerate reconstitution of immunomodulatory regulatory T cells, which may reduce GVHD risk [12,15,16]. The dual activity of azacitidine as an antileukemic agent and inhibitor of GVHD makes it a promising agent for post-transplant therapy. Encouraging preliminary data have been reported for s.c. azacitidine maintenance therapy after alloSCT in patients with MDS and AML [14,17,18], although challenges with exposure and compliance are limitations of s.c. administration. AML and MDS are associated with hypermethylation and subsequent silencing of tumor suppressor genes [19]. With the recommended dosing schedule of s.c. azacitidine (75 mg/m^2/day given on days 1 to 7 in 28-day treatment cycles), global DNA reduction is maximal at mid-cycle, whereupon remethylation begins and methylation returns to pretreatment levels by cycle end [20].

CC-486 is a novel oral formulation of azacitidine that allows for prolonged azacitidine exposure and sustained DNA hypomethylation over the entire 28-day treatment cycle by using extended dosing schedules [21,22]. Here, we report final results of a prospective phase I/II dose-finding study of CC-486 maintenance treatment after alloSCT in patients with AML or MDS.

METHODS
Study Design

This multicenter, open-label study was conducted in accordance with Good Clinical Practice, per the International Conference on Harmonization Guideline E6, and with ethical principles outlined in the Declaration of Helsinki. The protocol was approved by the institutional review boards of all participating centers. All patients provided written informed consent. This study is registered at ClinicalTrials.gov (NCT01835587).

Patients

Patients aged ≥ 18 years with a diagnosis of MDS or AML according to World Health Organization criteria [23] who had undergone alloSCT with myeloablative or reduced-intensity conditioning regimens were eligible. Related and unrelated donors were permitted. Stem cells could be from peripheral blood or bone marrow. Donors could have a single mismatch at the HLA-A, -B, -C, -DRB1, or -DQB1 loci. Patients must have had Eastern Cooperative Oncology Group performance status score ≤ 2 and were to be in morphologic complete remission (CR; ie, $\leq 5\%$ bone marrow blasts) with absolute neutrophil counts $\geq 1.0 \times 10^9$/L and platelets $\geq 75 \times 10^9$/L before CC-486 treatment initiation, which was to occur 42 to 84 days after alloSCT. This post-alloSCT interval was to allow for adequate marrow recovery before starting CC-486 treatment, based on our previous experience with parenteral azacitidine [17].

Key exclusion criteria were use of hypomethylating agents, lenalidomide, thalidomide, pomalidomide, chemotherapy, or any other investigational agent after alloSCT; grade $\geq$II acute GVHD or evidence of gastrointestinal GVHD at screening; or malignancies other than MDS or AML, unless disease-free for ≥ 1 year.

Endpoints

The primary objectives were to determine a safe and effective CC-486 dosing regimen and the maximum tolerated dose (MTD) of CC-486 in patients with MDS or AML in the post-alloSCT setting. Secondary endpoints included overall survival (OS), cumulative 1-year relapse- and progression-free survival (RPFS), time to relapse, relapse rate, incidence of acute and chronic GVHD, time to treatment discontinuation, and pharmacokinetic parameters. The safety population included all patients who received ≥ 1 CC-486 dose. The efficacy population included all patients who received ≥ 1 CC-486 dose and had ≥ 1 post-baseline efficacy assessment. The pharmacokinetic population comprised a subset of study patients.

Determination of CC-486 Dose

A standard 3+3 dose-escalation design was followed to evaluate 4 CC-486 dosing schedules in repeated 28-day cycles: CC-486 200 mg (Cohort 1) or 300 mg (Cohort 2) once daily (QD) for 7 days per cycle or CC-486 150 mg (Cohort 3) or 200 mg (Cohort 4) QD for 14 days per cycle. Patients received enough CC-486 doses at a site visit on day 1 of each cycle to complete dosing for that cycle. The MTD was established if 2 dose-limiting toxicities (DLTs) occurred in a cohort during the first 2 treatment cycles. At the MTD, or if the MTD was not reached, a cohort could be expanded with an additional 10 to 12 patients to further evaluate that dosing regimen.

