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Hematologic Malignancies

Oral Azacitidine (CC-486) for the Treatment of Myelodysplastic Syndromes and Acute Myeloid Leukemia

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Disclosures of potential conflicts of interest may be found at the end of this article.

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ABSTRACT

The myelodysplastic syndromes (MDS) comprise a heterogeneous group of clonal myeloid malignancies characterized by multilineage cytopenias, recurrent cytogenetic abnormalities, and risk of progression to acute myeloid leukemia (AML). AML, which can occur de novo as well as secondary to MDS, is characterized by malignant clones of myeloid lineage in the bone marrow and peripheral blood, with dissemination into tissues. The cytidine nucleoside analog and epigenetic modifier azacitidine is approved in the U.S. for the treatment of all French-American-British subtypes of MDS and in many countries for the treatment of AML with 20%–30% blasts and multilineage dysplasia according to the World Health Organization classification. Benefits of azacitidine treatment of patients with AML with >30% blasts have also been shown in a recent phase III trial. Oral administration of azacitidine may enhance patient convenience, eliminate injection-site reactions, allow for alternative dosing and scheduling, and enable long-term treatment. Phase I studies with oral azacitidine (CC-486) have shown biological activity, clinical responses, and tolerability in patients with MDS and AML. Extended dosing schedules of oral azacitidine (for 14 or 21 days of 28-day cycles) are currently under investigation as frontline therapy in patients with lower risk MDS, as maintenance therapy for patients with AML not eligible for stem cell transplant, and as maintenance therapy for patients with MDS or AML following stem cell transplant. This review presents clinical data supporting the use of injectable azacitidine in MDS and AML and examines the rationale for and results of the clinical development of oral azacitidine. ***The Oncologist*** 2015;20:1404–1412

Implications for Practice: Injectable azacitidine can prolong survival, reduce transfusions, and improve quality of life compared with conventional care regimens in patients with higher-risk myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). An oral formulation improves convenience and eliminates injection-site reactions but also enables testing of novel, longer term, low-dose schedules that may enhance therapeutic activity of azacitidine by increasing exposure to cycling malignant cells. In early phase trials, oral azacitidine (CC-486) in extended dosing regimens was biologically and clinically active in patients with MDS and AML. Oral azacitidine is being further evaluated in an ongoing phase III program.

INTRODUCTION

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal myeloid malignancies arising from a stem cell source and characterized by multiple genetic abnormalities and subclonal architectures [1–4]. There is considerable heterogeneity in genetic mutations among patients with MDS that may explain the diversity of clinical presentations that differ in the numbers and depths of cytopenias, risks toward progression to acute myeloid leukemia (AML), responses to treatment, and survival times [5–8]. Gene mutations affecting epigenetic chemical modifications, such as mutations in *TET2* and *DNMT3A,* are among the most common in MDS [9–11].

MDS is primarily a disease of older adults, and advanced age at diagnosis is associated with decreased overall survival (OS) [12, 13]. The reported incidence rate of MDS overall is 5.70 per 100,000 persons in the U.S. [14] and 1.82 per 100,000 persons in Europe [15]. In patients aged ≥65 years, the incidence rate is higher, at 12.97 per 100,000 persons or higher in the U.S. [14] and 5 per 100,000 persons or higher in Europe [15]; however, these are likely underestimates of true incidence. Large numbers of MDS cases go unreported by state cancer registries due to difficulties in disease diagnosis, underappreciation of MDS as a malignancy, under-reporting by

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outpatient clinics, changing guidelines for defining MDS, and lack of resources [15–18]. When accounting for the uncaptured cases, MDS is one of the most common hematologic malignancies.

The current MDS treatment paradigm is based on prognostic risk assessment [8, 13, 19, 20]. Patients at lower risk for early death or evolution to AML are treated with agents to primarily reduce or eliminate blood transfusions and to improve quality of life (QOL), whereas patients at higher risk for early death or AML progression are generally treated with more intensive therapies aiming to induce disease remission and lengthen survival [8, 21, 22].

