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LETTER

Prognostic stratification in venetoclax-based acute myeloid leukemia treatments: the molecular prognostic risk signature tested in a real-world setting

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Data Availability

The aggregated datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request

Authorship Contributions

GC, MP and AMV designed research, analyzed and interpreted data, and wrote the manuscript. FM, GG, BB, LF, FC, EQ, AP, JC, GR, FP, LS, CM, FV, PG contributed data. GC, MP, FM and AMV performed research. All authors participated in interpreting the data, checked and approved the final version of the manuscript.

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TO THE EDITOR:

Genotype-based stratification models used in acute myeloid leukemia (AML), such as the European LeukemiaNet (ELN) 2022 risk classification[1], have been developed based on patients treated in a conventional intensive chemotherapy setting and their performance in outcome prediction for patients treated with venetoclax (VEN)-based combinations is unsatisfactory. Bataller et al.[2] recently reported a single-center retrospective study in newly diagnosed (ND) AML treated with VEN and hypomethylating agents - either included in, or outside, a clinical trial - aiming to validate the molecular prognostic risk signature (mPRS) developed by Döhner et al. using mutational data from the phase 1b trial (NCT02203773) and the pivotal phase 3 VIALE-A trial.[3] In the particular study, according to the mutational status of 4 genes, patients were allocated to a lower benefit (*TP53*^{mut}), an intermediate benefit (*FLT3*-ITD^{mut} or *N/KRAS*^{mut}) and a higher benefit group (none of the above).[3] The construction of this model stemmed from evidence that refractoriness and adaptive resistance to VEN are largely attributable to the presence and/or emergence of clones harboring the aforementioned mutations.[4] In the study of Bataller et al., mPRS effectively stratified treatment naïve AML patients in the three risk groups with statistically significant differences in median overall survival (OS) and event free survival (EFS).[2] A different stratification model for relapsed/refractory (R/R) AML patients treated with VEN-based combinations, proposed by Krüger et al.[5], stratifies patients in three risk groups, based on the mutation profile of 8 genes, resulting in a favorable (*STAG2*^{mut}, *BCOR*^{mut} or *SF3B1*^{mut}), adverse (*TP53*^{mut}, any *FLT3*^{mut}, *CBL*^{mut}, *PTPN11*^{mut} or *NF1*^{mut}) and intermediate risk category (none of the above).

We set out to assess the reproducibility of those observations in ND AML patients and also to extend the analysis to R/R patients in our institutional real-world cohort of patients receiving VEN-based combinations from January 2015 to December 2023. The study was approved by the local institutional review board. Written informed consent was obtained in accordance with the Declaration of Helsinki. The performance of different stratification models was assessed and compared using Harrell's concordance index (C-index).

We identified 89 R/R and 61 ND patients; their clinical characteristics are summarized in Table S1. Partner drug was azacitidine in 129 (86%), decitabine in 8 (6%) and low-dose cytarabine in 12 (8%) patients.

According to the mPRS stratification model in the ND cohort, 35 (57%), 16 (26%) and 10 (17%) patients were allocated to the higher-, intermediate- and lower-benefit group, respectively. The overall response rate (ORR) - that included patients experiencing complete remission (CR) and CR with incomplete hematological recovery (CRi) - was 77%, 19% and 40% ($p<0.001$) respectively. When using the ELN 2022 risk stratification model, ORR was 54%, 37%, and 57% in the favorable, intermediate and adverse category, and the difference was not statistically significant ($p=0.593$). Among patients in CR or CRi with available minimal residual disease (MRD) data, 11/24 (46%) in the higher-, 0/2 (0%) in the intermediate- and 0/3 (0%) in the lower-benefit mPRS group were MRD negative ($p=0.157$).

We then compared the predictive power of the mPRS model and the ELN 2022 classification system for OS and EFS. Median OS was 30, 11, and 4 months in the higher-, intermediate- and lower-benefit group according to the mPRS model ($p<0.001$; C-index=0.69 - Figure 1A and D) and not reached, 27, and 11 months for favorable, intermediate, and adverse

ELN 2022 category, respectively (p=0.177; C-index=0.590). Median EFS was 13, 1, and 2 months for the mPRS groups (p<0.001; C-index=0.70 - Figure 2A and D) and 25, 1, and 6 months for the ELN 2022 categories (p=0.088; C-index=0.49). The mPRS vs ELN 2022 Z-score was 2.22 (p=0.030, Figure 1D) for OS and 4.4 for EFS (p<0.001 Figure 2D). In keeping with the observations by Döhner et al.[3] and Bataller et al.[2], mPRS outperformed ELN 2022 in ND AML patients.