A DLT was defined as any of the following treatment-emergent adverse events (TEAEs), considered by the investigator to be related to CC-486: a clinically significant grade ≥ 3 nonhematologic toxicity, including nausea, diarrhea, or vomiting despite adequate medical intervention; absolute neutrophil counts $< .5 \times 10^9$/L lasting >1 week despite myeloid growth factor support; platelets $< 10 \times 10^9$/L lasting > 1 week despite transfusion support; failure to reach absolute neutrophil counts $\geq 1.0 \times 10^9$/L and/or platelets $\geq 25 \times 10^9$/L in the presence of a hypocellular bone marrow ($< 10\%$) within 56 days after the start of a treatment cycle; inability to initiate a subsequent cycle of CC-486 within 28 days of the anticipated start because of any treatment-related, non-hematologic TEAEs; and any toxic effect requiring dose reduction or treatment interruption.

CC-486 treatment continued until unacceptable toxicity, disease relapse or progression, development of grades III to IV acute or severe chronic GVHD, consent withdrawal, death, or until a maximum of 12 CC-486 cycles had been administered.

Efficacy and Safety

Efficacy and safety measurements were based on complete blood counts monitored weekly for the first 2 cycles (8 weeks) and then on days 1, 15, and 22 of each cycle thereafter. Bone marrow aspirates and cytogenetic studies were performed every 6 months or more frequently if clinically indicated.

OS was defined as the time from transplantation to death by any cause. RPFS was the time from transplantation to relapse, progressive disease, or death, whichever occurred first. Relapse and progressive disease were defined as the reappearance of $> 5\%$ or $> 10\%$ bone marrow blasts, respectively, lasting more than 4 weeks. Patients without a documented relapse were censored at the date of their last assessment or study completion. All patients were followed for survival until death, loss to follow-up, withdrawal of consent, or study closure. Progression to AML was collected during follow-up for patients with MDS.

Safety was assessed by TEAE reporting, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Patients were followed for TEAEs for 28 days after their last CC-486 dose.

Pharmacokinetic Analysis

Blood samples for CC-486 pharmacokinetic analyses were collected pre- and post-dose at .5, 1, 1.5, 2, 2.5, 3, 4, and 6 hours on day 1 of cycles 1 and 2. Plasma samples were analyzed using a validated proprietary HPLC/tandem mass spectrometric method. Pharmacokinetic parameters included maximum observed plasma concentration, time of maximum observed plasma concentration, area under the plasma concentration-time curve from zero to infinity, terminal elimination half-life, apparent total clearance, and apparent volume of distribution. Pharmacokinetic parameters were calculated using noncompartmental methods with Phoenix WinNonlin software (Pharsight Corp, Mountain View, CA). To evaluate potential drug−drug interactions, patients were alternately assigned to take their regular concomitant medications before the visit on day 1 of cycle 1 or 2 and to not to take their regular concomitant medications before the day 1 visit in the other cycle.

Statistical Methods

Demographic, efficacy, and safety outcomes are reported descriptively. No formal comparisons among the CC-486 dosing regimens were planned. OS was estimated using the Kaplan-Meier method. One-year cumulative RPFS rate was based on a competing risk method, in which death without documented progression or relapse is considered a competing risk for progression or relapse. Statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS
Patient Characteristics

Overall, 31 patients were enrolled between July 2013 and November 2015 at 5 study sites. Thirty patients received ≥ 1 dose of CC-486 and comprised the intention-to-treat population. In the combined 7-day dosing cohorts, 3 patients received CC-486 200 mg QD (Cohort 1) and 4 received 300 mg QD (Cohort 2). In the 14-day dosing cohorts, 4 patients received

CC-486 150 mg QD (Cohort 3) and 19 patients received CC-486 200 mg QD in an expansion cohort (Cohort 4).

