Scientific Letter

Azacytidine Failure Revisited: an Appraisal Based on Real-Life Data from the MDS Registry of the Hellenic Myelodysplastic Syndrome Study Group (HMDS).

To the editor.

5-azacytidine (AZA) is the mainstay of treatment for high-risk MDS,[1] but both primary and secondary, i.e., after an initial response, AZA failure confers a grave prognosis.[2,3] Allogeneic transplantation and trials with novel agents are the preferred strategies for AZA failure, but transplant eligibility and availability of relevant trials are key limiting factors for the vast majority of the patients. In addition, AZA failure is currently poorly defined, as reflected by the highly heterogeneous outcome of patients who fail AZA,[4,5] and either lumps together pathobiologically diverse disease states,[2] or excludes treatment failure due to toxicity,[3] a common reason of AZA discontinuation in real-life settings. Given the limited efficacy and availability of subsequent treatment options, the exact definition of AZA failure and the decision to discontinue AZA is of particular importance in everyday clinical practice. Furthermore, it is plausible to assume that the diverse prognosis of the above patients may confuse the results of trials with novel drugs in the setting of AZA failure.

We retrospectively analyzed data from 326 MDS, MDS/MPN, and low blast count AML (LBC-AML) patients enrolled to Hellenic MDS registry from July 2004 to May 2017. The data cutoff date for the analysis was July 7, 2017, and the current analysis included only patients who received AZA as 1st line treatment. All patients were treated in a non-clinical trial setting at an initial dose of 75mg/m^2 SC for seven days on 28-day cycles. Granulocyte colony-stimulating factors and erythropoiesis-stimulating agents were used at the discretion of the treating physician. Dose reductions of 25%-50% and/or treatment delays were considered for severe myelotoxicity or myelosuppression-related complications. Treatment response was evaluated using the IWG 2006 criteria.[6] Survival analysis was performed using a Kaplan-Meier estimate and Cox's

proportional hazards model. Overall survival (OS) was defined as the time from AZA initiation or failure to last follow up or death from any cause. Akaike Information Criteria with correction for finite sample sizes (AICc) was used to compare model fits.[7]

Table 1 lists the patients' characteristics. After a median follow-up of 41.7 months, the median OS from AZA initiation for the whole cohort was 14 (95% CI: 12.6–15.4) months. Though not designed for patients with MDS/MPN and low-risk IPSS the French Prognostic Scoring System (FPSS)[8] was the better survival discriminator compared to IPSS and IPSS-R (**Figure 1A**, AICc 1958,841 vs. 2276,767 vs. 2321,742, respectively). In multivariate analysis, FPSS (p<0.001), the best response to AZA (p<0.001) and, marginally, disease subtype (MDS/MPN vs others, p=0.01) were all independent predictors of OS (**supplementary Table 1**).

The median time to AZA discontinuation was 7.5 months (95% CI: 6.5–8.5) with 43 (13.2%) patients still receiving AZA at the time of analysis. The median OS from AZA failure (n=252), defined as AZA intolerance, no response after at least 4 cycles along with AZA intolerance, progressive disease or death while on treatment, and loss of response, was 5.6 (95% CI: 4.8–6.3) months, similar to the one reported in other studies.[2,3] Progressive disease while on treatment (n=77, 28%) and AZA intolerance (n=88, 31%) were the most common causes of AZA failure, followed by loss of an initial response (n=41, 15%) and no response after 4 cycles (n=25, 9%). Median OS after AZA failure was comparable for all of the above causes (p=0.1, **Figure 2**), indicating that the diverse pathobiology behind AZA failure does not influence the outcome and rather typical clinical parameters at the time of AZA failure, as those captured by the post-HMA model, determine patient survival. However, the 20% rate of early discontinuation and 7% rate of early

Table 1. Clinical information of 326 patients.

