Genetics of acute myeloid leukemia in the elderly: mutation spectrum and clinical impact in intensively treated patients aged 75 years or older

Victoria V. Prassek,[1] Maja Rothenberg-Thurley,[1] Maria C. Sauerland,[2] Tobias Herold,[1,3,4] Hanna Janke,[1] Bianka Ksienzyk,[1] Nikola P. Konstandin,[1] Dennis Goerlich,[2] Utz Krug,[5] Andreas Faldum,[2] Wolfgang E. Berdel,[2] Bernhard Wörmann,[6] Jan Braess,[7] Stephanie Schneider,[1] Marion Subklewe,[1] Stefan K. Bohlander,[8] Wolfgang Hiddemann,[1,3,4] Karsten Spiekermann[1,3,4] and Klaus H. Metzeler[1,3,4]

[1]Laboratory for Leukemia Diagnostics, Department of Medicine III, University Hospital, LMU Munich, Germany; [2]Institute of Biostatistics and Clinical Research, University of Münster, Germany; [3]German Cancer Consortium (DKTK), Partner Site Munich, Germany; [4]German Cancer Research Center (DKFZ), Heidelberg, Germany; [5]Hospital Leverkusen, Germany; [6]Charité – University Hospital Berlin, Germany; [7]Department of Oncology and Hematology, Hospital Barmherzige Brüder, Regensburg, Germany and [8]Department of Molecular Medicine and Pathology, University of Auckland, New Zealand

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Correspondence: klaus.metzeler@med.uni-muenchen.de

Supplemental Appendix

to

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Genetics of acute myeloid leukemia in the elderly: mutation spectrum and clinical impact in intensively treated patients aged ≥75 years

Supplemental Methods

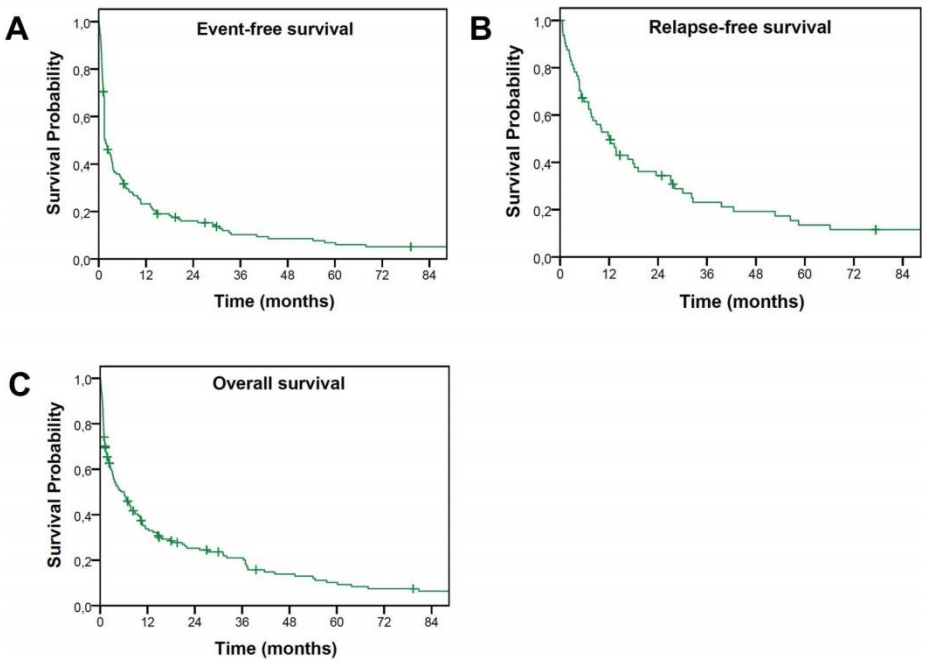
Treatment Protocol

Participants aged ≥60 years were randomized to receive intensive induction chemotherapy with one cycle of TAD-9 (thioguanine 100 mg/m^2 twice daily on days 3-9, cytarabine 100 mg/m^2/d continuous infusion on days 1+2 and 100 mg/m^2 twice daily on days 3-8, and daunorubicin 60 mg/m^2 on days 3-5) or HAM (cytarabine 1 g/m^2 twice daily on days 1-3 and mitoxantrone 10 mg/m^2 on days 3-5). A second induction cycle (HAM) was administered from day 21 only if ≥5% residual blasts were present in a day 15 BM aspirate. Another cycle of TAD-9 was given as a consolidation therapy, followed by monthly cytarabine-based maintenance chemotherapy.