Baseline characteristics were generally comparable between the 7-day and 14-day dosing groups (Table 1). Twenty-six patients (87%) had AML and 4 (13%) had MDS, including 3 patients with International Prognostic Scoring System [24] higher-risk MDS. Patients were generally older (median age, 64.5 years [range, 28 to 80]). All patients had Eastern Cooperative Oncology Group performance status scores ≤ 1. At time of transplantation, 27 patients (90%) were in CR, 25 in first remission and 2 in second remission, and 3 patients (10%) had ≥ 5% bone marrow blasts. Eighteen patients had received a myeloablative conditioning regimen (busulfan

and fludarabine, n = 14; busulfan and cyclophosphamide, n = 3; total body irradiation, cyclophosphamide, and thiotepa, n = 1) and 12 patients received a reduced-intensity conditioning regimen with fludarabine and melphalan. Twenty patients had unrelated donors, and 10 received stem cells from a sibling. Eight patients received stem cells from bone marrow and 22 patients from peripheral blood. Median time from alloSCT to start of CC-486 therapy was 81.5 days (range, 45 to 85). The median follow-up for patients in this study was 19.0 months (range, 1.0 to 41.3).

The MTD of CC-486 was not reached at doses up to 200 mg/day for 14 days per cycle. No DLT was observed in Cohorts 1 to 3. In Cohort 4 (200 mg QD × 14 days) 1 patient experienced a

Table 1
Baseline Characteristics and CC-486 Treatment Exposure

	200 mg QD for 7 Days (n = 3)	300 mg QD for 7 Days (n = 4)	150 mg QD for 14 Days (n = 4)	200 mg QD for 14 Days (n = 19)	Total (N = 30)
Diagnosis					
AML	2 (67)	4 (100)	4 (100)	16 (84)	26 (87)
MDS	1 (33)	0	0	3 (16)	4 (13)
Median time from MDS/AML diagnosis to alloSCT, mo (range)	6.2 (3.3-16.2)	4.6 (3.4-12.8)	3.5 (1.4-5.6)	4.8 (2.7-75.0)	4.8 (1.4-75.0)
Median time from initial diagnosis to CC-486, mo (range)	8.2 (5.8-17.7)	6.8 (6.1-15.4)	6.2 (4.1-8.3)	12.9 (5.3-77.7)	7.0 (4.1-77.7)
Median time from alloSCT to CC-486, days (range)	63.0 (45-78)	81.5 (55-85)	85.0 (84-85)	81.0 (45-85)	81.0 (45-85)
Median BM blasts before alloSCT, % (range)	0 (0-2)	4.0 (2-8)	0 (0-1)	2.0 (0-6)	2.0 (0-8)
Median BM blasts after alloSCT, % (range)	1.0 (1-1)	.5 (0-2)	1.0 (0-1)	1.0 (0-2)	1.0 (0-2)
Median HCT-CI score (range)	1.0 (0-1)	0 (0-1)	2.0 (0-3)	0 (0-3)	.5 (0-3)
Disease status at study entry					
CR1	2 (67)	2 (50)	3 (75)	18 (95)	25 (83)
CR2	1 (33)	1 (25)	0	0	2 (7)
Active disease	0	1 (25)	1 (25)	1 (5)	3 (10)
AML WHO classification	n = 2	n = 4	n = 4	n = 16	n = 26
Recurrent genetic abnormalities	0	2 (50)	0	7 (44)	9 (35)
Myelodysplasia-related changes	0	0	1 (25)	2 (13)	3 (12)
Therapy-related myeloid neoplasms	0	0	1 (25)	0	1 (4)
Not otherwise specified	2 (100)	2 (50)	2 (50)	7 (44)	13 (50)
MDS WHO classification	n = 1	n = 0	n = 0	n = 3	n = 4
RA / RCMD	0	0	0	2 (67)	2 (50)
MDS-U	0	0	0	1 (33)	1 (25)
del(5q)	1 (100)	0	0	0	1 (25)
MDS IPSS risk classification	n = 1	n = 0	n = 0	n = 3	n = 4
Low / Intermediate-1	0	0	0	1 (33)	1 (25)
Intermediate-2 / High	1 (100)	0	0	2 (67)	3 (75)
NCCN cytogenetic risk at AML diagnosis	n = 2	n = 4	n = 4	n = 16	n = 26
Favorable	0	2 (50)	0	1 (6)	3 (12)
Intermediate	2 (100)	1 (25)	3 (75)	12 (75)	18 (69)
Poor	0	0	0	1 (6)	1 (4)
Missing	0	1 (25)	1 (25)	2 (13)	4 (15)
MDS cytogenetic risk at diagnosis	n = 1	n = 0	n = 0	n = 3	n = 4
Good	0	0	0	1 (33)	1 (25)
Intermediate	0	0	0	1 (33)	1 (25)
Poor	0	0	0	1 (33)	1 (25)
Missing	1 (100)	0	0	0	1 (25)
Molecular abnormalities					
NPM1	0	0	0	2 (11)	2 (7)
CEBPA	0	0	1 (25)	3 (16)	4 (13)
FLT3-ITD	1 (33)	1 (25)	0	3 (16)	5 (17)
ECOG performance status					
0	1 (33)	1 (25)	1 (25)	8 (42)	11 (37)
1	2 (67)	3 (75)	3 (75)	11 (58)	19 (63)
≥2	0	0	0	0	0
Prior injectable HMA use	1 (33)	0	1 (25)	7 (37)	9 (30)
Median CC-486 treatment cycles (range)	7 (6-12)	5.5 (1-7)	11.5 (4-12)	12 (1-12)	9 (1-12)