Parameters (median, range)	(at AZA initiation, n=326)	(at AZA discontinuation, n=283)
Age	73.6 (34.6-88.8)	74.3 (34.7-88.5)
>65	69 (21.1%)	59 (21%)
<65	257 (78.9%)	224 (79%)
Sex		
Male	223 (68.4%)	193 (68%)
Female	103 (31.6%)	90 (32%)
WHO classification		
RCMD	19 (5.9%)	16 (5.7%)
RAEB-I	60 (18.4%)	50 (17.6%)
RAEB-II	137 (42%)	115 (40.7%)
CMML/ MDS/MPN	47 (14.4%)	43 (15.2%)
Low blast count AML	63 (19.3%)	59 (20.8%)
Baseline counts		
Hemoglobin (g/dl)	9 (4.3-14.7)	N/A
ANC(x 10^9/L)	0.91 (0.03-10.5)	N/A
Platelets (x 10^9/L)	74 (3-553)	39 (1-520)
Bone marrow blasts	12 (1-29)	18 (1-87)
IPSS		
Low/Intermediate-1	77 (23.6%)	
Intermediate-2	149 (45.7%)	
High	82 (25.2%)	
N/A	18 (5.5%)	
WPSS		
Low/Intermediate-1	20 (6.1%)	
High	136 (41.7%)	
Very high	55 (16.9%)	
N/A	115 (35.5%)	
IPSS-R		
Low	36 (11%)	
Intermediate	53 (16.3%)	
High	119 (36.5%)	
Very high	96 (29.4%)	
N/A	22 (6.7%)	
FPSS (GFM)		
Low	38 (11.7%)	
Intermediate	199 (61%)	
High	33 (10.1%)	
N/A	56 (17.2%)	
Post HMA model		
Low	-	64 (22.7%)
High	-	134 (47.3%)
N/A	-	85 (30%)
IPSS Cytogenetic risk		
Good	177 (54.3%)	
Intermediate	60 (18.2%)	
Poor	71 (21.8%)	
N/A	18 (5.5%)	

IPSS-R Cytogenetic risk		
Good/Very Good	179 (54.9%)	
Intermediate	61 (18.7%)	
Poor	34 (10.4%)	
Very poor	34 (10.4%)	
N/A	18 (5.5%)	
Number of completed cycles		
Median (range)	7 (1-59)	
Red cell transfusion dependency		
Yes	216 (66.3%)	
No	93 (28.5%)	
N/A	17 (5.2%)	
Best response		
CR+CRi+PR	87 (26.7%)	
Hematologic improvement (platelets +/- neutrophils)	60 (18.4%)	
Stable disease	71 (21.8%)	
Failure	91 (28,2)	
N/A	17 (5.2%)	

