NOVEL PREDICTIVE INDICATORS IN PATIENTS WITH HIGHER-RISK MYELODYSPLASTIC NEOPLASMS (HR-MDS) TREATED WITH 5-AZACYTIDINE: CUMULATIVE DATA FROM THE HELLENIC MDS STUDY GROUP

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Introduction: 5-azacytidine (AZA) is the mainstay of treatment for HR-MDS patients. Currently there is neither a widely accepted predictive model nor a serviceable biomarker of response and/ or outcome that could offer a timely and valid estimation of the expected benefit from AZA and help to tailor treatment.

Herein we summarize data from relevant studies of the Hellenic National Registry of Myelodysplastic and Hypoplastic Syndromes (HNRMHS), a nationwide retrospective observational study which collected data from **1167 patients** who were **treated with AZA** from 28 centers in Greece.

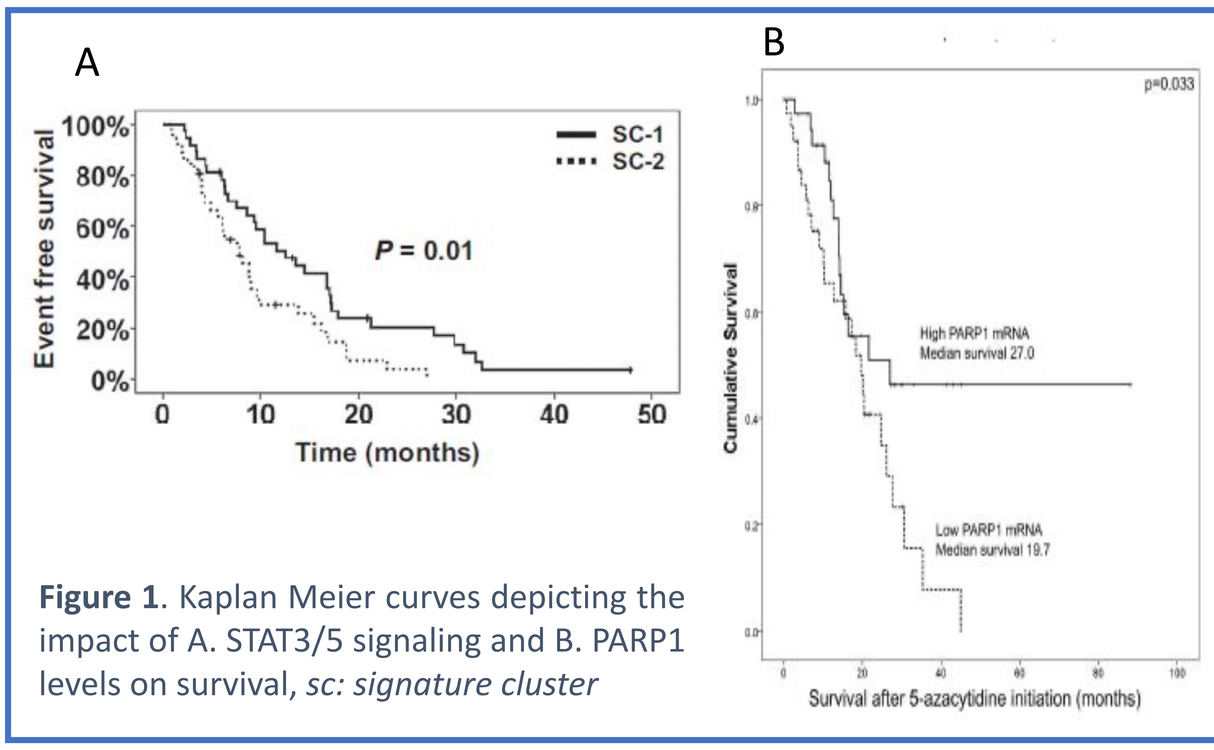

Figure 1. Kaplan Meier curves depicting the impact of A. STAT3/5 signaling and B. PARP1 levels on survival, *sc: signature cluster*

Results: We identified cytogenetic and molecular characteristics such as monosomal karyotype[1], the STAT3/5 biosignature in pretreatment CD34$^+$ cells[2], low bone marrow levels of PARP1[3] (poly ADP-ribose polymerase 1) and HIF-1a[4] (hypoxia inducible factor -1 alpha subunit) and increased levels of the M1 subunit of the RNR[5] (ribonucleotide reductase) that compromise response and/ or overall survival after AZA therapy (**Figure 1**).

Easily measurable biomarkers that proved useful in predicting poor response to AZA treatment include baseline serum ferritin levels >520 ng/ml (*p=0.003*) and an estimated GFR <45ml/min/1.73m^2 (**Figure 2**, *p=0.039*)[6].
Body mass index and relative dose intensity had no effect on predicting outcome after treatment with AZA (*p=0.77*)[7].

