CDKN1B, encoding the cyclin-dependent kinase inhibitor 1B (p27), is located in the minimally deleted region of 12p abnormalities in myeloid malignancies and its low expression is a favorable prognostic marker in acute myeloid leukemia

Claudia Haferlach,[1] Ulrike Bacher,[2] Alexander Kohlmann,[1] Sonja Schindela,[1] Tamara Alpermann,[1] Wolfgang Kern,[1] Susanne Schnittger,[1] and Torsten Haferlach[1]

[1]MLL, Munich Leukemia Laboratory, Munich; [2]Interdisciplinary Clinic for Stem Cell Transplantation, University of Hamburg, Germany

Citation: Haferlach C, Bacher U, Kohlmann A, Schindela S, Alpermann T, Kern W, Schnittger S, and Haferlach T. CDKN1B, *encoding the cyclin-dependent kinase inhibitor 1B (p27), is located in the minimally deleted region of 12p abnormalities in myeloid malignancies and its low expression is a favorable prognostic marker in acute myeloid leukemia. Haematologica 2011;96(6):829-836. doi:10.3324/haematol.2010.035584*

Online Supplementary Appendix

Correlation of CDKN1B *expression with clinical outcomes in acute myeloid leukemia*

A. Separation of the patients with acute myeloid leukemia according to quartiles based on CDKN1B *expression levels as determined in the cohorts of patients with acute myeloid leukemia and myelodysplastic syndrome*

When the AML patients (n=286) were separated according to quartiles of *CDKN1B* expression resulting from analysis of the AML/MDS cohorts in combination, patients from the 1st quartile had superior median overall survival (not reached) than those from the 2nd (361 days; *P*=0.002), 3rd (551 days; *P*=0.046), and 4th quartiles (453 days; *P*=0.050; Figure S1A). Patients from the 1st quartile had superior event-free survival (947 days) when compared to those in the 2nd (164 days; *P*=0.006) and 3rd quartiles (331 days; *P*=0.059) (Figure S1B).

B. Separation of the patients with acute myeloid leukemia based on CDKN1B *expression levels as separately determined in the cohort of patients with acute myeloid leukemia*

These analyses were repeated in the AML patients (n=286) using *CDKN1B* expression levels determined separately in this cohort alone. Patients were subdivided into four quartiles as follows: *CDKN1B* expression levels from the patients of the (lowest) 1st quartile (n=71 patients) ranged from 83.6 to 1,142.2. The 2nd quartile (n=72) showed expression ranging from 1,142.5 – 1,505.8, the 3rd (n=72) from 1,508.6 to 1,962.8, and the 4th (n=71) from 1,973.2 to 4,498.2. According to the upper range of the expression levels encompassing the 1st quartile, an expression level of 1,142.5 was used as the threshold to separate cases with low expression (expression level ≤1,142.5; "low expressers"; 1st quartile) from those with intermediate/high *CDKN1B* expression (expression level >1,142.5; 2nd - 4th quartiles; "intermediate/high expressers"). Seventy-one AML patients (25.0% of the cohort) showed an expression level <1,142.5 and were considered to be "low *CDKN1B* expressers" according to the above definition.

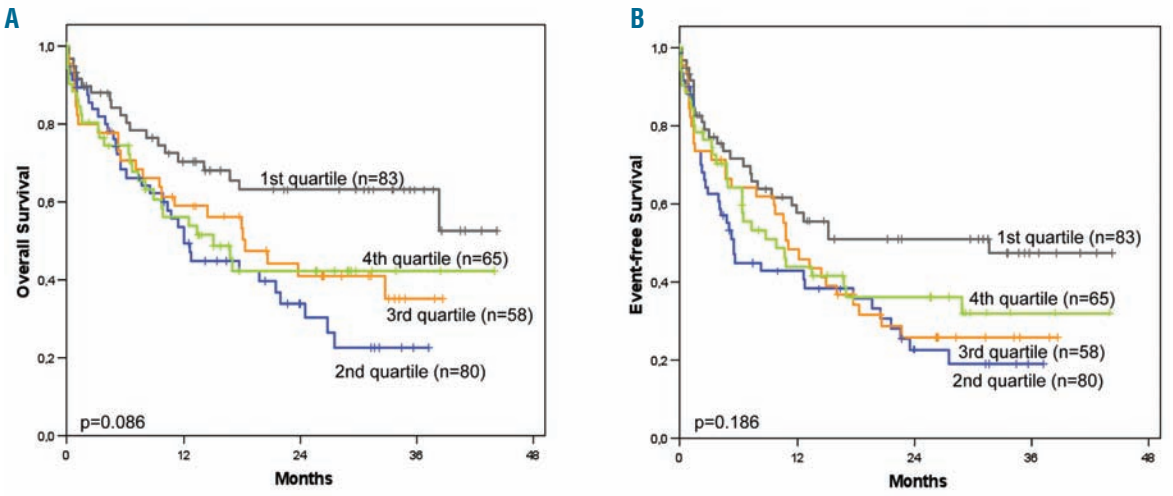
The "low *CDKN1B* expressers" had a significantly better median overall survival compared to the "intermediate/high expressers" (1150 *versus* 509 days; *P*=0.028; Figure S2A) and superior median event-free survival (not reached *versus* 292 days; *P*=0.005; Figure S2B).

Separation of the cohort into four quartiles according to the cut-offs determined separately in the AML cohort resulted in superior median overall survival (1150 days) of the 1st quartile compared to the 2nd (533 days; *P*=0.038) and 3rd quartiles (540 days; *P*=0.058; Figure S3A). Median event-free survival was also superior for the 1st quartile (not reached) compared to the 2nd (157 days; *P*=0.004), 3rd (325 days; *P*=0.010), and 4th quartiles (321 days; *P*=0.077; Figure S3B).