Abbreviations: IPSS = International Prognostic Scoring System, IPSS-R = revised International Prognostic, Scoring System, WPSS = World Health Organization classification-based Prognostic Scoring System, FPSS = French Prognostic Scoring System, RCMD = refractory cytopenia with multilineage dysplasia, RAEB = refractory anemia with excess blasts, CMML=chronic myelomonocytic leukemia, AML=acute myeloid leukemia, MDS/MPN=Myelodysplastic/myeloproliferative neoplasm, N/A=not available/applicable
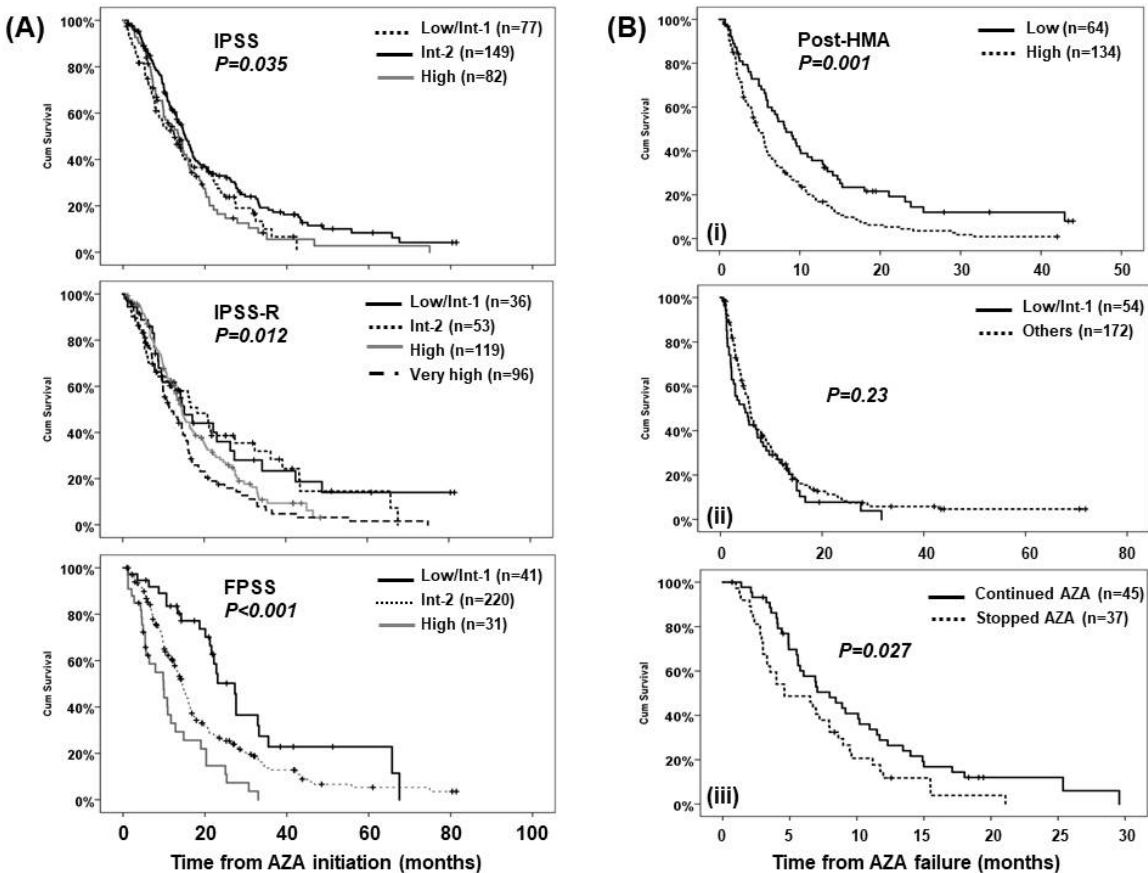
Figure 1. Overall survival at azacytidine initiation and at the time of azacytidine failure.
(**A**) Kaplan-Meier analysis by IPSS, IPSS-R and FPSS patient stratification at azacytidine initiation. (**B**) Overall survival after azacytidine failure, i) according to the post-HMA model, ii) in IPSS low/intermediate-1 risk vs all other patients and iii) in patients who continued or immediately stopped azacytidine after losing the initial response.
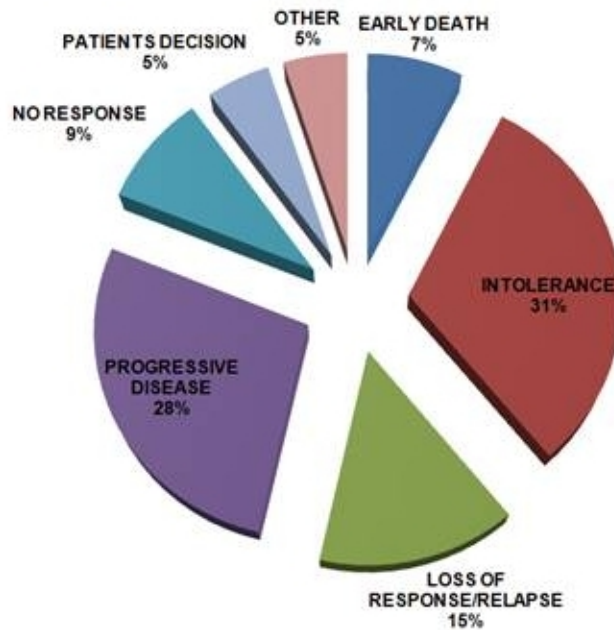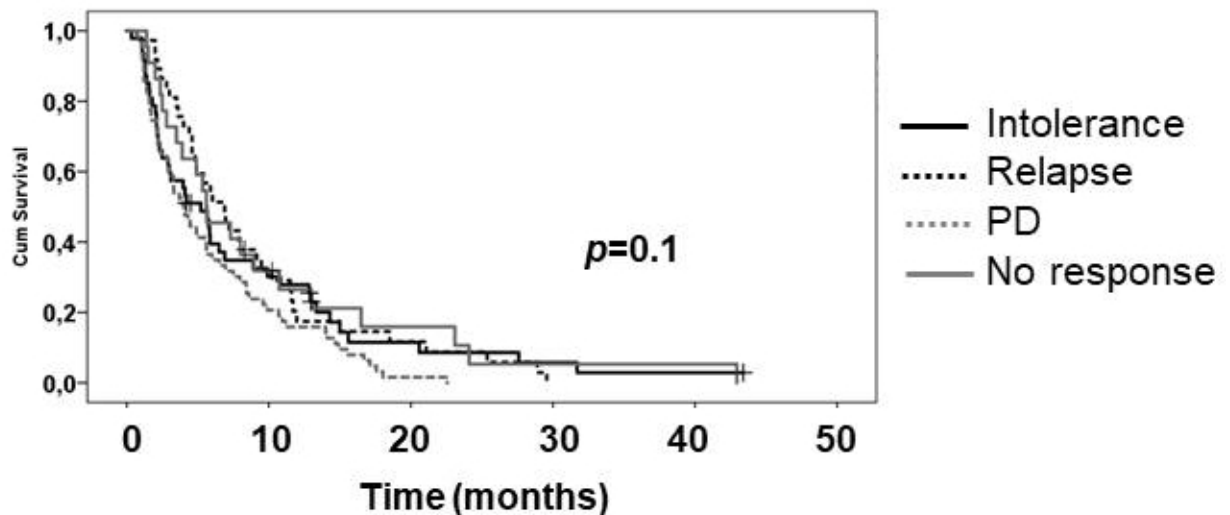
Figure 2. Causes of AZA failure and their effect on outcome.
(**A**) Failure causes in the patient cohort (n=280). Other causes include second neoplasms, local treatment policies and inclusion in clinical trials. (**B**) Overall survival after AZA failure according to the reason of failure. Early death, patient's decision and other causes were excluded from the analysis (n=225). PD: progressive disease.