We then set our focus on R/R patients receiving VEN-based lower intensity salvage treatments and replicated the above analyses in this setting. Forty-eight (54%), 31 (35%) and 10 (11%) of patients were stratified as higher-, intermediate- and lower-benefit group, respectively. The ORR was 73%, 48% and 20% in the three groups (p=0.003) and 80%, 52%, 58% in the favorable, intermediate and adverse ELN 2022 risk categories (p=0.147). In the relapsed subcohort, the ORR was 68%, 50% and 33% in the three mPRS groups (p=0.361) and 71%, 40% and 63%, in the three ELN 2022 categories (p=0.032). In the refractory subcohort, the ORR was 69%, 44% and 14% in the mPRS groups (p=0.051) and 100%, 43% in the intermediate and adverse category by using the ELN 2022 risk stratification (p= 0.197). Among patients of the R/R cohort in composite CR with available MRD data, 18/35 (51%) in the higher-, 6/15 (40%) in the intermediate- and 2/2 (100%) in the lower-benefit mPRS group were MRD negative (p=0.268). HSCT actualization rate differed in the three mPRS categories, with borderline statistical significance (90%, 67% and 63% respectively, p=0.064). Median OS of R/R patient was 24, 9, and 6 months in the higher-, intermediate- and lower-benefit group according to the mPRS (p=0.011; C-index=0.61 - Figure 1B and D); median EFS was 15, 6, and 1 months, respectively (p<0.001; C-index=0.63 - Figure 2B and D). Similar figures for median OS using ELN 2022 categorization were 46, 11 and 11 months for favorable, intermediate and adverse risk

categories (p=0.091; C-index=0.54) and 46, 9 and 6 months for median EFS, respectively (p=0.024; C-index=0.58). The mPRS vs ELN 2022 Z-score was 1.20 (p=0.220) for OS and 1.00 (p=0.310) for EFS. Comparable results were obtained by censoring at the time of hematopoietic stem cell transplantation.

Then we evaluated the goodness of fit for outcome prediction of the model independently developed by Krüger et al. in our R/R cohort. The mutational frequency of the genes that are included in Kruger algorithm in our series is shown in Table S1. According to the model, 8 (9%), 51 (57%) and 30 (34%) patients were allocated to the favorable, intermediate and adverse group, with respective ORR of 88%, 71% and 40% (p=0.006). The median OS was 37, 14 and 9 months for the favorable, intermediate and adverse category according to the model (p=0.061; C-index 0.58 - Figure 1C and D); the median EFS was 15, 6 and 1 month, respectively (p <0.001; C-index 0.64 - Figure 2C and D). This risk stratification model exhibited slightly better performance than the ELN 2022, but not the mPRS model. In detail, the Z-score for OS for the Krüger's vs ELN 2022 model was 0.59 (p=0.550) and versus the mPRS -0.81 (p=0.410, Figure 1D).

Finally, we evaluated the performance of the mPRS model in the entire cohort of patients treated with VEN-based treatments (Figure S1). Median OS was 30, 9, and 6 months in the higher, intermediate and lower benefit group according to mPRS (p<0.001; C-index=0.64) and 46, 14, and 11 months for favorable, intermediate, and adverse ELN 2022 category (p=0.016; C-index=0.56). Median EFS was 15, 3, and 1 months in the mPRS groups (p<0.001; C-index=0.66) and 46, 6, and 6 months in the ELN 2022 categories, respectively (p=0.013; C-index=0.55). The calculated Z-score for mPRS vs ELN 2022 was 2.28 (p=0.020) and 3.21 (p=0.001) for OS and EFS,

respectively, in the entire cohort of VEN-treated patients, reinforcing better performance of the mPRS model for prediction of OS and EFS.

As VEN-based regimens are steadily taking the lead in the management of elderly/unfit patients, it became soon apparent that conventional stratification algorithms (i.e., ELN 2022 risk stratification) are shortcoming in effectively predicting clinical outcomes in such therapeutic context. In fact, susceptibility and resistance to VEN and conventional intensive therapy are believed to originate from different mechanisms. As a consequence, there is an unmet need for stratification model(s) that could provide a reliable tool for clinicians to inform their decisions and to facilitate communication with patients and families. The recently developed mPRS model holds the promise to effectively inform prognosis in ND patients, but whether it is accurate also in the R/R settings, remains unclear. On the other hand, the purpose of VEN-based treatment in the two clinical settings (ND and R/R) often differs, as do the relative patient populations. The former context generally involves elderly/unfit patients with the primary aim of prolonging survival and the observed inadequacy at estimating initial response does not diminish the utility of mPRS. Conversely, in R/R setting, VEN provides an effective and less-toxic bridge-to transplant, and prediction model performance should be measured accordingly. Furthermore, the observed variability in genotypic groups from different models (i.e., mPRS, Krüger) likely reflects the inadequacy of conventional bulk sequencing in capturing the dynamics of sub-clones, their varying dominance, and sensitivity to VEN-based therapies.