Values are n (%) unless otherwise defined. BM indicates bone marrow; CR, complete remission; CR1, first CR; CR2, second CR; ECOG, Eastern Cooperative Oncology Group; HCT-CI, hematopoietic cell transplantation−specific comorbidity index; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; MDS-U, MDS-undefined; NCCN, National Comprehensive Cancer Network; RA, refractory anemia; RCMD, refractory cytopenia with multilineage dysplasia; WHO, World Health Organization.

DLT during the first 2 treatment cycles (grade 4 neutropenia, grade 3 pneumonia), but no additional DLTs occurred and the criteria for MTD were not met. Based on observed efficacy and tolerability of the CC-486 200 mg 14-day dosing regimen, Cohort 4 was subsequently expanded to a total of 19 patients to further assess the clinical activity, safety, and tolerability of this regimen. Based on patient safety considerations with regenerating bone marrows and concern for the development of significant neutropenias or thrombocytopenia post-transplant, no higher dosing regimen was evaluated.

CC-486 Exposure

The median number of CC-486 treatment cycles for all patients was 9.0 (range, 1 to 12) (Table 1). Median duration of treatment was 252.5 days (range, 3 to 371). Thirteen patients (43%) completed all 12 treatment cycles, including 1 of 7 patients (14%) in the combined 7-day dosing group and 12 of 23 patients (52%) in the combined 14-day group. Among the 17 patients (57%) who discontinued treatment before completing 12 cycles, median time to discontinuation was 283.5 days (range, 21 to 401). Reasons for discontinuation included MDS or AML relapse (n = 6, 20% of all patients), withdrawal of consent (n = 5, 17%), GVHD (n = 2, 7%), non-GVHD TEAEs (n = 2, 7%), death (n = 1, 3%), or "other" (n = 1, 3%). "Other" involved a patient in the CC-486 300-mg 7-day dosing arm who had a history of central nervous system leukemia at study entry and was receiving intrathecal methotrexate before and during CC-486 treatment. Because of presentation of central nervous system features characteristic of a transient ischemic attack and suspected central nervous system relapse at cycle 4, as well as administration of radiation therapy, the patient was discontinued because of risk of bleeding. The patient was in CR at all evaluations after discontinuing therapy, was not included in an on-study relapse rate, and was alive and in CR at the end of the study according to bone marrow aspirate samples.

Disease Relapse and Survival

Two patients discontinued in the first treatment cycle and withdrew consent for further follow-up. For the 28 remaining patients, the 1-year rate of relapse or progressive disease during treatment was 21% (n = 6). Three of these 6 patients relapsed during the first treatment cycle (Figure 1). The 3 patients who had ≥ 5% bone marrow blasts at the time of transplant all relapsed on-study, 1 of whom relapsed during treatment cycle 1. The 1-year cumulative incidence of relapse was 3 of 7 (43%) in the combined 7-day dosing group and 3 of 23 (13%) in the combined 14-day dosing group. One-year RPFS rates were 54% and 72% in the 7-day and 14-day CC-486 dosing groups, respectively.

Median OS was not reached in any dosing cohort (range for all patients was 86 to 1324 days) (Figure 2), and estimated 1-year survival rates in the 7-day and 14-day dosing cohorts were 86% and 81%, respectively.

