

Azacitidine in Lower-Risk Myelodysplastic Syndromes: A Meta-Analysis of Data from Prospective Studies

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

Key Words. Meta-analysis • Azacitidine • Lower-risk myelodysplastic syndromes

ABSTRACT

Background. After erythropoiesis-stimulating agent (ESA) failure, lenalidomide and hypomethylating agents are the only remaining treatment options for most patients with lower-risk myelodysplastic syndromes (LR-MDS). Optimal choice of these agents as front-line therapy in non-del(5q) LR-MDS is unclear. Because azacitidine clinical data mainly describe experience in higher-risk MDS, we performed a meta-analysis of patient-level data to evaluate azacitidine in patients with red blood cell (RBC) transfusion-dependent LR-MDS.

Materials and Methods. We searched English-language articles for prospective phase II and III azacitidine clinical trials and patient registries published between 2000 and 2015, and Embase abstracts from 2015 conferences. Patient-level data from identified relevant studies were provided by investigators. Meta-analyses followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Efficacy endpoints were RBC transfusion independence (TI) and Clinical Benefit

(RBC-TI, erythroid response, and complete or partial remission, per International Working Group 2006 criteria for MDS).

Results. Data for 233 patients from 6 clinical studies and 1 registry study met criteria for inclusion in analyses. Overall, 90.3% of patients had non-del(5q) LR-MDS. Pooled estimates from random-effects models of RBC-TI and Clinical Benefit were 38.9% and 81.1%, respectively; for the ESA-refractory subgroup, they were 40.5% and 77.3%; and for patients with isolated anemia, they were 41.9% and 82.5%. In multivariate analyses, planned use of ≥ 6 azacitidine treatment cycles was significantly predictive of response.

Conclusion. Azacitidine effects in these patients, most with non-del(5q) LR-MDS, were promising and generally similar to those reported for lenalidomide in similar patients. The choice of initial therapy is important because most patients eventually stop responding to front-line therapy and alternatives are limited. *The Oncologist* 2018;23:159–170

Implications for Practice: Lower-risk myelodysplastic syndromes (LR-MDS) are primarily characterized by anemia. After erythropoiesis-stimulating agent (ESA) failure, lenalidomide and hypomethylating agents are the only remaining treatment options for most patients. This meta-analysis of 233 azacitidine-treated red blood cell (RBC) transfusion-dependent patients with LR-MDS (92.3% non-del[5q]) from 7 studies showed 38.9% became RBC transfusion-independent. There is no clear guidance regarding the optimal choice of lenalidomide or hypomethylating agents for patients with non-del(5q) LR-MDS following ESA failure. Clinical presentation (e.g., number of cytopenias) and potential outcomes after hypomethylating agent failure are factors to consider when making initial treatment decisions for LR-MDS patients.

INTRODUCTION

Myelodysplastic syndromes (MDS) comprise a heterogeneous group of clonal myeloid neoplasms characterized by ineffective hematopoiesis and by increased risk of transformation to acute myeloid leukemia (AML) [1]. Lower-risk MDS (LR-MDS; i.e., International Prognostic Scoring System [IPSS]-defined Low or

Intermediate-1 risk) is characterized mainly by peripheral cytopenias [2]. Approximately 80% of patients with MDS are initially diagnosed because of symptoms related to anemia [3]. Although not approved by the U.S. Food and Drug Administration for treatment of MDS, erythropoiesis-stimulating agents

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(ESAs) and growth factors (e.g., granulocyte colony-stimulating factor [G-CSF]) are widely used as initial therapy for patients with LR-MDS with symptomatic anemia or who are red blood cell (RBC) transfusion-dependent [4]. However, many patients show primary resistance to ESAs, and those who respond to these agents typically become resistant to them within about 2 years [4–6].

Goals of LR-MDS treatment include reducing cytopenias (primarily anemia) and improving quality of life [7]. Because RBC transfusion dependence is an independent risk factor for decreased survival [8, 9], a primary objective is to eliminate the need for blood product transfusions. Currently, there are only three treatment modalities available for patients with MDS who are resistant or unlikely to respond to ESAs: lenalidomide, the hypomethylating agents (HMAs), azacitidine and decitabine, and immunosuppressive therapy (IST) with antithymocyte globulins with or without cyclosporine for younger patients below 60 years of age or patients with RBC transfusion dependence of short duration [10].

Lenalidomide is an immunomodulatory drug and the disease-modifying treatment of choice for patients with LR-MDS with a deletion in chromosome 5 (del[5q]) [10]; for those patients, lenalidomide is associated with durable erythroid responses and RBC transfusion-independence (TI) rates of 60%–70% [11, 12]. Lenalidomide has also been studied in LR-MDS patients without the del(5q) karyotype in two large controlled trials. In the phase II MDS-002 study of lenalidomide in RBC transfusion-dependent patients with non-del(5q) LR-MDS, lenalidomide was associated with an RBC-TI rate of 26% with median duration of 41 weeks [13]. Additionally, in the randomized, phase III MDS-005 study, lenalidomide was associated with significantly higher rates of RBC-TI compared with placebo (26.9% vs. 2.5%, respectively; $p < .001$) in RBC transfusion-dependent patients with non-del(5q) LR-MDS who were ineligible for or refractory to ESAs [14]. Median duration of RBC-TI in patients with non-del(5q) LR-MDS in the MDS-005 study was ~31 weeks [14].

HMAs are the standard of care for treatment of higher-risk MDS [15–17]. The therapeutic effects of azacitidine and decitabine in hematologic disorders are believed to be due in part to methylation reductions in promotor regions of DNA, leading to re-expression of tumor suppressor genes [18]. Both HMAs are indicated in the U.S. for treatment of all French-American-British (FAB) [19] subtypes of MDS and for low-blast-count AML (i.e., 20%–30% bone marrow [BM] blasts) [20]. Azacitidine is approved in the European Union for treatment of higher-risk MDS and for adult patients with AML (any BM blast count) who are not candidates for allogeneic hematopoietic stem cell transplantation [21], and decitabine is approved for adult patients with newly diagnosed AML who are not eligible for induction chemotherapy [22]. In the randomized, phase III AZA-001 clinical trial in patients with higher-risk MDS and low-blast-count AML, azacitidine was shown to significantly prolong overall survival (OS) compared with conventional care regimens [15, 16]. Although azacitidine clinical data are primarily based on use in patients with higher-risk MDS, it has also shown efficacy in patients with LR-MDS, with or without del(5q) [23, 24], including in patients who were refractory to ESAs [25, 26].