AML is a multigenetic malignancy characterized by malignant clones and subclones of myeloid lineage in the bone marrow and peripheral blood, with dissemination into tissues [23–25]. It is the most common acute leukemia in adults [23], with an estimated incidence rate of 4.06 per 100,000 persons in the U.S. [14] and 3.62 per 100,000 persons in Europe [15]. Similar to MDS, AML incidence increases with advancing age, with incidence rates in the U.S. and Europe of 10 per 100,000 persons or higher for patients aged ≥65 years [14, 15]. AML has a poor prognosis, particularly in older patients and those with adverse disease characteristics (e.g., secondary AML, complex cytogenetic abnormalities, or *FLT3* mutation) [26–30]. Three-quarters of patients with AML die within 5 years of diagnosis, and survival decreases with increasing age [26]. Disease characteristics and performance status are closely considered when evaluating patient eligibility for treatment with intensive therapies (e.g., induction followed by consolidation chemotherapy or stem cell transplant [SCT]) versus low-intensity options such as injectable azacitidine or decitabine [27–29, 31–33].

Azacitidine for Injection

Azacitidine is a cytidine nucleoside analog with a substitution of the carbon at position 5 with nitrogen that prevents methylation by covalently binding DNA methyltransferases [32, 34] (Fig. 1). The epigenetic modifier azacitidine is incorporated into DNA and RNA [34, 35]. Antileukemic effects of azacitidine are thought to include direct cytotoxicity from inhibition of protein synthesis and DNA damage and re-expression of aberrantly silenced tumor suppressor genes due to DNA hypomethylation [32, 34–37]. Azacitidine is approved in the U.S. for the treatment of all French-American-British (FAB) subtypes of MDS [32] and is approved in many countries (e.g., European Union, Australia, Republic of Korea, Taiwan) for patients not eligible for SCT with intermediate-2 (Int-2) and high-risk MDS according to the International Prognostic Scoring System (IPSS) and patients with AML with 20%–30% blasts and multilineage dysplasia according to World Health Organization (WHO) classification [38]. Azacitidine is also approved by the U.S. Food and Drug Administration for chronic myelomonocytic leukemia (CMML) and by the European Medicines Agency for "CMML with 10%–29% marrow blasts without myeloproliferative disorder."

The approved dosing of azacitidine is 75 mg/m^2 per day on days 1–7 of 28-day cycles [32, 38]. Alternative dosing schedules have been explored, including 5-day and 5-2-2-day dosing regimens to avoid weekend administration [39–41], but are

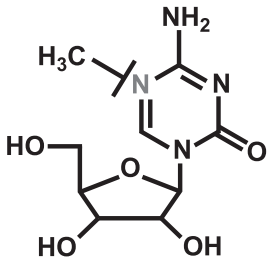

Figure 1. Structure of azacitidine. Substitution of carbon at position 5 with nitrogen prevents DNA methylation [34].

5-day dosing in patients with MDS is compelling, clinicians should not extrapolate data for injectable azacitidine based on the approved 7-day dosing regimen, especially in patients with higher risk MDS. The 5-day and 5-2-2-day alternate regimens require more rigorous testing.

Initial approval was based primarily on results from two phase III studies. CALGB-9221 was a phase III multicenter randomized controlled trial of subcutaneous (s.c.) azacitidine (75 mg/m^2 per day on days 1–7 in 28-day cycles; $n = 99$) versus best supportive care (BSC; $n = 92$) in patients with all FAB MDS subtypes [42]. In this trial, the overall response rate (ORR) with azacitidine was significantly improved versus BSC (60% vs. 5%, $p < .0001$) [42]. Response rates to azacitidine were comparable in patients with lower and higher risk MDS [42]. Myelosuppression was the most common toxicity, and adverse events (AEs) were generally transient, resolving before the next treatment cycle [42].