Acute and Chronic GVHD

One-year cumulative incidence of acute or chronic GVHD was 50% (n = 15). Grade III acute GVHD was reported in 1 patient (3%) in the CC-486 200-mg 14-day dosing cohort. No grade IV acute GVHD was observed. Chronic GVHD was reported in 9 patients (30%) with similar frequency within 3 dosing groups (no chronic GVHD was reported in the 300-mg 7-day dosing cohort). Three of 9 patients had severe chronic GVHD, and the remaining 6 patients had mild or moderate chronic GVHD. Among patients with any GVHD, organ

involvement included skin in 8 patients, the lower intestinal tract in 7 patients, and the liver in 2 patients.

Safety and Tolerability

The most frequent TEAEs were gastrointestinal and hematologic events. Twenty-two patients (73%) experienced at least 1 grade 3-to-4 TEAE (Table 2; Supplementary Table 1 shows common TEAEs by CD34+ cell dose threshold at transplant). The most common (≥ 5% of patients) grades 3-to-4 TEAEs occurred at similar frequencies across all 4 dosing cohorts: diarrhea (20%), lymphopenia (20%), vomiting (17%), neutropenia (17%), nausea (13%), anemia (13%), thrombocytopenia (10%), and abdominal pain (7%). Treatment-related serious TEAEs were reported in 4 patients and included hemolysis, thrombocytopenia, neutropenia, diarrhea, nausea, vomiting, asthenia, pyrexia, pneumonia, and intracranial hemorrhage. One TEAE-related death occurred on-study (intracranial hemorrhage) in the patient who experienced the DLT at cycle 2. This patient had raised lactate dehydrogenase at baseline and subsequently developed hemolysis, progressive thrombocytopenia, and a progressive rise in lactate dehydrogenase, and was considered to have had tacrolimus-associated thrombotic thrombocytopenic purpura.

Pharmacokinetics

Pharmacokinetic data were available for patients receiving 200 mg CC-486 doses, including 4 patients with and without concomitant medications after CC-486 dose administration on day 1 of cycles 1 and 2 (per protocol), 2 patients after CC-486 administration who had not taken concomitant medications, and 9 patients after CC-486 administration who had taken concomitant medications. Thus, azacitidine pharmacokinetic data were available at the CC-486 200-mg dose for a total of 6 patients without concomitant medications and 13 patients with concomitant medications. There were too few patients in the 150-mg/day CC-486 dosing group with meaningful pharmacokinetic data to report (pharmacokinetic outcomes with 300 mg QD CC-486 have been reported elsewhere [22]).

Azacitidine was rapidly absorbed, reaching mean maximum observed plasma concentration within approximately 1 hour post-dose and then decreasing in a multiphasic manner to a nonquantifiable level by the 6-hour time point (Supplementary Figure 1). After CC-486 200-mg dose administration, azacitidine plasma concentration profiles and other pharmacokinetic parameters (Figure 3) were not significantly different when taken with or without standard concomitant medications. Concomitant medications included (but were not limited to) prophylactic antibiotics, calcineurin inhibitors, antifungals, and antiviral agents; red blood cell and platelet transfusions; myeloid growth factors; antiemetics; and drugs to manage gastrointestinal complications. Moreover, pharmacokinetic parameters were within range of those reported for nontransplant patients treated with CC-486 in a different study [22].

DISCUSSION

Disease recurrence is a major therapeutic challenge in patients with MDS or AML undergoing alloSCT, and treatment options are limited [4,5]. Risk of disease relapse after alloSCT is a composite of many factors, including age, cytogenetic and molecular status at diagnosis, and remission status at the time of transplantation [4,25-27]. Remission duration is one of the strongest predictors of post-transplant survival [5,28,29]. This is the first prospective trial to evaluate post-transplant CC-486 therapy as a strategy to prevent or delay relapse in patients with AML or MDS. Therapy with CC-486 for 1 year was

Figure 1. Patient profiles and duration of CC-486 treatment.