death, i.e., occurring before cycle 4, underline the considerable toxicity of AZA in real-life settings, highlighting the need for early predictive factors to avoid a costly, ineffective and potentially even harmful treatment.

The post-HMA model[4] was applicable in 198 patients (**Figure 1B**); 64 patients (32.5%) were classified as low and 134 (67.5%) as high risk, with a significant difference in median OS after AZA failure (8.3, 95% CI: 5.8–10.8 vs. 4.8, 95% CI: 3.7–5.9 months respectively, p<0.001). Eight out of 9 patients who proceeded to allogeneic transplantation were classified as low and only one as high risk, whereas even after censoring these patients at the time of

transplantation, the median OS of the two groups remained identical (data not shown). In multivariate analysis, only the post-HMA model retained its independent predictive value (**supplementary Table 2**). Of note, our cohort included a considerable proportion of patients categorized as a low/intermediate-1 risk by IPSS (23.6%) at AZA initiation. The reported median OS after the failure of AZA in patients with IPSS low/int-1-risk score is 17 months.[9,10] By contrast, the median OS after AZA failure in our cohort of IPSS lower risk patients (n=54) was only 4.7 (95% CI: 1.6–7.8) months similar to one of the high-risk patients (n=172, **Figure 1B**). Though not easily interpretable, this inconsistency may be

attributable to selection biases due to clinical judgment in real-life settings, i.e., administration of AZA mainly in poor prognosis, multi-treated patients. Indeed, at AZA initiation, only 24/75 (32%) of IPSS lower-risk patients were categorized as low risk by IPSS-R and 13/57 (23%) by FPSS. In addition, at the time of HMA failure 31/41 (76%) of the evaluable IPSS lower risk patients fell into the post-HMA high risk category, although, as expected, significantly more IPSS, WPSS and IPSS-R higher risk patients were classified as high risk by the post-HMA model (**supplementary Figure S1**).

After AZA discontinuation, most patients were treated with supportive care, and only 9 patients proceeded to allo-SCT. Median OS after AZA failure was identical among patients treated with best supportive care, low dose AraC and intensive chemotherapy (p=0.22), whereas 14 patients treated with decitabine showed significantly improved mOS compared to all other treatments (21.1, 95% CI: 12–30.1 months, p=0.003, **Supplementary Figure S2**). Regarding the above patients, 5/11 evaluable cases were low and 6/11 high risk by post-HMA, whereas 4 discontinued AZA because of relapse after an initial response, 2 for disease progression, 2 for toxicity, 2 for failure to achieve a response after 4 cycles and one by his own decision. The overall response rate with second-line decitabine after AZA failure ranges from 19.4% to 63%[2,11,12] and the median OS from 7.3 to 17.8 months, but the small patient cohorts, the heterogeneous definitions of AZA failure and the obvious selection biases, preclude the identification of predictive factors for response in decitabine. Therefore, though selected patients who failed AZA may benefit from second line decitabine, no solid recommendation can be made, also considering the toxicity and cost of decitabine treatment.