National Comprehensive Cancer Network (NCCN) guidelines for treatment of MDS recommend azacitidine for patients

with non-del(5q) LR-MDS who have clinically relevant thrombocytopenia or neutropenia, or increased BM blasts, and for those with LR-MDS with serum erythropoietin (EPO) >500 mU/mL who are unlikely to respond to immunosuppressive therapy [10]. NCCN guidelines also recommend lenalidomide for all patients with del(5q) LR-MDS and symptomatic anemia, and for patients with non-del(5q) LR-MDS with symptomatic anemia who are not likely to respond to ESAs [10].

Following ESA failure, there is no clear guidance regarding the choice of lenalidomide or an HMA as initial disease-modifying therapy for patients with non-del(5q) LR-MDS, who mainly require treatment to reduce anemia and the need for transfusions. The choice of initial therapy is important because most patients will eventually stop responding to first-line therapy and alternatives are limited.

No large, randomized, controlled trials or large prospective studies of azacitidine specific to LR-MDS have yet been reported. To assess the effectiveness of first-line azacitidine in RBC transfusion-dependent LR-MDS, we performed a prospective meta-analysis of azacitidine treatment in this population in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, using individual patient-level data obtained from investigators from relevant studies.

MATERIALS AND METHODS

Data Sources

The PubMed database was searched for English-language articles published between January 1, 2000, and December 31, 2015. Embase was searched for abstracts from hematology conferences published in 2015. The key words used for this search were azacitidine, azacytidine, 5-azacitidine, myelodysplastic syndrome, and MDS.

Study Selection, Meta-Analysis Inclusion Criteria, and Data Extraction

Meta-analysis data were collected from prospective clinical trials (phase II or phase III) and patient registries that included RBC transfusion-dependent patients with LR-MDS. Criteria for including patient data in meta-analyses were as follows: (a) the study included patients with LR-MDS defined by IPSS, FAB, or World Health Organization (WHO) treated with azacitidine; (b) rates of RBC-TI were assessed; and (c) no concomitant chemotherapy, immunotherapy, hematopoietic stem cell transplant, other epigenetic therapy, or investigational treatments were included in the study.

Not included in these analyses were data from review articles, editorials, preclinical studies, retrospective analyses, case reports, studies specific to oral azacitidine, studies in which azacitidine was not used as first-line treatment, studies with nonclinical endpoints (e.g., with translational focus), transplant-specific studies, or studies limited to patients with higher-risk MDS or AML.

Data Collection

Available patient-level data were obtained from respective study investigators. Although studies included in meta-analyses required enrollment of patients with IPSS-, FAB-, or WHO-defined LR-MDS, patient-level data in some cases did not differentiate LR-MDS from higher-risk MDS. Therefore, LR-MDS was

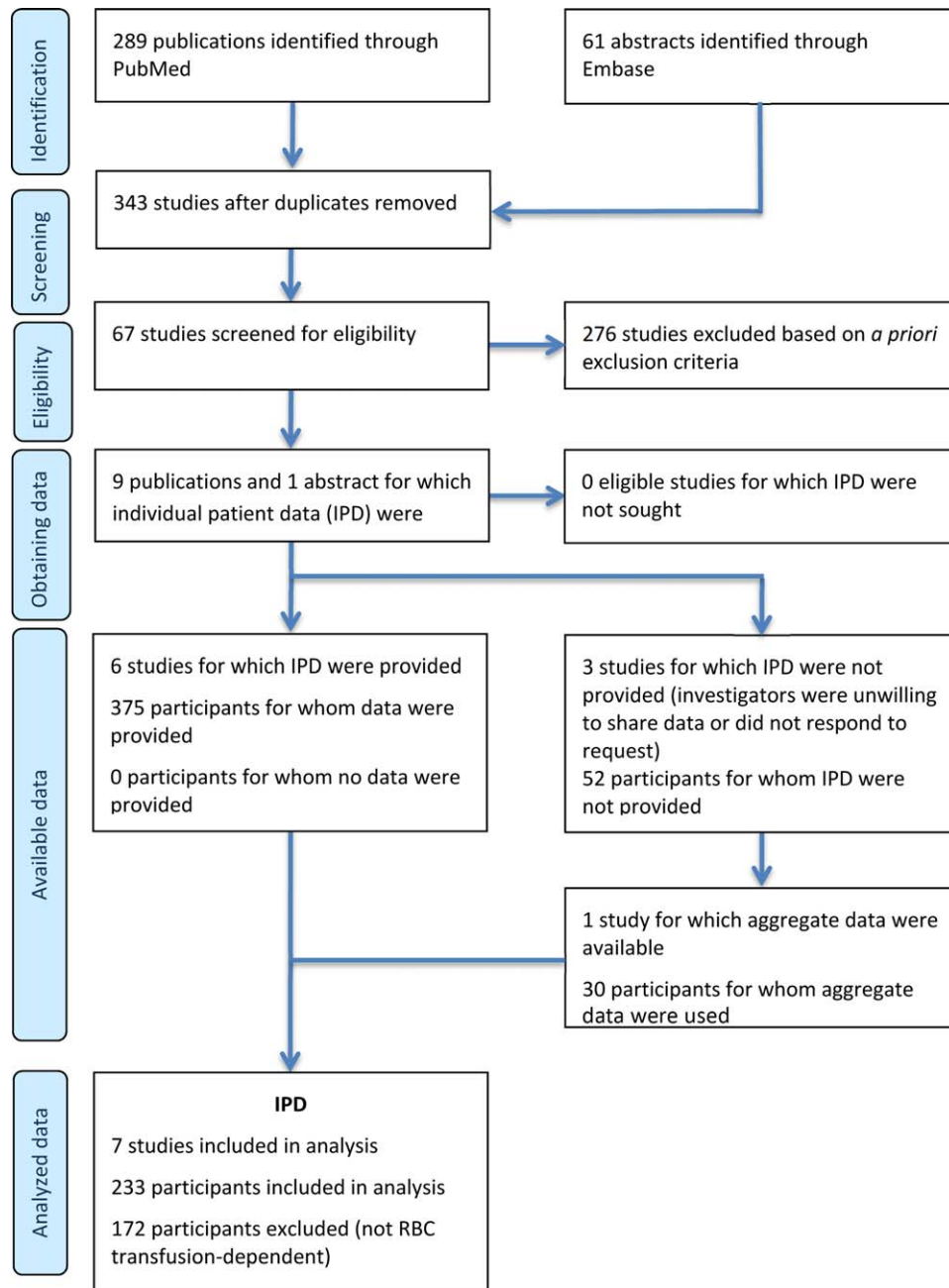


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses analysis. Abbreviations: IPD, individual patient data; RBC, red blood cell.