AZA-001 was a phase III multicenter randomized controlled trial of s.c. azacitidine (75 mg/m^2 per day on days 1–7 in 28-day cycles) versus conventional care regimens (CCR: BSC, low-dose cytarabine [LDAC], or intensive chemotherapy [IC]) in patients with IPSS-defined higher risk (Int-2 or high-risk) MDS ($N = 358$) [43]. Azacitidine treatment resulted in significantly longer OS (median: 24.5 vs. 15 months; $p = .0001$), higher rates of hematologic response ($p = .0001$) and HI ($p < .0001$) assessed by International Working Group (IWG) 2000 criteria [21], and longer durations of response (median: 13.6 vs. 5.2 months; $p = .0002$) versus CCR [43]. Azacitidine prolonged OS compared with CCR regardless of IPSS cytogenetic risk group [43].

A multivariate analysis of AZA-001 showed that achievement of hematologic response or HI (IWG 2000 criteria [21]) was associated with improved OS with azacitidine treatment [44], and patients who achieved a hematologic response to azacitidine had significantly prolonged OS and reduced risk of death versus patients who achieved a response to CCR [44]. In addition, stable disease or achievement of complete response (CR), marrow CR (mCR), partial response (PR) or HI (IWG 2003 [45] and 2006 criteria [22]) with alternative dosing schedules of azacitidine has been shown to significantly reduce the risk of death versus disease progression ($p < .001$) [39].

In the AZA-001 study, the median time to first response with azacitidine was 2 cycles (range: 1–16), with 91% of responding patients achieving first response within 6 cycles and all but 1 achieving first response by cycle 12 [46]. Continued treatment improved response quality in 48% of

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response. By cycle 12, 92% of responding patients achieved their best response. Based on this experience, some clinicians have advised administering at least six cycles of azacitidine [47], and the National Comprehensive Cancer Network guidelines for MDS recommend at least four to six cycles before assessing for treatment failure [8]. Assessments for treatment failure include evaluation of peripheral blood, bone marrow aspiration or biopsy, cytogenetic testing, and genetic studies. If response is achieved, azacitidine is typically continued until disease progression, unacceptable toxicity, or definitive therapy with SCT. If no response is achieved after six cycles of azacitidine, then prognosis is generally poor [48, 49]. Small case series have shown that decitabine treatment after azacitidine failure yields modest responses (ORR: 0%–28%) that are generally short lived [48, 50–53]; however, this is not currently standard treatment practice. The current standard of care for patients with MDS who have not responded after at least six cycles of azacitidine treatment is to consider clinical trials [48, 49] or proceed with SCT [51].

The most common grade 3/4 AEs with azacitidine treatment in patients with MDS in the AZA-001 trial were cytopenias [43], and most were transient and resolved during therapy [54]. The highest rates of AEs reported with azacitidine in AZA-001 occurred during cycles 1–2, with decreased frequency with continued treatment. Median duration of hematologic AEs was 14–16 days.

Azacitidine has also been investigated for the treatment of patients with AML. In a subanalysis of AZA-001 of low-blast-count AML (20%–30% blasts; $n = 113$), the 2-year OS rate for patients treated with azacitidine was 50%, and the median OS was 24.5 months compared with 16.0 months for patients treated with CCR ($p = .005$) and 16.4 months for patients not preselected to receive IC (BSC or LDAC; $p = .004$) [31]. Survival benefits with azacitidine may not require CR because CR rates were similar for azacitidine versus CCR (18% vs. 16%; $p = .8$), whereas rates of red blood cell transfusion independence (RBC-TI) were significantly higher with azacitidine (41% vs. 18%; $p = .04$) [31].