According to the latest International Working Group (IWG) criteria,[6] a hemoglobin drop of ≥ 1.5 g/dL or $\geq 50\%$ decrement of maximum response levels of neutrophils or platelets signifies the loss of response. However, even large fluctuations in blood counts during AZA treatment can occasionally be observed in responding patients and, in the face of limited subsequent therapeutic options, many physicians are reluctant to immediately stop AZA simply only on the base of strictly defined loss of response. In our series, 45/82 patients, who continued AZA despite loss of response, had a significantly better OS (8.0 months, 95% CI: 5.5–10.5) compared to those (n=37) who stopped AZA immediately at loss of response (4.6 months, 95% CI: 1.5–7.9, p=0.027, **Figure 1B**). The decision to stop or not AZA when the response is lost according to the IWG criteria is subjected to bias, of course. However, patients who continued AZA had still significantly longer OS even when the analysis was adjusted for gender, disease subtype at the time of AZA discontinuation and the post-HMA model (p=0.02), though both patient groups received comparable therapies after AZA discontinuation (**supplementary Tables 3 and 4**). In line with these findings, our group has recently shown that patients with stable disease as best response benefited significantly by the continuation of AZA compared to the ones who stopped treatment.[13] By contrast, prolonged survival was recently reported in patients who stopped AZA or decitabine without disease progression, but the study cohort consisted mainly of IPSS low-risk patients, most of whom discontinued treatment for extra medical causes.[14]

In summary, in our large patient dataset, we confirmed the superior efficacy of FPSS and post-HMA models in predicting OS at AZA start and failure, respectively. However, our data also indicate that in real life settings, AZA failure is rather ill-defined, and physicians' perceptions of the cause and timing of AZA discontinuation differ widely. Retrospective data are inherently susceptible to selection and analysis bias. Specifically for the setting of AZA failure, the highly diverse reasons of AZA discontinuation in our series emphasize that, since no uniform criteria for stopping AZA have been adopted,[15] any survival comparisons should be given with caution. Failure due to intractable toxicity and disease progression confers very poor outcome, while patients who lose the initial response may benefit from AZA continuation despite poor prognostic features, highlighting, on the one hand, the diversity of the resistance mechanisms to AZA and, on the other, the limitations of the applicability of prognostic models[16] and response criteria in everyday clinical practice.

Ioannis Kotsianidis[1], Sotirios G. Papageorgiou[2], Vassiliki Pappa[2], Athanasios G. Galanopoulos[3], Nora-Athina Viniou[4], Theodoros P. Vassilakopoulos[5], Menelaos Papoutselis[1], George Vrachiolias[1], Vasileios Papadopoulos[1], Panagiotis T. Diamantopoulos[3], Dimitris Tsokanas[4], Alexandra Kourakli[6] and Argiris Symeonidis[6].

[1] Department of Hematology, Democritus University of Thrace Medical School; Greece.
[2] Second Department of Internal Medicine, Hematology Unit, Attikon University General Hospital, Athens, Greece.
[3] Department of Clinical Hematology, G. Gennimatas Hospital, Athens, Greece.
[4] Hematology Unit, First Department of Internal Medicine, Laikon General Hospital, National and Kapodistrian University of Athens, Athens, Greece.

[5] Department of Hematology, Laikon General Hospital, National and Kapodistrian University of Athens, Athens, Greece.
[6] Department of Internal Medicine, University Hospital of Patras, Rio, Greece.

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Correspondence to: Ioannis Kotsianidis, MD, PhD. Professor of Hematology, Director, Department of Hematology Democritus University of Thrace, Medical School, Dragana, Alexandroupolis 68100, Greece. E-mail: ikotsian@med.duth.gr, jankots@yahoo.gr