established based on an IPSS score of ≤ 1 , derived from individual patient data, as the sum of BM blasts percentage (BMB) plus cytopenia (C) scores as follows [2]:

- BMB < 5%, BMB score = 0
- $5\% \leq \text{BMB} \leq 10\%$, BMB score = 0.5
- $10\% < \text{BMB} \leq 20\%$, BMB score = 1.5
- $20\% < \text{BMB} \leq 30\%$, BMB score = 2
- And
- 0 or 1 cytopenia, C score = 0
- 2 or 3 cytopenias, C score = 0.5

Cytopenias were defined as hemoglobin (Hgb) <10 g/dL, platelets < $100 \times 10^9/L$, and absolute neutrophil count (ANC) < $0.5 \times 10^9/L$.

Pretreatment patient data collected included age, gender, IPSS prognostic risk (if not provided, this was calculated from subscores as described above), number and depth of cytopenias, Eastern Cooperative Oncology Group (ECOG) performance status score, BM blast percentage, time since MDS diagnosis, presence of del(5q) abnormality, EPO level, and prior use of and responsiveness to ESAs. Treatment variables included azacitidine regimen and schedule in the individual studies, total azacitidine doses, and numbers of treatment cycles prospectively specified in the study designs.

Endpoints

Rates of RBC-TI and Clinical Benefit were assessed for patients in the individual studies with available data and for the group

Table 1. Studies from which patient-level data were provided and included in meta-analyses

Study	IPSS/FAB/WHO risk status	AZA patients with LR-MDS in the study, n	AZA patients with patient-level data in current analyses, n (% of all LR-MDS in the study)	ESA status	AZA regimen per cycle
Grinblatt et al., 2015 [28] (AVIDA, prospective registry)	FAB/WHO LR- and HR-MDS	228	133 (58)	52% of all patients received prior growth factors, including ESAs	75 mg/m ² × 7 days
Lyons et al., 2009 [24] (phase II)	FAB LR- and HR-MDS	65	33 (51)	Not described	75 mg/m ² SC × 5 days, followed by 2 days no treatment, then 75 mg/m ² × 2 days or 50 mg/m ² SC × 5 days followed by 2 days no treatment, then 50 mg/m ² /day × 5 days or 75 mg/m ² SC × 5 days
Martin et al., 2009 [33] (phase II)	LR- and HR-MDS	9	2 (22)	32% of all patients previously received growth factors	75 mg/m ² IV × 5 days
Sanchez-Garcia et al., 2015 [34] (phase II)	LR-MDS	20	20 (100)	ESA refractory or ineligible	75 mg/m ² × 5 days
Sayar et al., 2011 [29] (phase II)	LR-MDS	14	5 (36)	ESA refractory or ineligible	50 mg/m ² 3×/week for 2 weeks every 4 weeks, ±EPO
Silverman et al., 2002 [32] (CALGB, phase III)	LR- (in AZA arm) and HR-MDS	22	10 (45)	Not described	75 mg/m ² × 7 days
Tobiasson et al., 2014 [31] (phase II)	Low/Int-1	30	30 (100)	ESA refractory or ineligible	75 mg/m ² × 5 days for 6 cycles

Abbreviations: AZA, azacitidine; CALGB, Cancer and Leukemia Group B; EPO, serum erythropoietin; ESA, erythropoietin stimulating agent; FAB, French-American-British; HR, higher-risk; Int-1, intermediate-1; IPSS, International Prognostic Scoring System; IV, intravenous; LR, lower-risk; MDS, myelodysplastic syndromes; RAEB, refractory anemia with excess blasts; SC, subcutaneous; WHO, World Health Organization.

of all patients with available data. RBC-TI was defined as no RBC transfusions for a period of 56 consecutive days on-study. Clinical Benefit was defined as attainment of RBC-TI, hematologic improvement in the erythroid lineage (HI-E), complete remission (CR), or partial remission (PR), per International Working Group 2006 criteria for MDS [27].

Statistical Analysis

Baseline characteristics and treatment variables are summarized descriptively.

Three patient cohorts were identified for RBC-TI and Clinical Benefit outcomes: (a) the overall group of RBC transfusion-dependent patients with LR-MDS; (b) the subgroup of patients who had failed prior ESA use or with serum EPO level >500 mU/mL (“ESA refractory”); and (c) the subgroup of patients with isolated anemia (Hgb <10 g/dL with platelets ≥100 × 10⁹/L and ANC ≥0.5 × 10⁹/L).

Univariate analyses were performed using available data from the group of all patients to estimate the association between response and the following baseline variables: age (continuous variable), gender (male vs. female), Hgb level (≥10 vs. <10 g/dL), ANC (≥0.5 vs. <0.5 × 10⁹/L), platelet level (<100 vs. ≥100 × 10⁹/L), BM blast percentage (≥5% vs. <5%), ECOG performance status (0 vs. 1–3), number of cytopenias (0–1 vs. 2–3), presence of del(5q) (no vs. yes), isolated

anemia (yes vs. no), prior ESA usage (yes vs. no), and EPO level (≤500 vs. >500 mU/mL). Other factors in the univariate analysis were protocol-specified planned number of azacitidine cycles (<6 vs. ≥6 cycles) and total azacitidine dose (continuous variable).

Significant variables at $p < .1$ were included in the multivariate models for further assessment of factors associated with response (significant at $p < .05$) for all patients and in the ESA-refractory and isolated anemia patient subgroups.

Heterogeneity of available data from trials included in meta-analyses was assessed using the chi-square test of heterogeneity and the I² measure of inconsistency. Heterogeneity was considered present when the p value of the Cochran Q test was <.05 and the I² statistic was >50%. Response rates were calculated using random-effects models in cases of high heterogeneity, and by using fixed-effects models in cases of low heterogeneity.