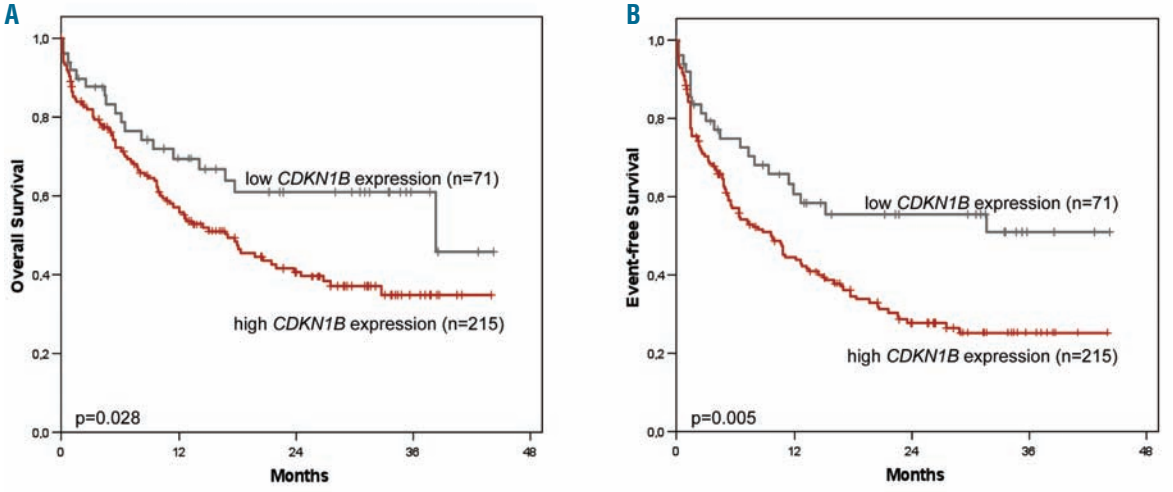
Online Supplementary Table S1. Results of gene expression analysis regarding the nine genes from the minimally deleted region (MDR) in the patients from this study: *CREBL2*, *CDKN1B*, *MANSC1*, *APOLD1*, *BCL2L14*, *DUSP16*, *GPR19*, *LOH12CR1*, and *LRP6*. SEE EXCEL FILE

Online Supplementary Table S2. Nearest single nucleotide polymorphism (SNP) defining the breakpoints of the minimally deleted region (MDR).

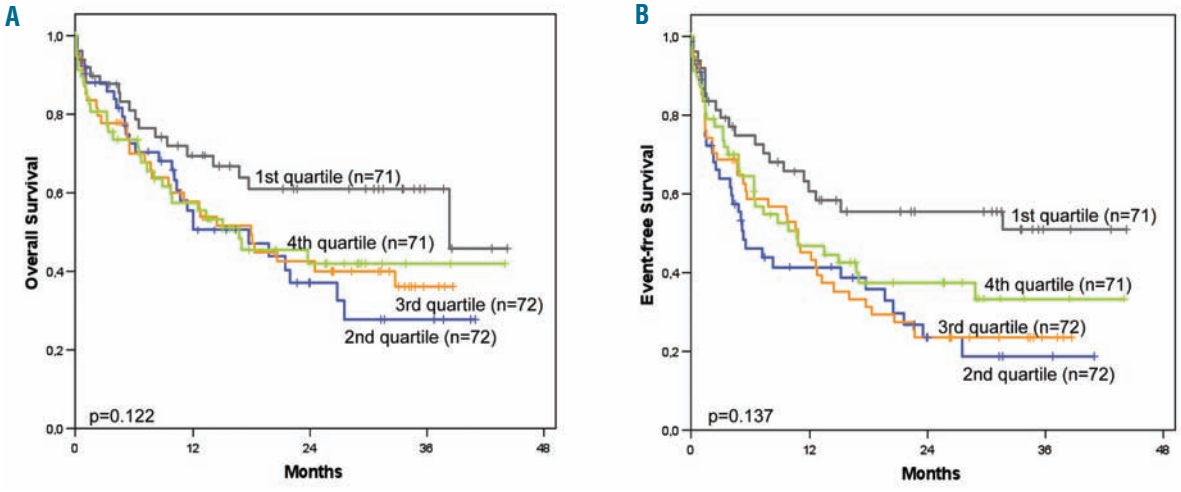
MDR	Marker	Nearest SNP marker	Reference SNP
Start marker	CN_606286	SNP_A-8594112	rs7312361
End marker	CN_617321	SNP_A-8350732	rs6488556



Online Supplementary Figure S1. Overall survival (A) and event-free survival (B) were compared in the AML patients after subdivision according to different quartiles of *CDKN1B* expression. The cut-off values of *CDKN1B* expression for these analyses were determined in the AML (n=286) and MDS (n=113) cohorts in combination.



Online Supplementary Figure S2. Overall survival (A) and event-free survival (B) according to *CDKN1B* expression of the AML patients separated into "low" and "intermediate/high" *CDKN1B* expressers. The cut-off values of *CDKN1B* expression for these analyses were separately determined in the AML cohort (n=286).



Online Supplementary Figure S3. Overall survival (A) and event-free survival (B) when the AML patients were separated into quartiles according to *CDKN1B* expression. The cut-off values of *CDKN1B* expression for these analyses were separately determined in the AML cohort (n=286).