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Supplemental Data
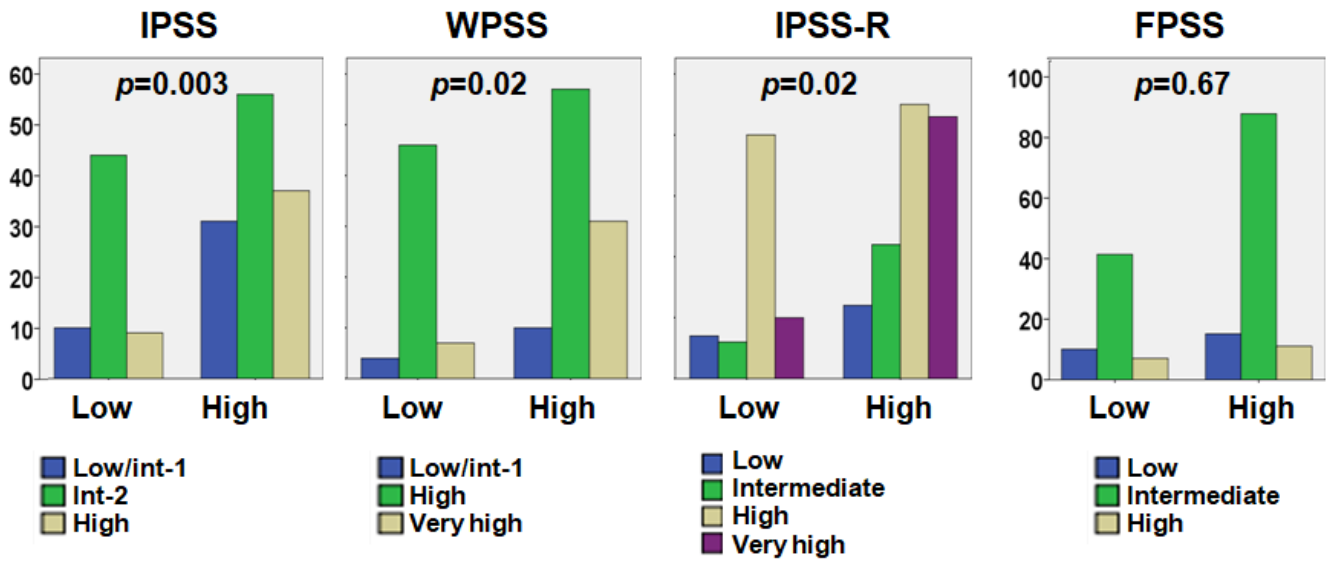
Supplementary Figure S1. Distribution of patients by the post-HMA model (n=198).
Patient disposition to the post-HMA risk categories according to their initial classification in IPSS, WPSS and IPSS-R models at AZA initiation. As expected significantly more higher-risk patients fell into the post-HMA high-risk category compared to the lower risk ones. However, these differences are not observed with FPSS.
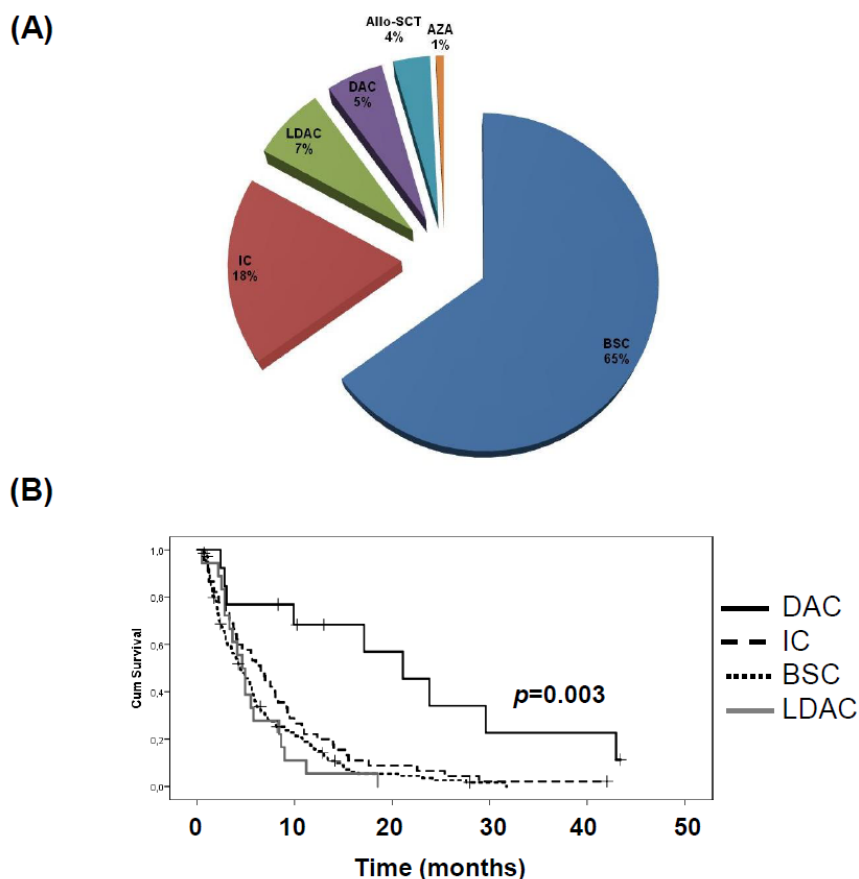
Supplementary Figure S2. Treatment modalities after AZA discontinuation (n=254).
(**A**) Treatments after AZA discontinuation (n=254). BSC: best supportive care +/- hydroxurea; IC: intensive chemotherapy; LDAC: low dose AraC, DAC: decitabine; Allo-SCT: allogeneic stem cell transplantation; AZA: retreatment with AZA