RESULTS

Data Sources

In all, 289 publications and 61 abstracts were initially identified based on literature search parameters (Figure 1). All but nine published studies and one abstract were excluded based on prospective search criteria [24–26, 28–34]. Investigators from

Table 2. Baseline characteristics for patients included in meta-analyses

Variable	Grinblatt (AVIDA) [28] (n = 133)	Sayar [29] (n = 5)	Tobiasson [31] (n = 30)	Sanchez-Garcia [34] (n = 20)	Martin [33] (n = 2)	Silverman [32] (CALGB) (n = 10)	Lyons [24] (n = 33)	All studies (n = 233)
Age, median (range)	76.0 (51.0–91.0)	68.0 (65.0–75.0)	68.0 (55.0–81.0)	NA (NA)	74.5 (66.8–82.2)	71.0 (62.0–77.0)	74.0 (37.0–85.0)	74.0 (37.0–91.0)
Sex								
Male, n/N (%)	93/133 (69.9)	4/5 (80.0)	21/30 (70.0)	NA	1/2 (50.0)	7/10 (70.0)	19/33 (57.6)	145/213 (68.1)
Female, n/N (%)	40/133 (30.1)	1/5 (20.0)	9/30 (30.0)	NA	1/2 (50.0)	3/10 (30.0)	14/33 (42.4)	68/213 (31.9)
Missing, n	0	0	0	20	0	0	0	20
del(5q) MDS, n/N (%)	13/129 (10.1)	0/5 (0.0)	5/30 (16.7)	0/20 (0.0)	0/2 (0.0)	NA	NA	18/186 (9.7)
Missing, n	4	0	0	0	0	10	33	47
Isolated anemia, n/N (%)	46/126 (36.5)	1/5 (20.0)	15/30 (50.0)	NA	0/2 (0.0)	4/5 (80.0)	15/32 (46.9)	81/200 (40.5)
Missing, n	7	0	0	20	0	5	1	33
Prior ESA usage, n/N (%)	89/133 (66.9)	1/5 (20.0)	26/30 (86.7)	20/20 (100)	2/2 (100)	NA	15/33 (45.5)	153/223 (68.6)
Missing, n	0	0	0	0	0	10	0	10
EPO								
≤500, n/N (%)	13/18 (72.2)	2/5 (40.0)	16/27 (59.3)	NA	NA	NA	NA	31/50 (62.0)
>500, n/N (%)	5/18 (27.8)	3/5 (60.0)	11/27 (40.7)	NA	NA	NA	NA	19/50 (38.0)
Missing, n	115	0	3	20	2	10	33	183
ESA refractory, n/N (%)	90/93 (96.8)	4/5 (80.0)	30/30 (100)	20/20 (100)	2/2 (100)	NA	15/15 (100)	161/165 (97.6)
Missing, n	40	0	0	0	0	10	18	68
No. of cytopenias								
0–1, n/N (%)	72/114 (36.8)	1/5 (20.0)	18/23 (78.3)	NA	0/2 (0.0)	9/9 (100)	21/21 (100)	121/174 (69.5)
2–3, n/N (%)	42/114 (63.2)	4/5 (80.0)	5/23 (21.7)	NA	2/2 (100)	0/9 (0.0)	0/21 (0.0)	53/174 (30.5)
Missing, n	19	0	7	20	0	1	12	59
ECOG performance status								
0, n/N (%)	37/132 (28.0)	1/5 (20.0)	NA	NA	NA	NA	9/33 (27.3)	47/170 (27.6)
1–3, n/N (%)	95/132 (72.0)	4/5 (80.0)	NA	NA	NA	NA	24/33 (72.7)	123/170 (72.4)
Missing, n	1	0	30	20	2	10	0	63
FAB								
MDS, n/N (%)	69/76 (90.8)	5/5 (100)	30/30 (100)	NA	NA	9/10 (90.0)	31/33 (93.9)	144/154 (93.5)
Non-MDS, n/N (%)	7/76 (9.2)	0/5 (0.0)	0/30 (0.0)	NA	NA	1/10 (10.0)	2/33 (6.1)	10/154 (6.5)
Missing, n	57	0	0	20	2	0	0	79

(continued)

Table 2. (continued)

Variable	Grinblatt (AVIDA) [28] (n = 133)	Sayar [29] (n = 5)	Tobiasson [31] (n = 30)	Sanchez-Garcia [34] (n = 20)	Martin [33] (n = 2)	Silverman [32] (CALGB) (n = 10)	Lyons [24] (n = 33)	All studies (n = 233)
Hgb (g/dL)								
Median (range)	9.1 (5.4–12.2)	8.8 (6.2–9.1)	9.2 (6.8–12.0)	NA	8.9 (8.9–8.9)	8.3 (5.6–10.0)	10.1 (5.9–14.5)	9.1 (5.4–14.5)
<10, n/N (%)	93/131 (71.0)	5/5 (100)	19/30 (63.3)	NA	2/2 (100)	8/9 (88.9)	15/32 (46.9)	142/209 (67.9)
Missing, n	2	0	0	20	0	1	1	24
Platelets (10 ⁹ /L)								
Median (range)	112.0 (11–784)	91.0 (47–397)	210.5 (20–1,753)	NA	95.5 (29–162)	198.0 (14–313)	237.0 (23–671)	155.5 (11–1,753)
<100, n/N (%)	60/131 (45.1)	3/5 (60.0)	5/30 (16.7)	NA	1/2 (50.0)	1/9 (11.1)	6/33 (18.2)	76/210 (36.2)
Missing, n	2	0	0	20	0	1	0	23
ANC (10 ⁹ /L)								
Median (range)	2.5 (0.1–60.4)	1.3 (0.2–3.0)	1.7 (0.2–10.5)	NA	1.9 (0.4–3.3)	7.1 (2.7–95.4)	2.9 (0.8–162.3)	2.5 (0.1–162.3)
<0.5, n/N (%)	11/121 (9.1)	1/5 (20.0)	4/30 (13.3)	NA	1/2 (50.0)	0/5 (0.0)	0/32 (0.0)	17/195 (8.7)
Missing, n	12	0	0	20	0	5	1	38
BM blasts %								
Median (range)	2.0 (0–10.0)	6.0 (4.0–9.0)	NA	NA	NA	2.0 (1.0–3.0)	1.7 (0–4.0)	2.0 (0–10.0)
≥5%, n/N (%)	39/133 (29.3)	4/5 (80.0)	NA	NA	NA	0/9 (0.0)	0/28 (0.0)	43/175 (24.6)
Missing, n	0	0	30	20	2	1	5	58
Years with MDS								
Median (range)	0.4 (0–12.4)	NA	NA	NA	NA	0.6 (0–3.7)	0.0 (0–8.0)	0.4 (0–12.4)
Missing, n	0	5	30	20	2	0	1	58
No. of AZA cycles								
Median (range)	5.0 (1–22)	4.0 (4–25)	9.0 (1–20)	NA	17.5 (15–20)	4.0 (1–23)	6.0 (1–18)	6.0 (1–25)
≥6 cycles, n/N (%)	59/133 (44.4)	1/5 (20.0)	21/29 (72.4)	NA	2/2 (100)	2/10 (20.0)	25/33 (75.8)	110/212 (51.9)
Missing, n	0	0	1	20	0	0	0	21
Total dose (mg)								
Mean (SD)	2,958 (2,444)	2,460 (2,817)	2,793 (1,391)	NA	8,625 (1,591)	3,717 (2,816)	6,871 (4,219)	3,621 (3,083)
Missing	0	0	1	20	0	2	0	23
AZA cycle length (d)								
Median (range)	28.0 (3–154)	24.0 (24–150)	45.0 (5–100)	NA	115.0 (100–130)	28.0 (7–158)	58.0 (7–136)	31.5 (3–158)
Missing	0	0	1	20	0	0	0	21