Overall, our data from a real-world setting are confirmatory of the goodness of mPRS in terms of OS and EFS prediction in the ND setting, where it clearly identifies three distinct prognostic groups, and suggest its potential role also for R/R patients, at least for the prediction

of the likelihood of response, which is of paramount importance in this subset; therefore, mPRS model might be suitably used in clinical practice for all patients receiving VEN-based regimens and - together with already validated criteria to assess the fitness[6] - could be used to guide the choice between different therapeutic strategies for AML patients. This notwithstanding, further efforts are warranted to develop and validate on larger series new models to predict response in VEN-based regimens, specifically for R/R patients who are treated with the intent of bridging to stem cell transplantation; otherwise, in case of predicted unfavorable outcome, these patients might be more suitably addressed to agents in clinical development.

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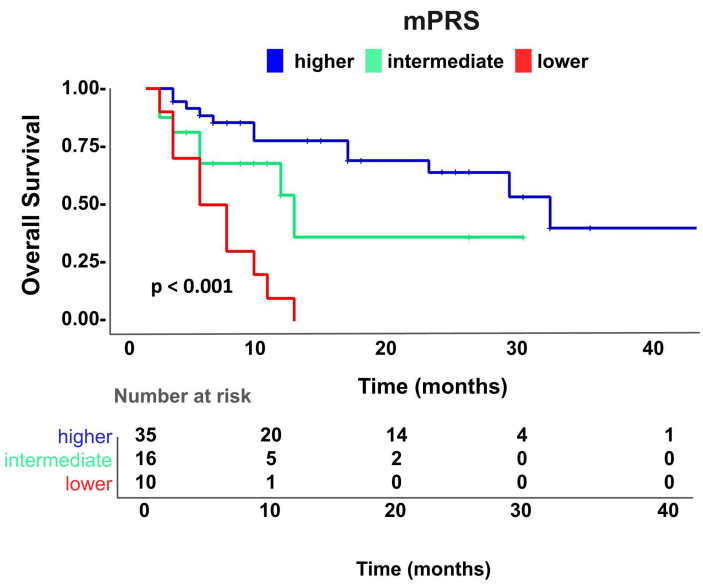
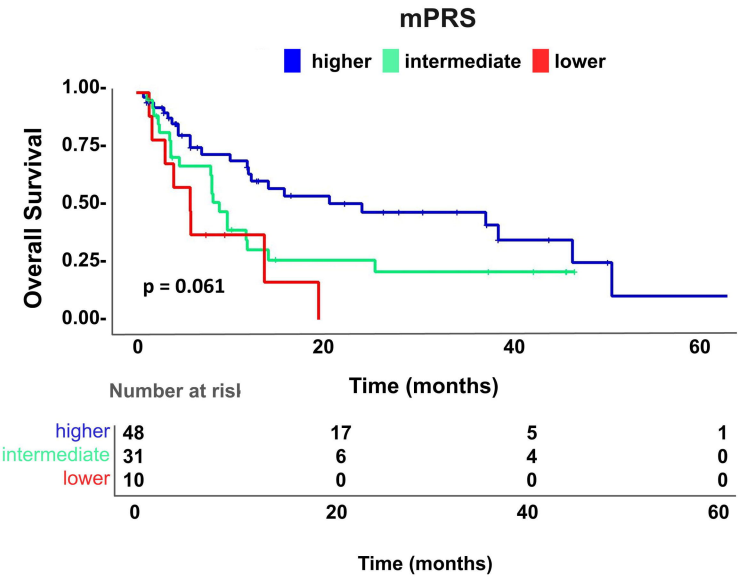
FIGURE 1. Clinical outcome according to the mPRS model in the ND cohort and to the mPRS and the Krüger model in the RR cohort - OS according to the mPRS in the ND cohort. (A) OS according to the mPRS in the RR cohort. (B) OS according to Krüger model in the RR cohort. (C) C-index comparisons (D). *Abbreviations: OS, overall survival; mPRS, molecular prognostic risk signature; ELN, European LeukemiaNet; HR, hazard ratio; CI, confidence interval; ND, newly diagnosed; RR, relapsed or refractory.*

FIGURE 2. Clinical outcome according to the mPRS model in the ND cohort and to the mPRS and the Krüger model in the RR cohort - EFS according to the mPRS in the ND cohort. (A) EFS according to the mPRS in the RR cohort. (B) EFS according to Krüger model in the RR cohort. (C) C-index comparisons (D). *Abbreviations: EFS, event free survival; mPRS, molecular prognostic risk signature; ELN, European LeukemiaNet; HR, hazard ratio; CI, confidence interval; ND, newly diagnosed; RR, relapsed or refractory*.