Recently, the global phase III randomized open-label AZA-AML-001 study of azacitidine (75 mg/m^2 per day on days 1–7 in 28-day cycles) versus CCR extended these findings in patients aged ≥65 years with newly diagnosed AML with >30% blasts ($N = 488$) [55]. Azacitidine treatment demonstrated a clinically meaningful improvement in median OS of 10.4 months versus 6.5 months with CCR ($p = .1009$). Azacitidine significantly improved 1-year survival: 46.5% versus 34.2% with CCR, a 12.3% difference (95% confidence interval: 3.5%–21.0%). In patients who did not achieve CR (IWG 2003 criteria [45]), median OS was prolonged from 6.9 months with azacitidine versus 4.2 months with CCR ($p = .0170$).

The safety profile of azacitidine for the treatment of AML was consistent with previous observations [31, 43, 55]. The most common grade 3/4 hematologic AEs were cytopenias, which occurred more frequently during earlier treatment cycles [31, 55].

Rationale for Oral Administration of Azacitidine

Oral administration of azacitidine avoids injection-site reactions with an injectable formulation [56, 57]. It allows for the evaluation of alternative doses and schedules, including extended dosing schedules. Early trials with injectable azacitidine showed decreased toxicity and increased efficacy at lower doses over several days versus a single higher dose [58–61]. In addition, in patients with MDS, continued treatment with s.c. azacitidine was shown to improve response quality [46].

The benefits of extended azacitidine dosing and long-term treatment are likely related to the impact on hypomethylation. Hypomethylating effects are cell cycle dependent [62], and serial cycles of DNA replication are needed to induce hypomethylation [63, 64]. Extensive demethylation requires prolonged drug exposure [63]. Due to the short plasma half-life of azacitidine [34, 38] and cell cycle-restricted DNA incorporation [62], extended dosing schedules enabled by oral administration have the potential to enhance clinical activity of azacitidine by increasing exposure to cycling malignant cells.

Clinical Investigations With Oral Azacitidine (CC-486)

Pilot Study of Oral Azacitidine

The bioavailability and safety of oral azacitidine was initially studied in an open-label, pharmacokinetic (PK), and feasibility pilot study of patients with MDS, leukemia, or solid tumors [56]. Four patients received 60- or 80-mg single doses of oral azacitidine. All four patients had measurable plasma concentrations, allowing for comparison with historical s.c. azacitidine PK data. The 80-mg oral azacitidine dose had mean bioavailability of 17% of that of s.c. azacitidine [56, 65]. No severe drug-related toxicities were observed, and results from this pilot study led to the development of a phase I study of oral azacitidine.

Dose-Finding Study of Oral Azacitidine

Because of the demonstrated safety and efficacy of injectable azacitidine in patients with MDS and AML [32, 38], the oral azacitidine phase I program initially focused on these patient populations. AZA PH US 2007 CL 005 was a phase I open-label dose-escalation study that evaluated the safety, PK, and pharmacodynamics (PD) of oral azacitidine in patients with MDS, CMML, or AML [66]. This trial had two parts (Fig. 2) [57, 66]: In part 1, 41 patients (71% MDS, 10% CMML, 20% AML) received 7-day dosing of s.c. azacitidine for a single 28-day cycle, followed by oral azacitidine for 7 days of 28-day cycles (cycles 2 and beyond; Table 1). During cycles 1 and 2, PK (days 1 and 7) and PD (days 1, 3, 8, 15, 22, and 28) profiles were assessed.

The maximum tolerated dose (MTD) of oral azacitidine was 480 mg once daily (QD) for 7 days [66]. Dose-limiting toxicities (DLTs) were reported in 2 of 3 patients treated with oral azacitidine 600 mg QD for 7 days (1 grade 3 diarrhea and 1 grade 4 diarrhea despite medical intervention) with no other DLTs observed. Gastrointestinal AEs were the most common nonhematologic AEs and were primarily grade 1/2 and manageable [66] with gastric