Abbreviations: ANC, absolute neutrophil count; AZA, azacitidine; BM, bone marrow; CALGB, Cancer and Leukemia Group B; d, days; ECOG, Eastern Cooperative Oncology Group; EPO, serum erythropoietin; ESA, erythropoietin stimulating agent; FAB, French-American-British; Hgb, hemoglobin; HR, higher-risk; LR, lower-risk; MDS, myelodysplastic syndromes; NA, not available; SD, standard deviation.

Table 3. Response in individual studies and overall for patients with available data

Outcome		n (% of patients with available data ^a)							
		Grinblatt [28] (AVIDA) (n = 133)	Sayar [29] (n = 5)	Tobiasson [31] (n = 30)	Sanchez-Garcia [34] (n = 20)	Martin [33] (n = 2)	Silverman [32] (CALGB) (n = 10)	Lyons [24] (n = 33)	All studies (n = 233)
RBC-TI	Yes	87 (65)	0 (0)	6 (20)	5 (31)	0 (0)	2 (20)	20 (61)	120 (54)
	No	46 (35)	0 (0)	24 (80)	11 (69)	2 (100)	8 (80)	13 (39)	104 (46)
	Missing, n	0	5	0	4	0	0	0	9
Clinical benefit	Yes	87 (81)	0 (0)	9 (30)	7 (100)	2 (100)	7 (88)	22 (100)	134 (76)
	No	21 (19)	0 (0)	21 (70)	0 (0)	0 (0)	1 (12)	0 (0)	43 (24)
	Missing, n	25	5	0	13	0	2	11	56

^aDenominators for proportions do not include the numbers of “missing” patients.

Abbreviations: CALGB, Cancer and Leukemia Group B; RBC-TI, red blood cell transfusion-independent.

these 10 studies were contacted to request published and unpublished patient-level data for inclusion in analyses, which was kindly provided by investigators from 6 studies (Table 1). Appropriate patient-level data were available in another study reported in abstract form [34] and are also included in analyses. Together, data for 233 patients from 7 studies met the relevant criteria [24, 28, 29, 31–34]. Of these seven studies, six were clinical trials and one was a prospective community-based registry study (AVIDA [28]). In the current analysis, the number of patients with data provided from the AVIDA registry ($n = 133$) was greater than the number from the other six clinical trials combined ($n = 100$).

All patients in these analyses were RBC transfusion-dependent before treatment; however, baseline data were missing for other demographic or disease-related variables in some cases (Table 2). ESA-refractory and isolated anemia statuses were not mutually exclusive; of patients with available data, 161/165 patients (97.6%) were ESA refractory and 81/200 patients (40.5%) had isolated anemia. The median age of all patients was 74 years (range 37–91). Of patients with available information, 68.1% were male, 90.3% of patients had non-del(5q) LR-MDS, and 67.9% had Hgb levels of <10 g/dL at entry into the individual studies.

Table 3 shows RBC-TI and Clinical Benefit rates for included patients in each individual study and a combined response rate. Overall RBC-TI and Clinical Benefit rates for patients with available data were 54% and 76%, respectively; however, there was significant heterogeneity of response results among the seven studies. The Cochran Q test values were $p < .01$ for all analyses and I^2 values ranged from 81.5% to 83.2% for RBC-TI and from 80.2% to 84.2% for Clinical Benefit. Thus, using random-effects models, the pooled estimates of RBC-TI rate in meta-analysis was 38.9% for all patients, 40.5% in the ESA-refractory subgroup, and 41.9% in patients with isolated anemia (Figure 2). Pooled estimates of Clinical Benefit rates were 81.1% for all patients, 77.3% in ESA-refractory patients, and 82.5% in patients with isolated anemia (Figure 3).

In univariate analysis, significant predictors of RBC-TI were older age, baseline ANC $\geq 0.5 \times 10^9/L$, higher total azacitidine dose, and studies with ≥ 6 prospectively planned azacitidine treatment cycles. Significant predictors of Clinical Benefit were no prior ESA usage, baseline presence of 0 or 1 cytopenia, baseline ANC $\geq 0.5 \times 10^9/L$, higher total azacitidine dose, and ≥ 6 planned azacitidine treatment cycles. These variables were added to multivariate models.

In multivariate analyses, participation in a study with a prospective plan to treat patients with ≥ 6 azacitidine treatment cycles was a significant predictor of RBC-TI in all three cohorts (i.e., in the overall patient group and in the ESA-refractory and isolated anemia subgroups; Table 4). Prospectively planned use of at least 6 azacitidine treatment cycles was also significantly predictive of attaining Clinical Benefit for the overall population and for patients who were ESA refractory. In the group of all patients, no prior ESA use was also significantly predictive of attaining Clinical Benefit. For patients with isolated anemia, no factor emerged as significantly predictive of Clinical Benefit.