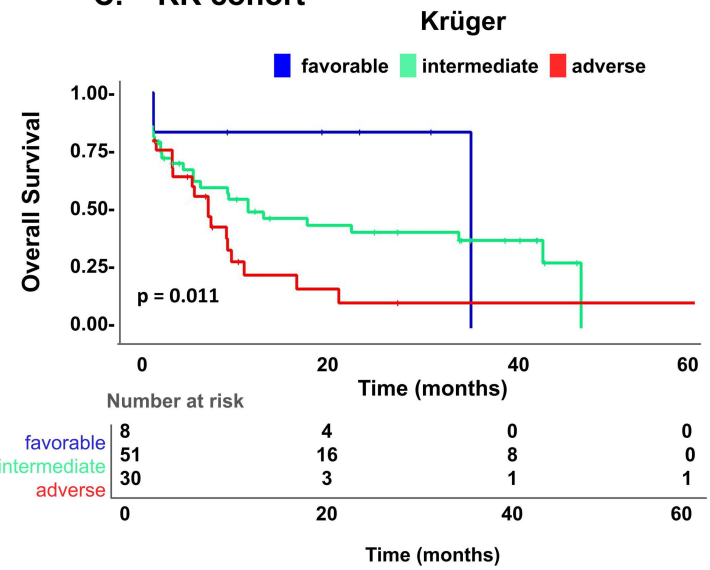
A. ND cohort



B. RR cohort



C. RR cohort

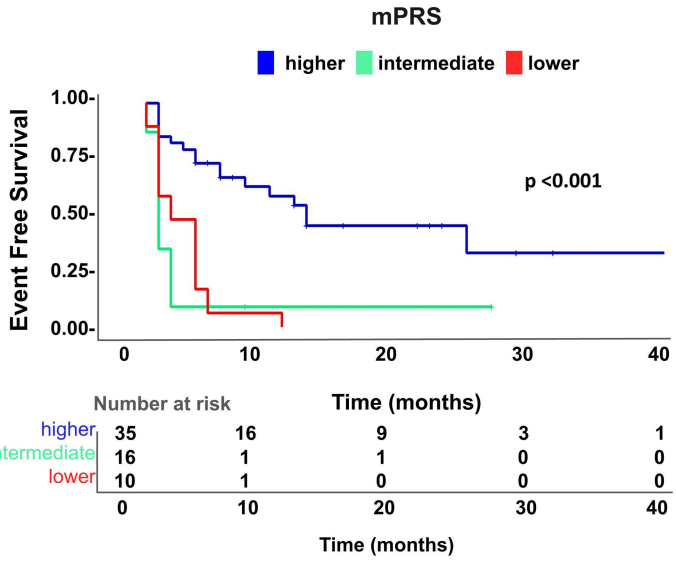


D. C-INDEX

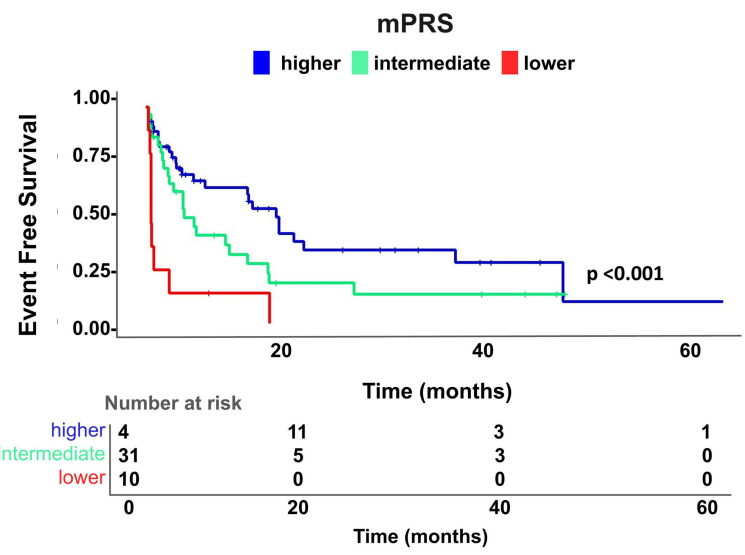
	C-INDEX mPRS	C-INDEX ELN 2022	C-INDEX Krüger model	Z-SCORE
ND cohort	0.69	0.59	-	**2.22** (p=0.030)
RR cohort	0.61	0.54	0.58	mPRS vs ELN2022 **1.20** (p=0.220) Krüger's vs mPRS **-0.81** (p=0.410)

	Median OS, months (95% CI)	HR (95% CI)	P
mPRS - ND cohort (panel A)			
higher benefit	30.0 (19.0-40.9)		**<0.001**
intermediate benefit	11.0 (3.2-18.8)	2.30 (0.87-6.06)	0.091
lower benefit	4.0 (0.9-7.0)	7.23 (2.83-18.43)	**<0.001**
mPRS - RR cohort (panel B)			
higher benefit	23.6 (0.0-51.9)		**0.015**
intermediate benefit	8.7 (6.7-10.7)	1.81 (0.98-3.34)	0.056
lower benefit	5.6 (2.9-8.4)	3.16 (1.37-7.25)	**0.007**
Krüger model - RR cohort (panel C)			
favorable	37.0 (NA-NA)		0.073
intermediate	13.8 (2.1-25.5)	2.33 (0.56-9.85)	0.246
adverse	9.5 (6.8-12.2)	3.94 (0.92-16.95)	0.066