*Patient had ≥5% bone marrow blasts at the time of alloHSCT

†Patient had an ongoing history of CNS leukemia at entry and was receiving intrathecal methotrexate before and during study treatment. After cycle 4, the patient was discontinued for "other" reasons, due to risk of bleeding with administration of radiation and intrathecal therapy for relapse of CNS leukemia

‡Death due to intracranial hemorrhage. This patient had a dose-limiting toxicity of pneumonia accompanied by neutropenia; the patient also showed evidence of transplant-related thrombotic micro-angiopathy

AML-MRC, AML with myelodysplasia-related changes; AML-NOS, AML not otherwise specified; AML-RGA, AML with recurrent genetic abnormalities; BM, bone marrow; Int1, Intermediate-1 risk MDS; Int2, Intermediate-2 risk MDS; MAC, myeloablative conditioning; PB, peripheral blood; RIC, reduced-intensity conditioning; T-AML, therapy-related AML

associated with a relatively low (21%) overall rate of disease relapse during treatment.

In the current study the RPFS rate was higher in the combined 14-day dosing cohort than in the 7-day dosing group, supporting the rationale for extended CC-486 dosing. The 1-year cumulative rate of relapse/disease progression with CC-486 maintenance administered for 14 days per cycle (13%) compares favorably with rates reported in studies of with 5-day dosing of low-dose s.c. azacitidine maintenance after alloSCT [14,17], although meaningful conclusions are elusive when comparing results of different studies with different patient populations and endpoints. For example, a phase I study evaluating low-dose s.c. azacitidine 8 to 40 mg/m^2/day administered for 5 days per cycle after alloHSCT in patients with high-risk MDS or AML showed a 53% relapse rate at a median follow-up of 20.5 months. However, that study

included a high proportion of patients with advanced disease characteristics, and most patients were not in CR at the time of transplant [17]. In any case, at-home administration of oral maintenance therapy may be more convenient for patients than making multiple daily clinic visits for parenteral drug administration. In the current study patients received enough CC-486 at the clinic on day 1 of each cycle to complete CC-486 dosing for that cycle at home.

Survival outcomes associated with CC-486 maintenance were also relatively favorable. Median OS was not reached in any dosing cohort at a median follow-up of 19 months, and estimated 1-year survival rates were above 80%.

Expected rates of post-transplant serious chronic GVHD range from approximately 25% to 30% [30,31] The incidence of severe chronic GVHD in our study was low (10%), and only 2 patients discontinued the study due to a GVHD event. The
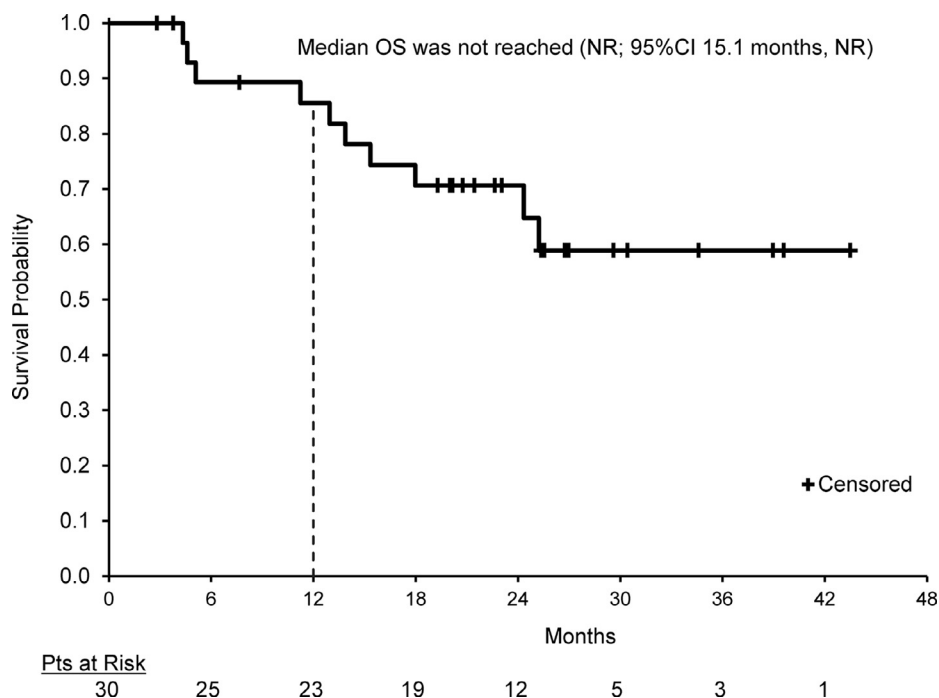
Figure 2. OS from time of alloSCT.

generally mild presentation and low incidence of GVHD in this study support the hypothesis that CC-486 maintenance may permit epigenetic manipulation of the alloreactive response after transplantation. Two mechanisms have been proposed by which azacitidine is believed to induce tolerance and reduce the risk of GVHD: conversion of alloreactive donor T cells into suppressive regulatory T cells via hypomethylation of the FOXP3 promoter and suppression of alloreactive T cell proliferation [12,15,16,32].