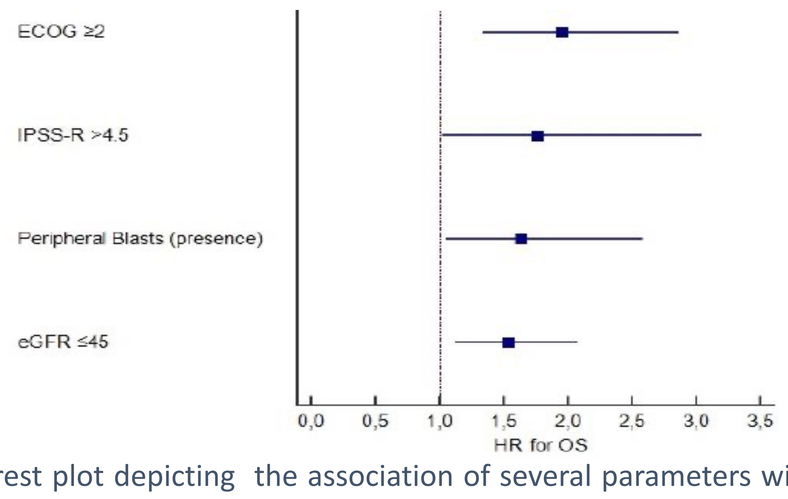

Figure 2. Forest plot depicting the association of several parameters with overall survival, *eGFR: estimated glomerular filtration rate, HR: hazard ratio, OS: overall survival*

Finally, in the largest series to date we found no benefit of AZA in unselected patients with intermediate-risk MDS[8] (**Figure 3**), but we showed that AZA is still beneficial in patients older than 80 years and those achieving stable disease as best response after 6 months of treatment[9].

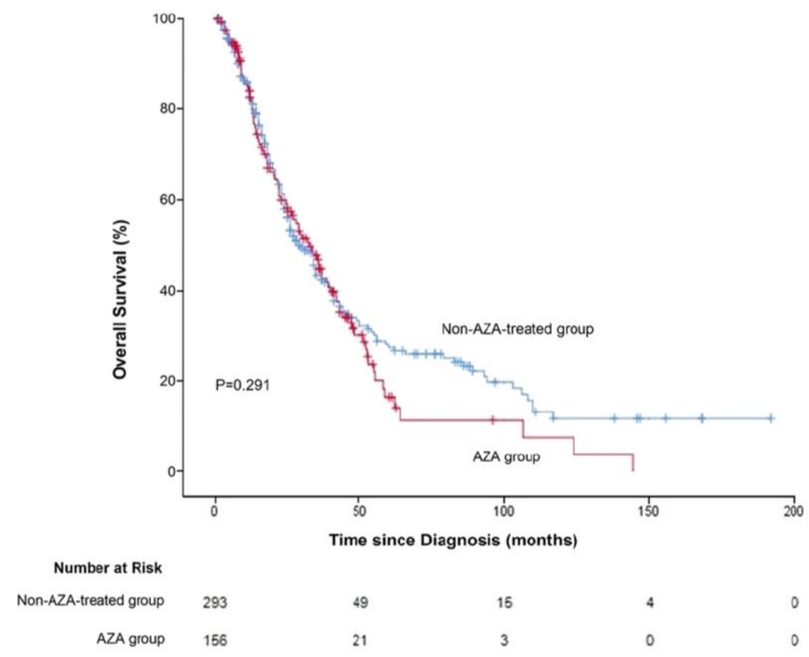

Figure 3. Kaplan-Meier curve of OS among patients with intermediate-risk MDS who received AZA, as compared with patients who did not

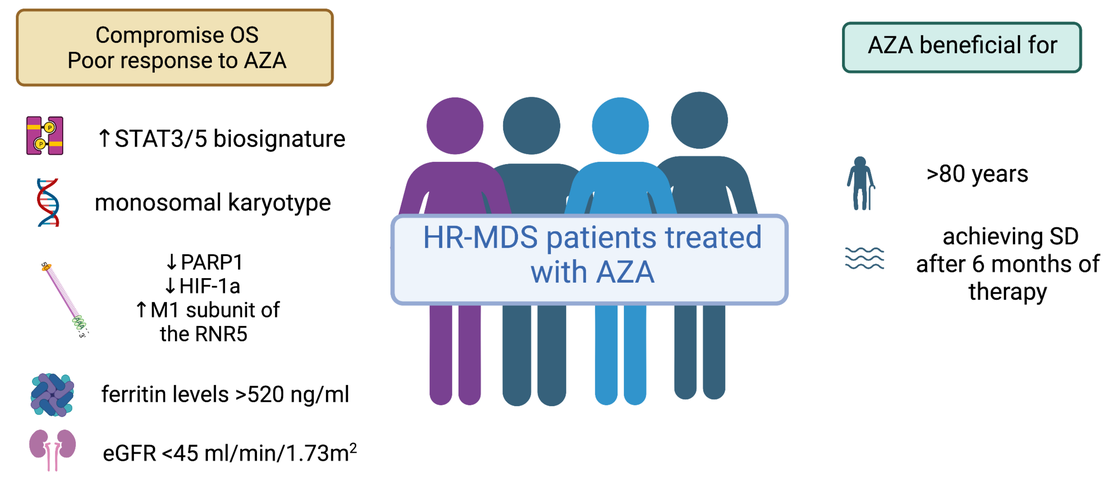

Figure 4. Clinical, laboratory and molecular parameters have been identified as potential predictors of response and outcome to AZA therapy in HR-MDS patients

Conclusions: Numerous clinical, laboratory and molecular parameters have been identified as potential predictors of response and outcome to AZA therapy in HR-MDS patients (**Figure 4**). Validation of our findings in independent cohorts may help clinical decision making in routine practice, but also enable the appropriate patient stratification in clinical trials of AZA combinations in HR-MDS.

Literature
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