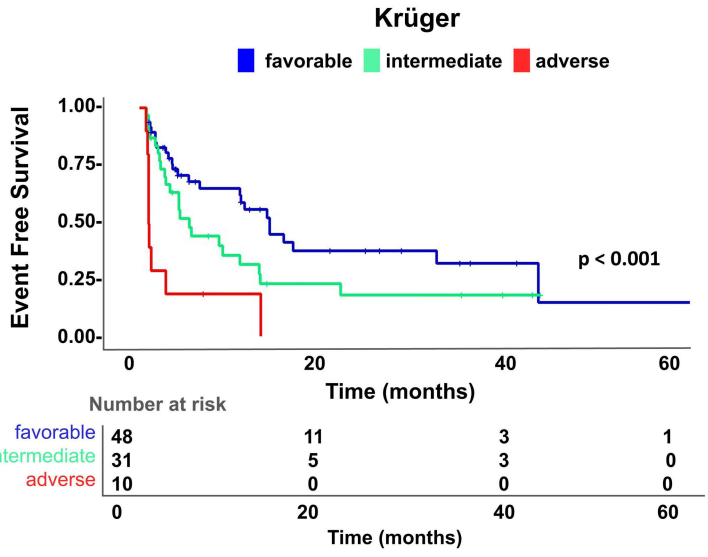
A. ND cohort



B. RR cohort



C. RR cohort



D. C-INDEX

	C-INDEX mPRS	C-INDEX ELN 2022	C-INDEX Krüger model	Z-SCORE
ND cohort	0.70	0.49	-	**4.40** (p<0.001)
RR cohort	0.63	0.58	0.64	mPRS vs ELN2022 **1.00** (p=0.310)

	Median EFS, months (95% CI)	HR (95% CI)	P
mPRS - ND cohort (panel A)			
higher benefit	13.0 (0.2-25.7)		**<0.001**
intermediate benefit	1.0 (0.5-1.5)	4.17 (1.98-8.80)	**<0.001**
lower benefit	2.0 (0.0-4.3)	3.93 (1.75-8.89)	**0.001**
mPRS - RR cohort (panel B)			
higher benefit	14.9 (9.4-20.3)		**<0.001**
intermediate benefit	5.7 (3.5-7.9)	1.63 (0.92-2.89)	0.098
lower benefit	1.0 (0.8-1.2)	4.83 (2.20-10.62)	**<0.001**
Krüger model - RR cohort (panel C)			
favorable	14.9 (11.5-NA)		**0.003**
intermediate	5.7 (3.5-13.8)	2.79 (0.66-11.70)	0.162
adverse	1.1 (1.0-NA)	6.09 (1.43-25.93)	**0.015**

SUPPLEMENTARY TABLE 1. Clinical characteristics of the study patients

Characteristic	Whole cohort (n = **150**)	ND cohort (n = **61**)	RR cohort (n = **89**)	P*	mPRS groups - whole cohort			P**
					Higher benefit (n = **83**, 56%)	Intermediate benefit (n = **47**, 31%)	Lower benefit (n = **20**, 13%)	
Age (range) y	64 (19-86)	72 (35-86)	58 (19-74)	**<.001**	65 (25-83)	65 (19-81)	60 (42-86)	.745
Male sex	89 (59%)	36 (59%)	53 (59%)	.949	52 (62%)	23 (49%)	14 (70%)	.180
ELN 2022, n (%)								
favorable	31 (21%)	11 (18%)	20 (23%)	.509	22 (27%)	9 (19%)	0 (0%)	**.030**
intermediate	29 (19%)	8 (13%)	21 (23%)	.110	15 (18%)	14 (30%)	0 (0%)	**.017**
adverse	90 (60%)	42 (69%)	48 (54%)	.066	46 (55%)	24 (51%)	20 (100%)	**<.001**
Cytogenetics, n (%)								
normal	82 (55%)	34 (56%)	48 (54%)	.826	52 (67%)	26 (55%)	4 (20%)	**.003**
t(8;21) or inv(16)	9 (6%)	2 (3%)	6 (7%)	.353	5 (6%)	4 (8%)	0 (0%)	.406
Chromosome 5 or 7 or 17 abnormality	7 (5%)	3 (5%)	4 (4%)	.902	4 (5%)	2 (4%)	1 (5%)	.986
Complex karyotype	19 (13%)	10 (16%)	9 (10%)	.255	4 (5%)	0 (0%)	13 (65%)	**<.001**
Mutation, n (%)								
NPM1	34 (23%)	11 (18%)	23 (26%)	.261	17 (20%)	15 (32%)	2 (10%)	.113
TET2	18 (12%)	10 (16%)	8 (9%)	.170	12 (14%)	4 (9%)	2 (10%)	.579
ASXL1	27 (18%)	17 (28%)	10 (11 %)	**.009**	16 (19%)	11 (23%)	0 (0%)	.066
DNMT3A	45 (30%)	14 (23%)	31 (35%)	.118	25 (30%)	17 (36%)	3 (15%)	.224
IDH1	13 (9%)	6 (10%)	7 (8%)	.673	8 (10%)	5 (11%)	0 (0%)	.328
IDH2	30 (20%)	10 (16%)	20 (23%)	.360	24 (29%)	6 (13%)	0 (0%)	**.004**
RUNX1	29 (19%)	15 (25%)	14 (16%)	.177	20 (24%)	8 (17%)	1 (5%)	.135
TP53	20 (13%)	10 (16%)	10 (11%)	.361	0 (0%)	0 (0%)	20 (100%)	NA
FLT3 ITD	25 (17%)	13 (21%)	12 (13%)	.206	0 (0%)	25 (53%)	0 (0%)	NA
FLT3 TKD	5 (3%)	3 (5%)	2 (2%)	.370	3 (4%)	1 (2%)	1 (5%)	.816
CBL	1 (1%)	0 (0%)	1 (1%)	.406	1 (1%)	0 (0%)	0 (0%)	.669
PTPN11	10 (6%)	3 (5%)	7 (8%)	.477	5 (6%)	4 (8%)	1 (5%)	.818
NF1	1 (1%)	0 (0%)	1 (1%)	.406	1 (1%)	0 (0%)	0 (0%)	.669
STAG2	11 (7%)	8 (13%)	3 (3%)	.521	8 (10%)	3 (6%)	0 (0%)	.317
BCOR	13 (9%)	7 (11%)	6 (7%)	.311	11 (13%)	2 (4%)	0 (0%)	.070
SF3B1	8 (5%)	4 (6%)	4 (4%)	.580	6 (7%)	2 (4%)	0 (0%)	**.042**
Secondary AML, n (%)	31 (20%)	19 (31%)	12 (13%)	**.008**	16 (19%)	9 (19%)	6 (30%)	.541
Partner drug, n (%)								
Azacitidine	129 (86%)	60 (98%)	70 (79%)	**<.001**	72 (87%)	40 (85%)	17 (90%)	.864
Decitabine	8 (6%)	1 (2%)	7 (8%)	.095	3 (4%)	3 (6%)	2 (10%)	.484
LD-ARAC	12 (8%)	0 (0%)	12 (14%)	**.002**	8 (9%)	4 (9%)	0 (0%)	.357
Response, n (%)								
ORR (CR or CRi)	86 (57%)	33 (54%)	53 (59%)	.507	62 (75%)	17 (36%)	7(35%)	**<.001**