Once-daily CC-486 was generally well tolerated; the MTD was not reached in this study, and there was no meaningful difference in the frequency or severity of AEs among dosing regimens. The most common TEAEs were gastrointestinal and hematologic, consistent with previous reports of low-dose s.c. azacitidine post-transplant and of

front-line CC-486 in MDS and AML [17,21]. Rate of discontinuation due to TEAEs was low, with most discontinuations due to MDS or AML relapse (20% of all patients). Patients undergoing alloSCT are particularly vulnerable to myelosuppression and other toxicities [33,34]. Rates of hematologic TEAEs with CC-486 in this and other studies are lower than those seen with injectable hypomethylating agents [21,35-37]. Despite the pharmacokinetic testing protocol, investigators and patients may have been reluctant to forego the patients' prescribed concomitant medications in the post-transplant setting. Nevertheless, these data, albeit in a small patient sample, suggest a lack of significant drug−drug interactions with CC-486 and standard concomitant medications such as antibiotics or drugs to manage gastrointestinal events.

Table 2
Most Common (≥5% of All Patients) Grades 3-4 TEAEs

AE	CC-486 200 mg QD for 7 Days (n = 3)	CC-486 300 mg QD for 7 Days (n = 4)	CC-486 150 mg QD for 14 Days (n = 4)	CC-486 200 mg QD for 14 Days (n = 19)	Total (N = 30)
Patients with ≥1 grade 3-4 TEAE	2 (67)	3 (75)	3 (75)	14 (74)	22 (73)
Hematologic					
Lymphopenia	0	0	3 (75)	3 (16)	6 (20)
Neutropenia	0	0	1 (25)	4 (21)	5 (17)
Anemia	0	0	1 (25)	3 (16)	4 (13)
Thrombocytopenia	1 (33)	0	0	2 (11)	3 (10)
gastrointestinal					
Diarrhea	1 (33)	0	2 (50)	3 (16)	6 (20)
Vomiting	1 (33)	1 (25)	1 (25)	2 (11)	5 (17)
Nausea	1 (33)	0	0	3 (16)	4 (13)
GI GVHD*	0	0	0	3 (16)	3 (10)
Abdominal pain	0	0	0	2 (11)	2 (7)
Other					
Device-related infection	0	1 (25)	1 (25)	0	2 (7)
Dehydration	0	0	1 (25)	1 (5)	2 (7)
Pneumonia	0	0	1 (25)	1 (5)	2 (7)