Because AVIDA was the only registry study and the number of patients with data from AVIDA was disproportionately large, sensitivity meta-analyses were performed excluding AVIDA patient data. When AVIDA patients were removed from analyses, response rates decreased, with RBC-TI ranging from 29.4% to 31.8% and Clinical Benefit rates from 75.3% to 83.7%. In multivariate sensitivity analyses without AVIDA patients, significant predictors of attaining RBC-TI for the group of all patients were older age, no prior ESA use, Hgb ≥ 10 g/dL, and ≥ 6 planned azacitidine treatment cycles. In the subgroup of patients with refractory anemia, Hgb ≥ 10 g/dL was significantly predictive of achieving RBC-TI, and no prior ESA use was significantly predictive of RBC-TI in patients with isolated anemia. In the group of all patients, only planned administration of ≥ 6 azacitidine cycles was significantly predictive of Clinical Benefit.

DISCUSSION

MDS hemopathies are progressive disorders, and treatment options are limited; therefore, the choice of initial treatment should be made judiciously, with the understanding that at some point, alternate or additional treatment may be necessary. In this meta-analysis, azacitidine was associated with an RBC-TI rate of 38.9% in the group of all patients with RBC transfusion-dependent LR-MDS, more than 90% of whom had non-del(5q) disease. The RBC TI rate obtained with lenalidomide treatment in RBC transfusion-dependent patients with non-del(5q) LR-MDS in the MDS-002 study [13] and rates in patients with non-del(5q) LR-MDS in the phase III MDS-005 study who were RBC transfusion-dependent and unresponsive or refractory to ESAs was $\sim 27\%$ [14].

To determine whether the order of treatment made a difference in clinical response rates, Zeidan et al. retrospectively evaluated HI-E rates for 63 patients with non-del(5q) LR-MDS

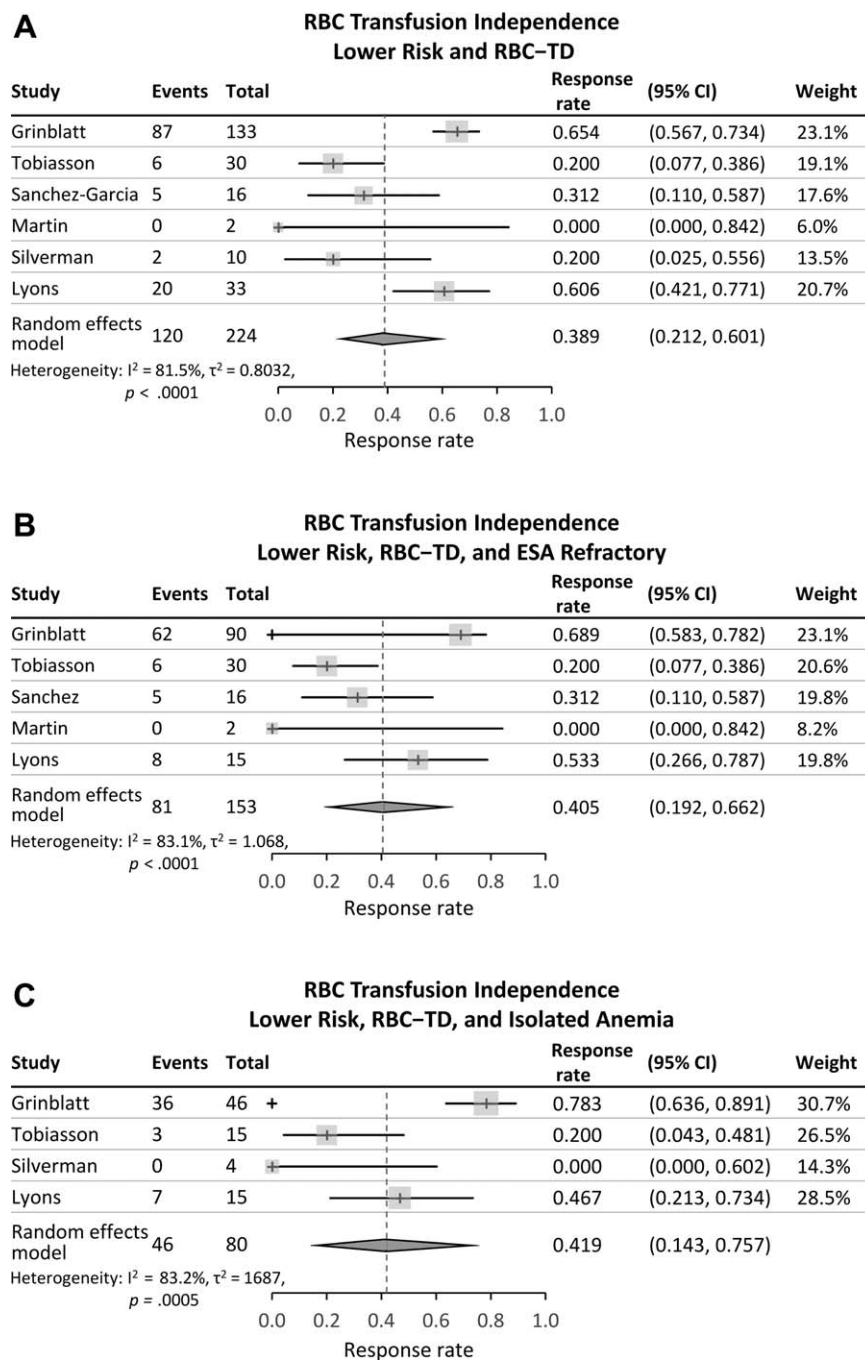


Figure 2. Transfusion-independence in patients with RBC transfusion-dependent lower-risk myelodysplastic syndromes. **(A):** All patients. **(B):** The subgroup of patients refractory to erythropoiesis-stimulating agents. **(C):** The subgroup of patients with isolated anemia.

Abbreviations: CI, confidence interval; ESA, erythropoiesis-stimulating agent; RBC, red blood cell; RBC-TD, RBC transfusion-dependent.

at a single institution who had received sequential treatment with both lenalidomide and azacitidine [35]. The HI-E rate with lenalidomide as first-line therapy was 38% compared with 12% when used as second-line therapy after azacitidine ($p = .04$), whereas response rates to azacitidine were similar whether it was used before or after lenalidomide (35% and 38%, respectively) [35]. Komrokji et al. reported similar outcomes for 144 patients from multiple sites (including the original 63 patients mentioned above) who had received sequential lenalidomide and azacitidine or decitabine [36], showing a 20% rate of HI-E with lenalidomide when it was used first-line compared with 11% HI-E when lenalidomide was used second-line after the

HMA ($p = .046$) [36]. Again, there was no significant difference in HI-E rates when an HMA was used as first- or second-line therapy (39% and 30%, $p = .2$). In this larger cohort, rate of transformation to AML was also significantly different based on treatment order, with 9% of patients developing AML when lenalidomide was used first-line compared with 22% of patients when it was used after an HMA ($p = .03$). Despite differences in response rates, treatment order had no influence on OS [36]. At this time, no randomized prospective data are available to confirm these findings.