after an interruption of >3 months (n=2). (**B**) Overall survival after AZA failure according to treatment modality. Allogeneic stem cell transplantation (Allo-SCT) and AZA retreatment were excluded from the analysis due to the very low number of cases.
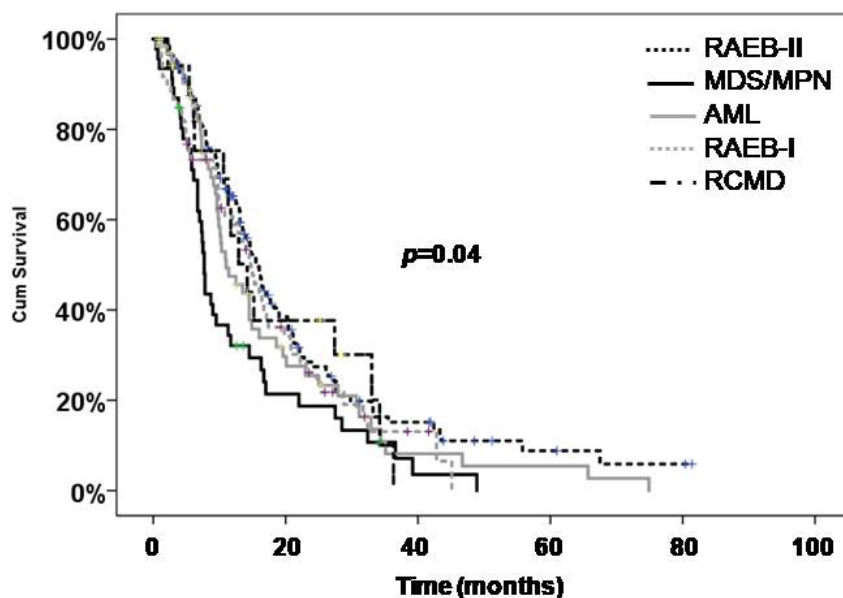
Supplementary Figure S3. Overall survival at azacytidine initiation according to WHO subtype (n=326).
Overall survival (OS) in first line azacytidine treated patients. Overlapping myeloproliferative/Myelodysplastic syndromes and CMML (collectively shown as MDS/MPN) diagnosis conferred significantly lower median OS compared to all other WHO subtypes.
RCMD = refractory cytopenia with multilineage dysplasia; RAEB = refractory anemia with excess blasts; CMML = chronic myelomonocytic leukemia; AML = acute myeloid leukemia; MDS/MPN = Myelodysplastic/myeloproliferative neoplasm.