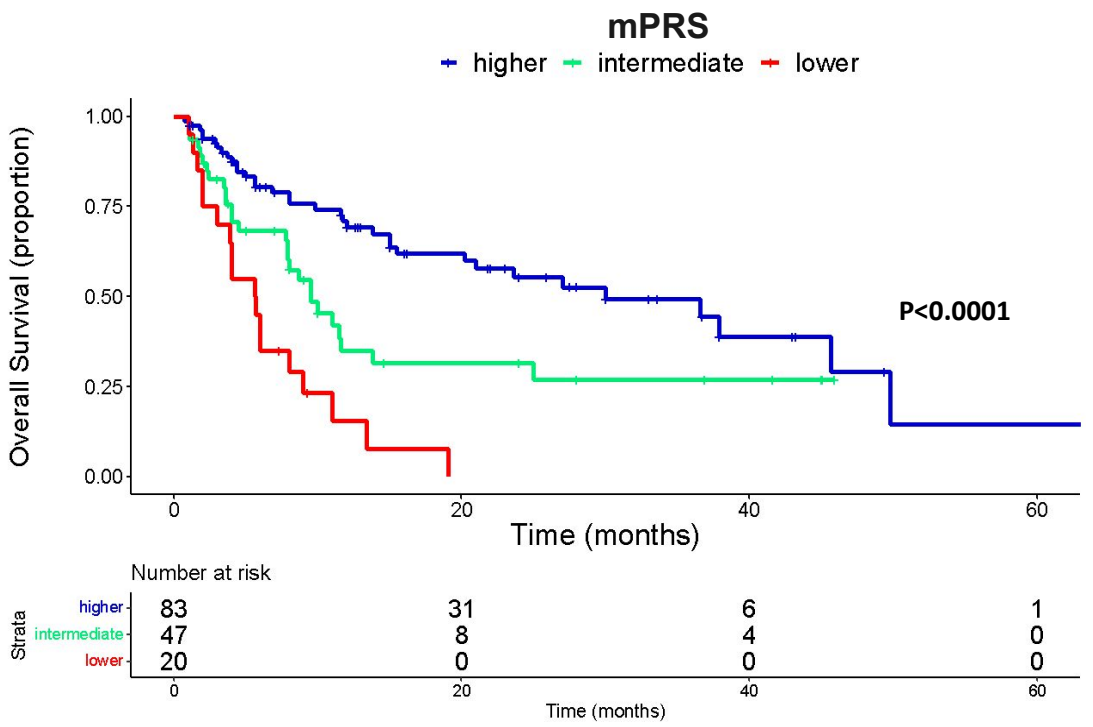
Abbreviations: AML, acute myeloid leukemia; ND, newly diagnosed; RR, relapsed or refractory; mPRS, molecular prognostic risk signature; ELN, European LeukemiaNet; LD-ARAC, low dose cytarabine; CR, complete remission; CRi, CR with incomplete hematological recovery; ORR, overall response rate; NA, not available.