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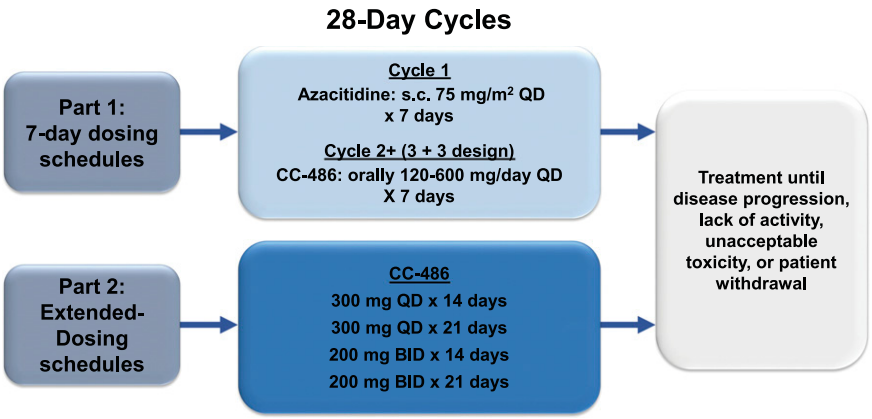

Figure 2. Trial schema for AZA PH US 2007 CL 005, the phase I trial of oral azacitidine (CC-486) in patients with myelodysplastic syndromes, acute myeloid leukemia, and chronic myelomonocytic leukemia [67].

Abbreviations: BID, twice daily; QD, once daily; s.c., subcutaneous.

Table 1. Summary of clinical results from the expanded phase I study of oral azacitidine (CC-486) in patients with MDS and AML [66, 69, 71]

Variable	Dose-finding study in MDS, CMML, and AML [66]	Extended-dosing in patients with lower risk MDS [69]	Subset analysis: 7-day and extended dosing in patients with AML [71]	
Dosing	Cycle 1: s.c. AZA 75 mg/m^2 QD × 7 days Cycles ≥2: CC-486 120–600 mg QD × 7 days	CC-486 300 mg QD × 14 or 21 days	Cycle 1: s.c. AZA 75 mg/m^2 QD × 7 days Cycles ≥2: CC-486 120–600 mg QD × 7 days	CC-486 300 mg QD or 200 mg BID × 14 or 21 days
Patient population, n (%)	MDS: 29 (71) CMML: 4 (10) AML: 8 (20)	IPSS low-risk MDS: 15 (28) IPSS Int-1 risk MDS: 38 (72) RBC-TD: 30 (57) Platelet-TD: 4 (8)	De novo AML: 13 (57) Secondary AML: 10 (43) RBC-TD: 14 (61) Platelet-TD: 8 (35)	
Key safety data	MTD: 480 mg QD × 7 days DLTs: grade 3 or 4 diarrhea Most common grade 3/4 AEs: febrile neutropenia (20%), diarrhea (12%)	Most common AEs (any grade) were gastrointestinal in origin Most common grade 3/4 AEs: neutropenia (13%) 8 patients D/C due to AEs	Most common AEs (any grade) were gastrointestinal in origin Most common grade 3/4 AEs: febrile neutropenia (35%), pneumonia (17%), syncope (17%), nausea (13%) 6 patients D/C due to AEs	
Key efficacy data	First-line patients: 73% ORR, 56% any HI, 33% mCR Previously-treated patients: 35% ORR, 38% any HI, 67% mCR	300 mg QD × 14 days: 42% ORR, 27% any HI, 20% RBC-TI sustained 84 days 300 mg QD × 21 days: 37% ORR, 30% any HI, 33% RBC-TI sustained 84 days	38% ORR, 13% HI, 25% mCR, 13% mPR, 25% RBC-TI[a]	47% ORR, 27% HI, 40% RBC-TI, 17% platelet-TI, 33% mPR[b]

[a]Eight evaluable patients for each, except four evaluable patients for RBC-TI.

[b]Fifteen evaluable patients for ORR and HI, 10 evaluable patients for RBC-TI, 6 evaluable patients for platelet-TI, and 9 evaluable patients for mPR.