Supplementary Table 1. Multivariate analysis of prognostic factors for overall survival after AZA initiation in the whole patient cohort (n=326; 253 with full data).

	Univariate analysis		Multivariate analysis	
	Median OS	p-value	HR (95% CI)	p-value
Age		0.019		
<65	17.1			
≥65	12.6			
Sex		0.93		
Male	14.5			
Female	12.9			
WHO classification		0.004		0.054
MDS and low blast count AML	14.5		1	
MDS/MPN	7.7		2.68 (0.98-7.32)	
French Prognostic Scoring System		<0.0001		
Low	27.3		1	
Intermediate	14.5		1.92 (1.22-3.01)	0.0005
High	9.9		3.83 (2.14-6.88)	<0.001
Response to AZA		<0.0001		
CR+CR+PR	27.6		1	
HI or SD	14.0		2.20 (1.53-3.15)	<0.0001
Failure	7.6		4.44 (2.98-6.62)	<0.0001

HR: Hazard ratio; 95% CI: 95% Confidence Intervals.

Supplementary Table 2. Multivariate analysis of prognostic factors for overall survival after AZA failure in patients with available post-HMA score (n=198; 194 with full data)**.**

	Univariate analysis		Multivariate analysis	
	Median OS after AZA failure	p-value	HR (95% CI)	p-value
Sex		0.58		
Male	6.1			
Female	4.9			
WHO classification		0.098		
MDS and low blast count AML	5.9			
MDS/MPN	2.8			
Post-HMA Score		0.0006		0.001
Low	8.3		1	
High	4.8		1.76 (1.27-2.45)	0.001
Response to AZA		0.071		
CR	8.4			
HI or SD	6.0			
Failure	2.9			

HR: Hazard ratio; 95% CI: 95% Confidence Intervals.

Supplementary Table 3. Multivariate analysis of prognostic factors for overall survival after loss of the initial response to AZA (n=82; 67 with full data).

	Univariate analysis		Multivariate analysis	
	Median OS after AZA failure	p-value	HR (95% CI)	p-value
Sex		0.32		
Male	7.9			
Female	4.9			
WHO classification		0.28		
Low blast count AML	6.7			
MDS	14.9			
Post-HMA Score		0.032		0.04
Low	9.2		1	
High	5.6		1.75 (1.03-2.97)	0.04
Immediate AZA withdrawal after loss of response		0.027		0.02
Yes	4.6		1	
No	8.0		1.85 (1.10-3.11)	0.02

HR: Hazard ratio; 95% CI: 95% Confidence Intervals.

Supplementary Table 4. Clinical information of 82 patients who relapsed after an initial response to azacytidine.

Parameters (median, range)	(Immediately stopped AZA, n=37)	(Continued AZA, n=45)	p-value
Age at relapse	73 (51.4-82.3)	73 (50,1-83.1)	0.59
Sex			0.5
Male	25 (67.5%)	27 (60%)	
Female	12 (32.5%)	18 (40%)	
WHO classification at relapse			0.6
RCMD	0 (0%)	2 (4.4%)	
RAEB-I	3 (8.1%)	3 (6.6%)	
RAEB-II	10 (27%)	11 (24.5%)	
Low blast count AML	14 (37.9%)	14 (31.1%)	
N/A	10 (27%)	15 (33.4%)	
IPSS at diagnosis			0.36
Low/Intermediate-1	7 (19%)	6 (13.3%)	
Intermediate-2	13 (35.1%)	24 (53.3%)	
High	13 (35.1%)	13 (28.9%)	
N/A	4 (10.8%)	2 (4.5%)	
IPSS-R at diagnosis			0.93
Low	2 (5.4%)	2 (4.5%)	
Intermediate	5 (13.5%)	5 (11.1%)	
High	15 (40.6%)	19 (42.2%)	
Very high	11 (29.7%)	17 (37.7%)	
N/A	4 (10.8%)	2 (4.5%)	
FPSS (GFM) at diagnosis			0.76
Low	6 (16.2%)	5 (11.1%)	
Intermediate	21 (56.8%)	28 (62.2%)	
High	5 (13.5%)	7 (15.6%)	
N/A	5 (13.5%)	5 (11.1%)	
Post HMA model			0.45
Low	10 (27%)	17 (37.7%)	
High	19 (51.3%)	22 (49%)	
N/A	8 (21.7%)	6 (13.3%)	
Treatment after AZA discontinuation			0.61
Supportive care	16 (43.3%)	20 (44.4%)	
Intensive chemo	10 (27%)	8 (17.6%)	
Low intensity chemo	1 (2.7%)	1 (2.2%)	
Decitabine	5 (13.5%)	2 (4.4%)	
Allo-BMT	4 (10.8%)	3 (6.6%)	
N/A	1 (2.7%)	11 (20.7%)	
Number of completed cycles			0.17
Median (range)	9 (2-30)	13 (4-59)	
Red cell transfusion dependency at diagnosis			0.28
Yes	23 (62.1%)	33 (73.4%)	
No	12 (32.4%)	10 (22.2%)	
N/A	2 (5.5%)	2 (4.4%)	

Abbreviations: IPSS = International Prognostic Scoring System, IPSS-R = revised International Prognostic. Scoring System, WPSS = World Health Organization classification-based Prognostic Scoring System, FPSS = French Prognostic Scoring System, RCMD = refractory cytopenia with multilineage dysplasia, RAEB = refractory anemia with excess blasts, AML=acute myeloid leukemia, N/A=not available/applicable.