HMAs do not selectively target anemia, but improve platelet and neutrophil counts [15]; thus, they may be a better

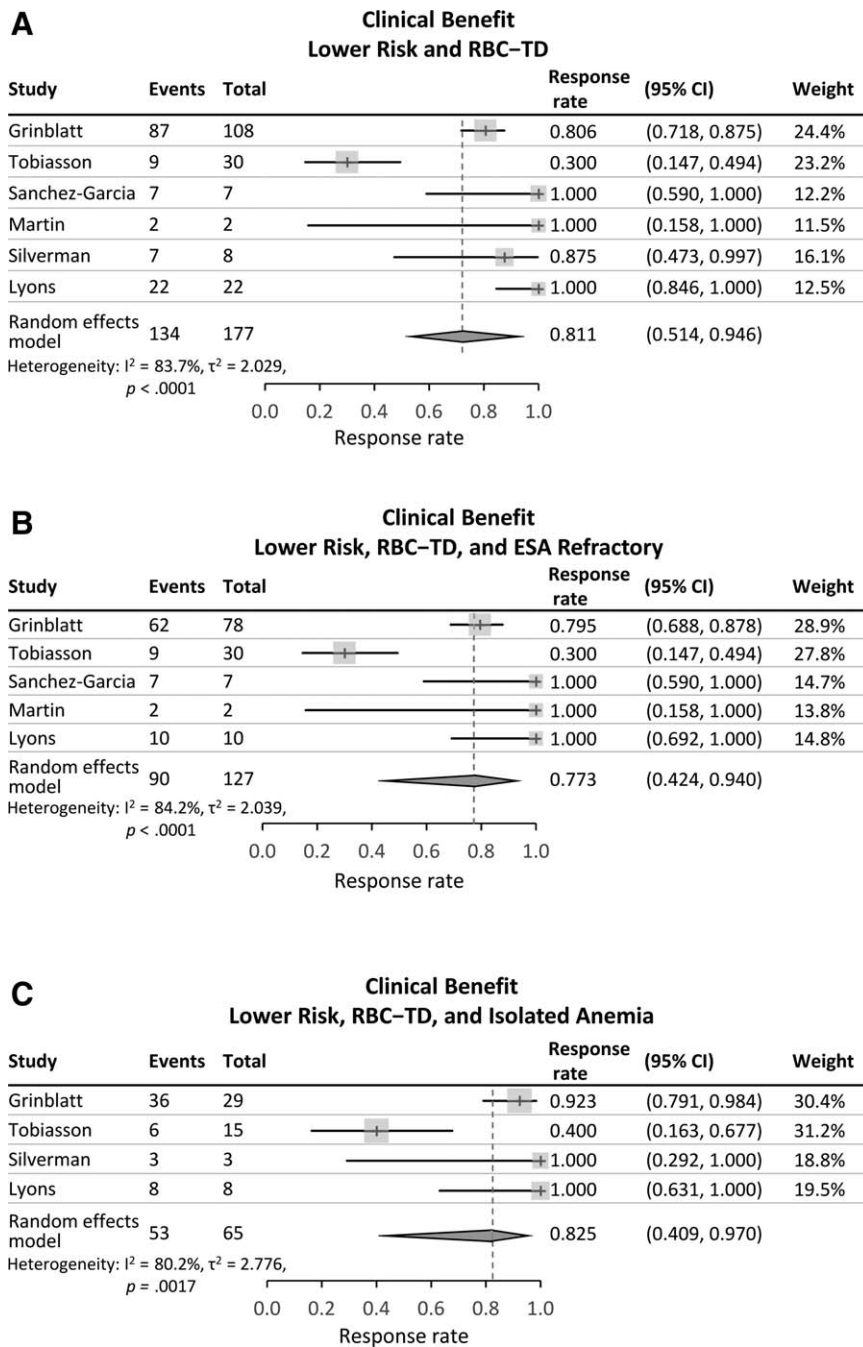


Figure 3. Clinical Benefit in patients with RBC transfusion-dependent lower-risk myelodysplastic syndromes. This composite endpoint comprises RBC transfusion independence, hematologic improvement in the erythroid lineage, and complete or partial remission, per the International Working Group 2006 criteria for myelodysplastic syndromes [27]. (A): All patients. (B): The subgroup of patients refractory to erythropoiesis-stimulating agents. (C): The subgroup of patients with isolated anemia.

Abbreviations: CI, confidence interval; ESA, erythropoiesis-stimulating agent; RBC-TD, red blood cell transfusion-dependence.

choice of first-line therapy for patients with LR-MDS and anemia accompanied by significant thrombocytopenia or neutropenia. Additionally, the presence of biomarkers of improved response may suggest preferential use of azacitidine for some patients. For example, *TET2* mutations, which occur in approximately 20% of patients with MDS, have been found to be predictive of better response to HMAs [37–39]. Mutations in *IDH* genes, found in ~5% of MDS patients, have also been linked to better response to treatment with HMAs [40, 41]. One study showed that although mutations in the histone modulators *ASXL1* or *EZH2* did not influence response rates, they were

associated with significantly prolonged OS in patients with higher-risk MDS treated with azacitidine [42]. There is contradictory evidence regarding the influence of *TP53* mutations on outcomes of azacitidine treatment. Some studies suggest azacitidine-treated patients with *TP53* mutations have poorer OS than those with wild-type *TP53* [39, 43], whereas other data suggest *TP53* mutational status has no influence on survival [44]. Response to lenalidomide may also be influenced by mutational status. Preliminary data suggest higher rates of RBC-TI in lenalidomide-treated patients with non-del(5q) LR-MDS who have *DNMT3A* mutations (~8% of MDS patients),

Table 4. Significant predictors of response in multivariate analyses of patients with RBC transfusion-dependent lower-risk myelodysplastic syndromes

Response	Subgroup	Covariate	Odds ratio (95% CI)	p value
RBC-TI	RBC-TD	≥6 vs. <6 azacitidine cycles ^a	4.54 (2.45–8.41)	<.0001
	RBC-TD + ESA refractory	≥6 vs. <6 azacitidine cycles	4.36 (2.02–9.43)	.0002
	RBC-TD + isolated anemia	≥6 vs. <6 azacitidine cycles	2.56 (0.97–6.79)	.0581
Clinical benefit	RBC-TD	≥6 vs. <6 azacitidine cycles	4.29 (1.70–10.79)	.0020
		Prior ESA yes vs. no	0.27 (0.09–0.85)	.0247
	RBC-TD + ESA refractory	≥6 vs. <6 azacitidine cycles	4.00 (1.51–10.60)	.0053
	RBC-TD + isolated anemia	No significant predictors		

^a≥6 versus <6 cycles describes the planned number of azacitidine treatment cycles in each study, not the actual number of treatment cycles received.