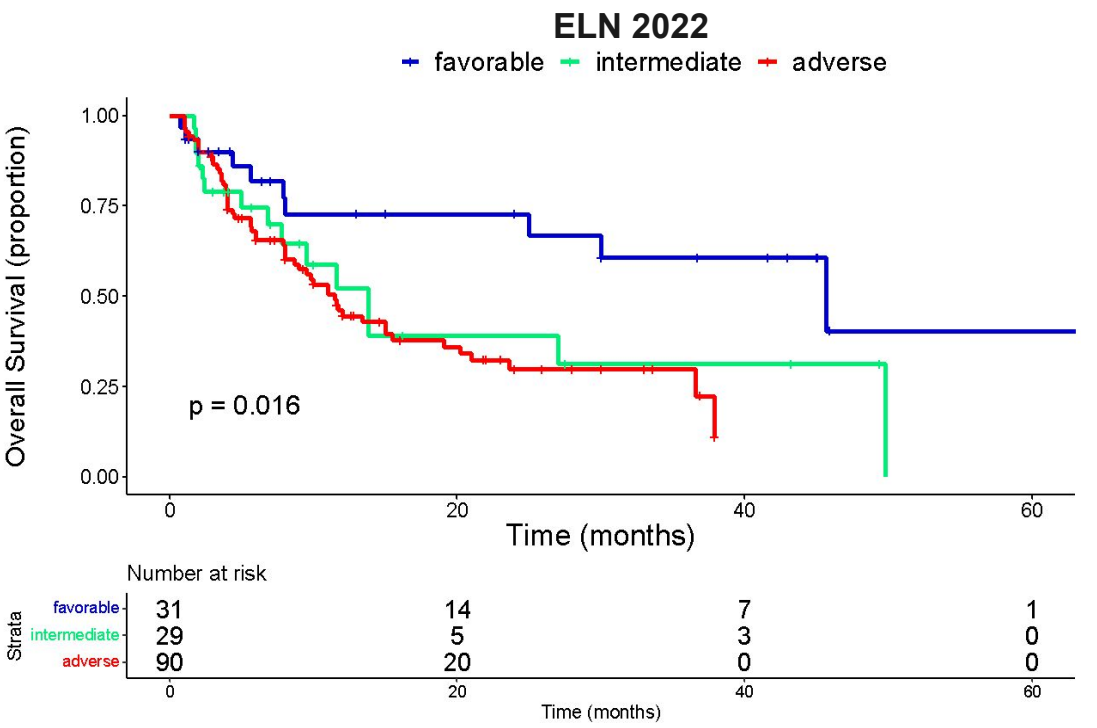
*p-value is calculated between ND cohort and RR cohort

**p-value is calculated between higher-, intermediate- and lower-benefit group

SUPPLEMENTARY FIGURE 1. Clinical outcome according to the mPRS and ELN2022 model in the entire cohort - OS according to the mPRS and ELN2022 model. (A) EFS according to the mPRS and ELN2022 model. (B) *Abbreviations: OS, overall survival; EFS, event free survival; mPRS, molecular prognostic risk signature; ELN, European LeukemiaNet; HR, hazard ratio; CI, confidence interval.*

A.





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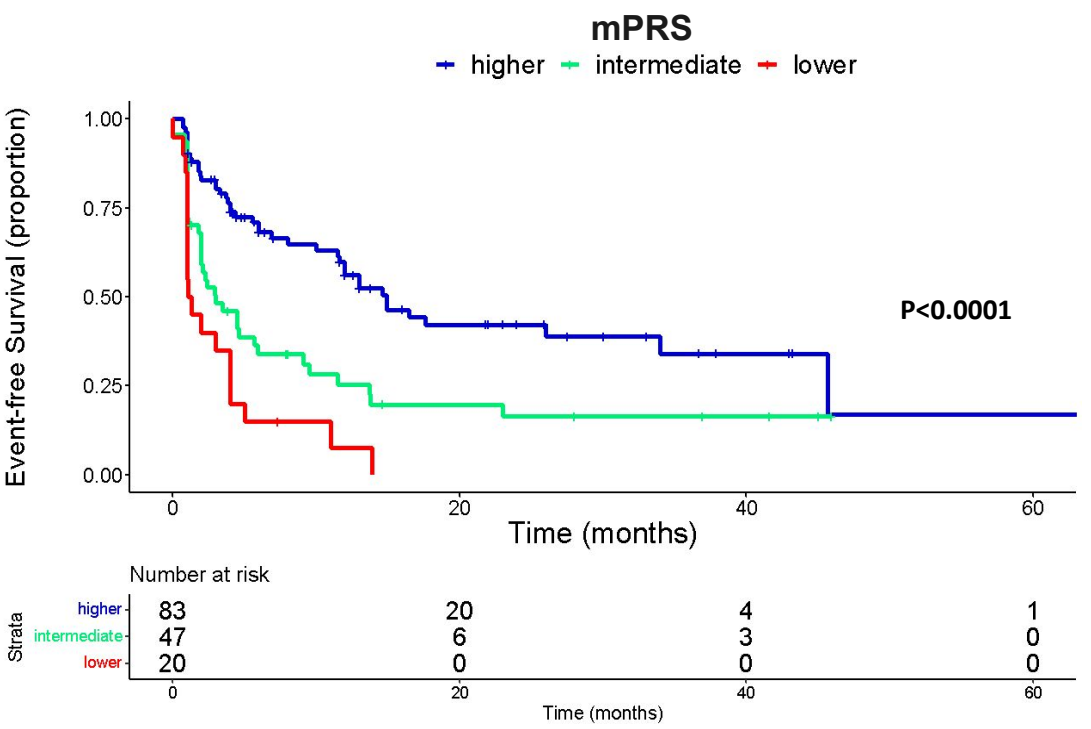