Values are n (%). GI indicates gastrointestinal.
* Acute or chronic.
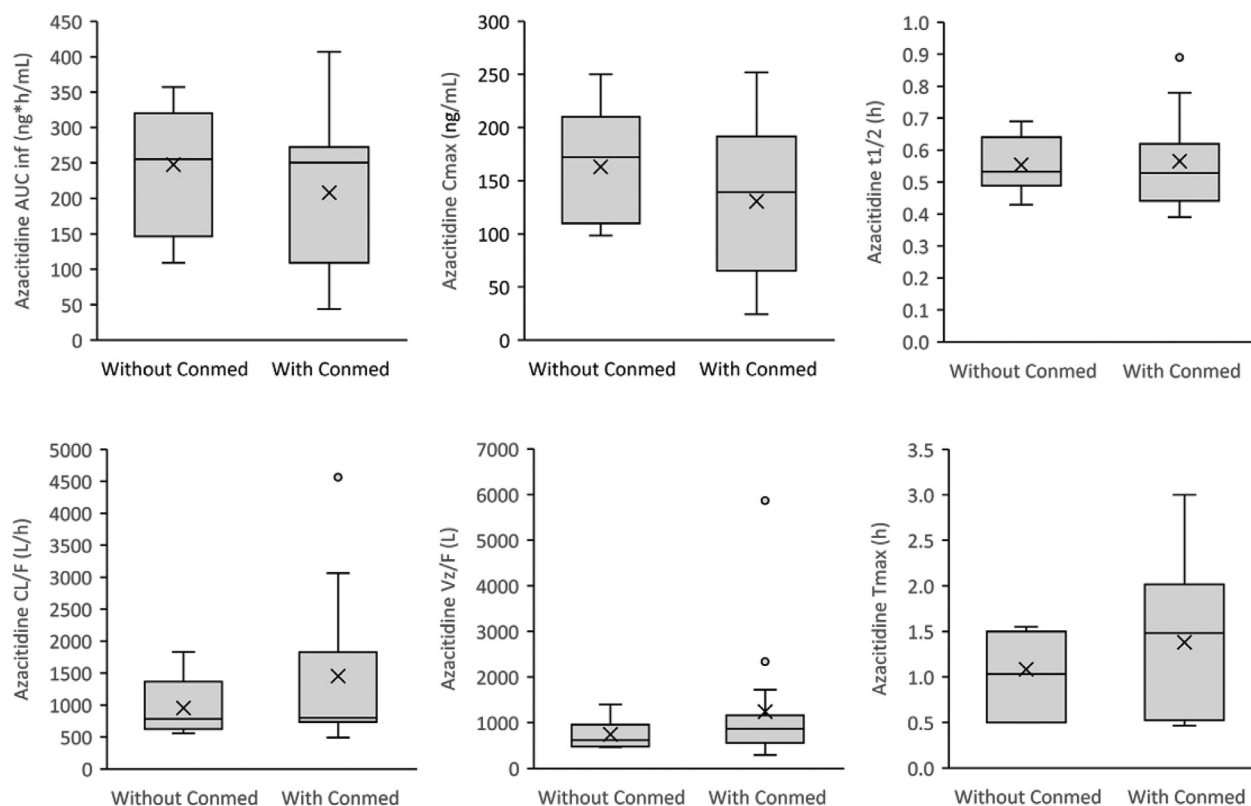
"x" indicates the mean; bar indicates median

Conmed, concomitant medications; Cmax, maximum observed plasma concentration; AUC0-∞, area under the plasma concentration-time curve from zero to infinity; t1/2, terminal half-life; CL/F, apparent total clearance; Vz/F, apparent volume of distribution; Tmax, time of maximum observed plasma concentration

Figure 3. Azacitidine pharmacokinetic parameters with and without concomitant medications after 200 mg CC-486.

Use of maintenance therapy in hematologic disorders remains controversial [38], and whether and when to initiate maintenance treatment and how long to continue it are unresolved issues. The increasing use of next-generation sequencing may allow detection of measurable residual disease (MRD), which can be a harbinger of relapse [39], to inform whether maintenance might benefit some patients, and sustained measurable residual disease negativity may suggest maintenance therapy is unnecessary or could be discontinued. The extent of donor chimerism may also suggest whether maintenance therapy might prolong remission post-transplant [18]. Here, we somewhat arbitrarily planned for 12 CC-486 treatment cycles, with the goal of offering therapy during the period of time with higher risk of AML or MDS relapse, based on historic data [4]. One cannot underestimate the logistic challenges of prolonged maintenance therapy after allogeneic transplantation, which frequently include monitoring by different physicians and hospitals, patient and caregiver fatigue, and need for more intensive monitoring.

Among limitations of these data are that this is a phase I dose-finding study, followed by a small phase II expansion, with no placebo-control group. It is unknown whether the benefit of CC-486 maintenance correlated with improvement in quality of life, because it was not evaluated. Additionally, no information regarding the presence of MRD before or after transplant was collected, and correlations between relapse status and changes in methylation levels during CC-486 study and extent of immune reconstitution were not assessed.

Nonetheless, these data support the clinical benefits and acceptable safety profile of CC-486 as maintenance treatment after alloSCT in patients with MDS or AML. Based on these data, the recommended CC-486 post-transplant maintenance dosing regimen is 200-mg daily for 14 days per 28-day cycle. Our findings warrant further study in a larger patient population.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.06.016.

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