Abbreviations: CI, confidence interval; ESA, erythropoietin stimulating agent; RBC, red blood cell; TD, transfusion-dependent; TI, transfusion-independent.

compared with patients without this mutation (44% vs. 25%, respectively; $p = .13$), and significantly lower RBC-TI rates in patients with *ASXL1* mutations (~20% of MDS patients) compared with wild-type (10% vs. 32%, respectively; $p = .031$) [45].

Results of the current multivariate analyses demonstrate the importance of azacitidine treatment duration. The likelihood of attaining RBC-TI was increased ~three- to four-fold when patients participated in studies that planned for at least 6 azacitidine treatment cycles. Compared with the rapid myeloablation incurred with intensive chemotherapy regimens, response to azacitidine is more gradual and 4–6 months of azacitidine treatment may be required to induce a response [46, 47].

A limitation of current analyses is the high heterogeneity of results among the seven studies and the large imbalance among the numbers of patients from each study. More patient data came from the AVIDA registry than from all other studies combined. Eligibility criteria for enrollment in the AVIDA registry were (a) having MDS or other hematologic disorder, (b) having had no prior azacitidine exposure, and (c) that patients be “candidates for initiation of azacitidine treatment” [28]. Inclusion of so many patients from AVIDA may have introduced unforeseen biases; for example, concomitant use of ESAs or growth factors may have elevated RBC-TI rates relative to what might have been achieved with azacitidine alone. Indeed, when AVIDA data were excluded in sensitivity analyses, rates of RBC-TI dropped by up to 10.4% and Clinical Benefit rate decreased by up to 5.8%. Other potential limitations of these analyses were that data regarding pretreatment disease or demographic characteristics were not available for some patients, increasing the chance that there may not have been a large enough dataset to robustly confirm whether a specific variable that was not significant in univariate or multivariate analyses actually did influence response. Additionally, methods of response assessment (e.g., local vs. central) varied among studies, and in some cases were not reported at all. Finally, information regarding durability of response were available for only a subset of patients from three of the seven studies, precluding robust analysis of those data.

Although current treatment options for patients with LR-MDS who are refractory to ESAs are limited to injectable HMAs and lenalidomide, there are several drugs now in various stages of clinical development that could substantially expand the LR-MDS therapeutic landscape. In a phase I/II study of patients

with LR-MDS, CC-486 (oral azacitidine) was associated with an RBC-TI rate of 34% [48]. CC-486 doses under investigation deliver lower cumulative azacitidine doses per cycle than the 7-days-per-cycle injectable regimen, and can be administered over longer periods of the 28-day treatment cycle to sustain hypomethylating effects [48, 49]. A phase III randomized study is currently underway to evaluate the efficacy and safety of CC-486 in patients with LR-MDS who have RBC transfusion-dependent anemia and thrombocytopenia ($\leq 75 \times 10^9/L$ platelets; NCT01566695). Another drug in phase III of development for use in LR-MDS is imetelstat, an intravenous 13-mer lipid-conjugated oligonucleotide that competitively inhibits telomerase enzymatic activity (NCT02598661) [50]. In a small pilot study (NCT01731951) with nine patients, most of whom had refractory anemia with ringed sideroblasts ($n = 8$), three of eight transfusion-dependent patients (38%) achieved RBC-TI. All patients experienced at least one (reversible) grade ≥ 3 cytopenia [50].

Several other drugs are in earlier stages of development. APG101 is a fusion protein comprising the extracellular domain of human CD95 receptor and the Fc domain of the IgG1 antibody [51]. APG101 appears to inhibit the interaction between the CD95 receptor and its cognate ligand to prevent a CD95-mediated blockade of erythrocyte production in BM. In a small phase I study (NCT01736436), 6 of 20 APG101-treated patients (30%) showed increases in Hgb levels and 8 (40%) required fewer RBC transfusions [51]. Luspatercept, a modified ActRIIB-Fc fusion protein, was evaluated in the extension period of a phase II study (PACE-MDS; NCT02268383) in 32 RBC transfusion-dependent patients with LR-MDS who were refractory to or unlikely to respond to ESAs [52]. Twenty-six patients (81%) attained HI-E and 11 of 22 patients (50%) attained RBC-TI [52]. Luspatercept is currently under investigation in a placebo-controlled, randomized phase III study with RBC transfusion-dependent patients with LR-MDS with ringed sideroblasts (NCT02631070). Luspatercept is the only new drug under investigation currently in phase 3 of clinical development. OPN-305 is an intravenous IgG4 kappa monoclonal antibody directed against the toll-like receptor type 2 (TLR2); signalling mediated by TLR2 leads to expression of multiple cytokines that can interfere with hematopoiesis [53]. OPN-305 is currently in a phase I/II dose-finding and expansion study for use as second-line treatment of LR-MDS (NCT02363491). Preliminary outcomes of a dose-finding trial in a small number of

patients with LR-MDS for whom prior HMA treatment had failed showed a 50% overall response rate (6 of 12 patients) and 17% RBC-TI [54]. At doses evaluated (4 and 10 mg/kg) no significant effect on cytokine levels was observed suggesting higher doses of OPN-305 should be evaluated [54].

CONCLUSION

Ultimately, determining the optimal choice of initial disease-modifying therapy may require investigation in a prospective, randomized clinical trial. As new treatment options become available, there will be greater flexibility in the choice of initial and subsequent therapies to improve hematopoiesis in LR-MDS. The impact of HMAs on the natural history of the disease among LR-MDS patients with higher-risk features identified by new clinical risk models [55], and on somatic mutations, are important subjects of research. Many factors influence the choice of initial treatment. These analyses suggest azacitidine is an effective therapy for LR-MDS; however, convenience, side-effect profiles, and cost may influence the choice of azacitidine as first-line treatment after ESA failure.

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DISCLOSURES

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