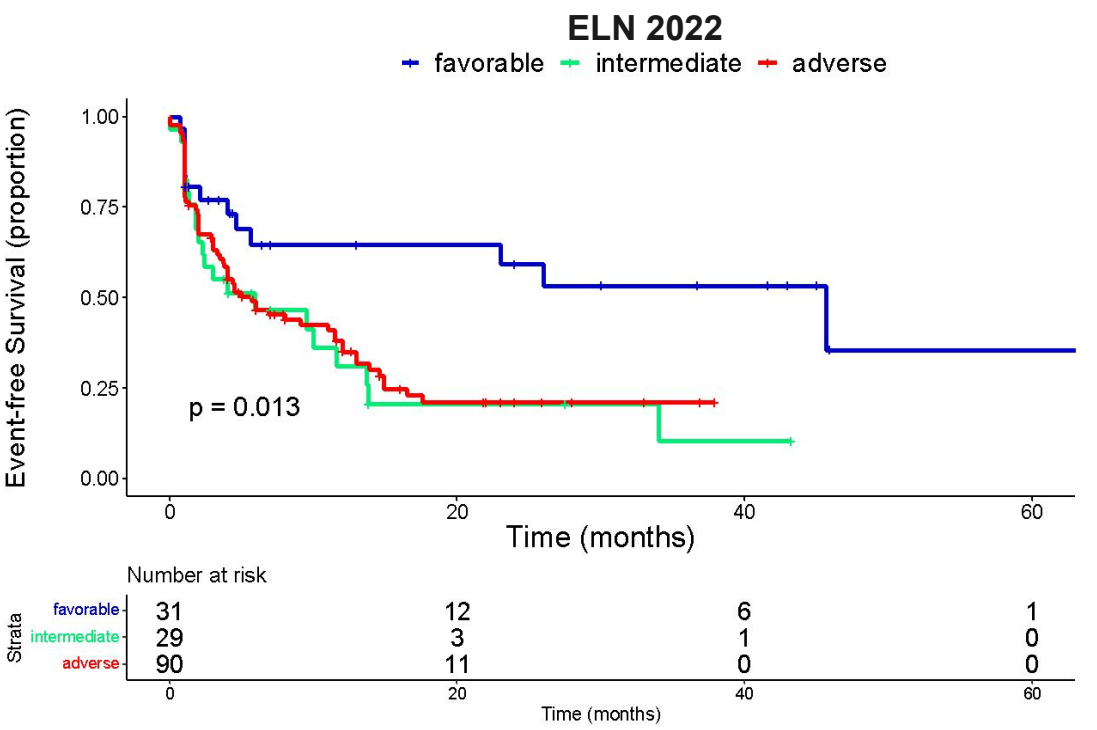

	Median OS, months (95% CI)	HR (95% CI)	P	Median EFS, months (95% CI)	HR (95% CI)	P
mPRS						
higher benefit	30.0 (13.8-46.2)		**<0.001**	14.9 (10.1-19.6)		**<0.001**
intermediate benefit	9.5 (6.5-12.6)	1.99 (1.19-3.32)	**0.008**	3.0 (0.2-5.6)	2.20 (1.40-3.44)	**0.001**
lower benefit	5.6 (2,0-9.3)	4.69 (2.58-8.55)	**<0.001**	1.1 (0.4-1.9)	4.28 (2.44-7.50)	**<0.001**
ELN 2022						
favorable	45.6 (18.3-73.0)		**0.022**	45.6 (15.4-75.9)		**0.020**
intermediate	13.8 (8.8-18.7)	2.21 (0.99-4.95)	**0.054**	5.9 (0.0-14.8)	2.57 (1.26-5.26)	**0.010**
adverse	11.5 (9.1-13.9)	2.66 (1.33-5.32)	**0.006**	5.7 (1.9-9.5)	2.30 (1.23-4.30)	**0.009**