Abbreviations: AE, adverse event; AML, acute myeloid leukemia; AZA, azacitidine; BID, twice daily; CMML, chronic myelomonocytic leukemia; D/C, discontinued; DLT, dose-limiting toxicity; HI, hematologic improvement; Int-1, intermediate-1; IPSS, International Prognostic Scoring System; mCR, marrow complete response; mPR, marrow partial response; MDS, myelodysplastic syndromes; MTD, maximum tolerated dose; ORR, overall response rate; QD, once daily; RBC, red blood cell; s.c., subcutaneous; TD, transfusion dependence; TI, transfusion independence.

medications [67]. The most common (≥10%) grade 3/4 AEs were febrile neutropenia (20%), diarrhea (12%), and fatigue (10%). Notably, 4 of 8 patients with grade 3/4 febrile neutropenia had an absolute neutrophil count ≤500/μL at baseline [66]. Grade 3/4 nausea and vomiting were each reported in 7% of patients. Three patients discontinued due to an AE. The investigators of part 1 of the trial concluded that 7-day oral azacitidine dosing was clinically active (Tables 1, 2). Responses in patients treated with oral azacitidine as first-line therapy included a 73% ORR, 56% with any HI, and 33% with mCR. Notably, responses were also achieved in previously treated patients: 35% ORR, 38% any HI, and 67%

Extended Dosing of Oral Azacitidine in Patients With Lower Risk MDS

Approximately two-thirds of newly diagnosed patients with MDS present with lower risk disease (IPSS low or Int-1 risk) [19]. Lower risk patients are generally viewed as having favorable prognoses, with a median OS of 5.7 years for low-risk and 3.5 years for Int-1 risk disease [19]. However, a subgroup within the lower risk MDS population actually has a worse prognosis, with shortened survival time and clonal evolution to AML [68]. Approximately one-third of patients with lower risk MDS were shown to have poor prognostic features, with a median OS of only 1.2 years [68], the same as that reported for patients with

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Table 2. Hematologic responses in patients with MDS, CMML, or AML treated with 1 cycle of s.c. azacitidine followed by oral azacitidine (CC-486) in 7-day dosing schedules [66]

Response	First-line-treated patients		Previously treated patients[a]		Total	
	EP, *n*	R, *n* (%)	EP, *n*	R, *n* (%)	EP, *n*	R, *n* (%)
Overall response[b]	15	11 (73)	17	6 (35)	32	17 (53)
CR[c]	15	6 (40)	17	0	32	6 (19)
Any HI	9	5 (56)	16	6 (38)	25	11 (44)
HI-E	4	2 (50)	10	3 (30)	14	5 (36)
HI-P	6	2 (33)	14	5 (36)	20	7 (35)
HI-N	7	2 (29)	10	0	17	2 (12)
mCR[d]	6	2 (33)	9	6 (67)	15	8 (53)[e]
TI	3	1 (33)	5	0	8	1 (13)
RBC	3	1 (33)	3	0	6	1 (17)
Platelet	0	0	4	0	4	0

[a]Includes erythropoiesis-stimulating agents, chemotherapy, hypomethylating agents, and investigational and/or other agents.
[b]Does not include patients with mCR only.
[c]Patients achieving CR were not included in other categories.
[d]Two patients with mCR in the first-line group also had HI (HI-P [$n = 1$] and HI-E and HI-N [$n = 1$]) and 1 patient with mCR in the previously treated group also had HI (both HI-E and HI-P); these patients were included in the mCR and HI categories.
[e]In the 8 patients with mCR, the response began in cycle 1 of s.c. dosing ($n = 4$) or very early in cycle 2 of CC-486 dosing ($n = 4$); therefore, a single cycle of azacitidine s.c. likely contributed to the response.
Abbreviations: AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CR, complete response; E, erythroid; EP, evaluable patients; HI, hematologic improvement; mCR, marrow complete response; MDS, myelodysplastic syndromes; N, neutrophil; P, platelet; R, responders; RBC, red blood cell; s.c., subcutaneous; TI, transfusion independence.

Table 3. Hematologic responses in patients with IPSS lower-risk MDS treated with oral azacitidine (CC-486) in extended dosing regimens [69]

Response	300 mg QD × 14 days		300 mg QD × 21 days		Total	
	EP, *n*	R, *n* (%)	EP, *n*	R, *n* (%)	EP, *n*	R, *n* (%)
Overall response[a]	26	11 (42)	27	10 (37)	53	21 (40)
Any HI	26	7 (27)	27	8 (30)	53	15 (28)
HI-E	23	4 (17)	25	6 (24)	48	10 (21)
HI-P	17	4 (24)	15	3 (20)	32	7 (22)
HI-N	10	3 (30)	6	0	16	3 (19)
RBC-TI						
Sustained 56 days	15	8 (54)	15	6 (40)	30	14 (47)
Sustained 84 days	15	3 (20)	15	5 (33)	30	8 (27)

[a]Complete response, partial response, any HI, and TI by International Working Group 2006 criteria.
Abbreviations: E, erythroid; EP, evaluable patients; HI, hematologic improvement; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; N, neutrophil; P, platelet; QD, once daily; R, responders; RBC, red blood cell; TI, transfusion independence.

are common poor prognostic features in patients with lower risk MDS [19, 68].

Although part 2 of AZA PH US 2007 CL 005 was initially designed to investigate extended dosing schedules of oral azacitidine (300 mg QD or 200 mg twice daily [BID] for 14 or 21 days per 28-day cycle) in patients with MDS, CMML, or AML (Fig. 2) [57], because of the new prognostic information about lower risk MDS, the trial was amended to focus on patients with lower risk MDS with poor prognostic features (low platelet count and/or low hemoglobin and/or RBC transfusion dependence [TD] and/or platelet TD). Part 2 included 53 patients with IPSS low-risk (28%) or Int-1 risk (72%) MDS; most patients were RBC-TD [69] (Table 1). Extended dosing with oral azacitidine (300 mg QD for 14 or 21 days of repeated 28-day cycles) resulted in response (IWG 2006 criteria [22]) in more than one-third of patients with lower risk MDS (Tables 1, 3), and the rate of RBC-TI increased from baseline with increasing cycles of treatment. The most common nonhematologic AEs were gastrointestinal, and there were no unexpected AEs based on the known safety profile of injectable azacitidine [32, 38, 69]. Eight patients (four in each arm) discontinued due to an AE. The most common grade 3/4 AEs (≥10%) were neutropenia (8% and and 7%), thrombocytopenia (12% and 4%), diarrhea (8% and 11%), and febrile neutropenia (4% and 11%) [69].

Preliminary data in patients with MDS, CMML, and AML suggest that oral azacitidine in extended dosing regimens may be associated with significant DNA hypomethylation through cycle end; however, this correlation must be confirmed in a larger patient population.

Oral Azacitidine in Patients With AML

IC is not appropriate for all patients with AML, and eligibility is influenced by age, performance status, comorbidities, and preexisting MDS [27–29, 70]. There is an unmet need for effective treatment options for patients who are ineligible or unwilling to receive IC [29]. Data from patients with AML in parts 1 and 2 of AZA PH US 2007 CL 005 were pooled ($n = 23$; 13 patients with de novo disease and 10 secondary to MDS) to assess response (IWG 2003 [45] and 2006 criteria [22]) to oral azacitidine [71] (Table 1). At baseline, 52% and 35% of patients had intermediate and unfavorable cytogenetics, respectively; 61% and 35% of patients were RBC-TD and platelet-TD, respectively; and 57% of patients were relapsed or refractory to prior treatment [71]. Of 8 patients treated with oral azacitidine at 120–600 mg QD for 7 days, 3 achieved a response (38%), including 1 with HI, 1 with RBC-TI, 2 with mCR, and 1 with marrow PR. Of 15 patients treated with oral azacitidine in extended dosing schedules (300 mg QD or 200 mg BID for 14 or 21 days), 7 achieved a response (47%)

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