Supplemental Results

We analyzed outcomes according to the randomized induction arm, stratified by MRC cytogenetic risk group. Favorable- and intermediate-risk patients treated with HAM induction tended to have longer OS than patients treated with TAD (median OS: TAD, 3.3 months vs. HAM, 8.8 months; p=0.16; Supplemental Figure 3B). MRC adverse-risk patients treated with HAM also tended to have a longer OS (median OS, TAD, 0.9 months vs. HAM, 4.6 months; p=0.10; Supplemental Figure 3C).

Supplemental Figure 1



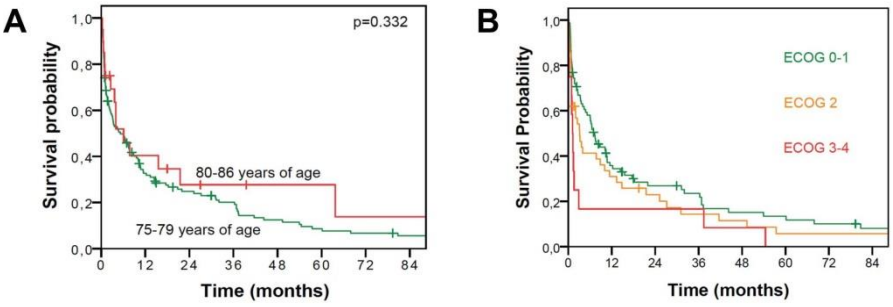
Supplemental Figure 1: Survival outcomes of intensively treated AML patients aged ≥75 years.

A) Event-free survival

B) Relapse-free survival

C) Overall survival

Supplemental Figure 2

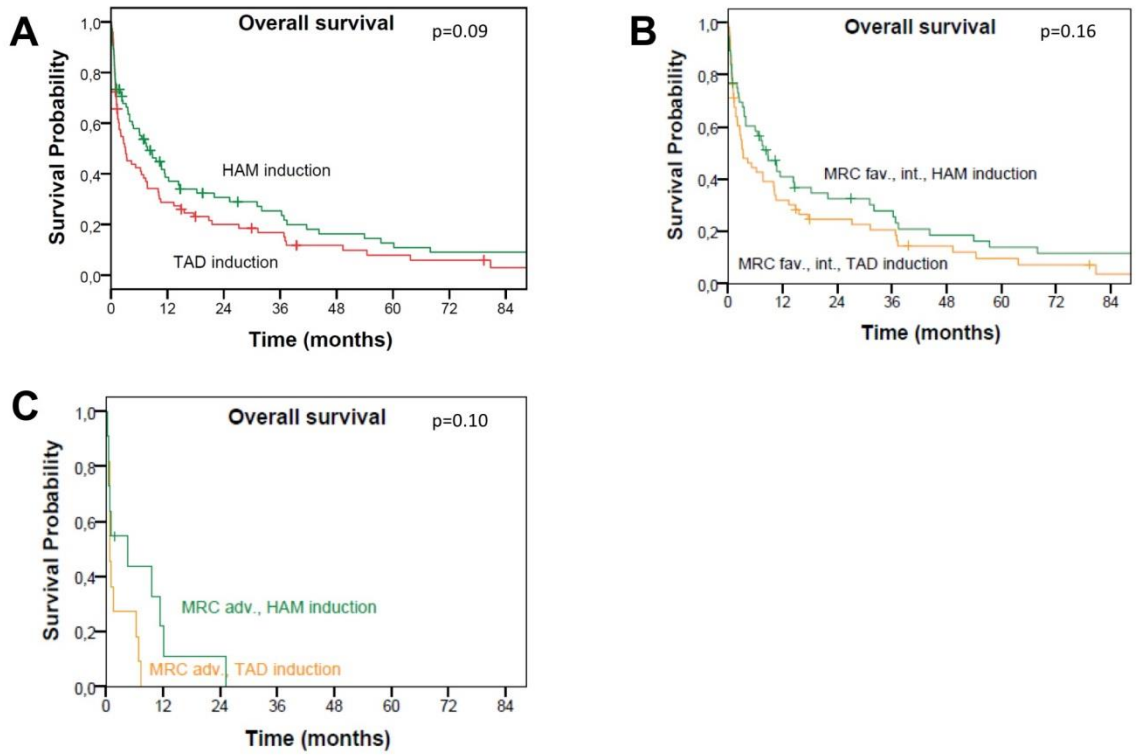


Supplemental Figure 2: Overall survival according to age and Eastern Cooperative Oncology Group (ECOG) performance status

A) Impact of age at diagnosis on overall survival. Patients aged 75-79 years at diagnosis are shown in green; patients aged 80-86 years at diagnosis are shown in red.

B) Impact of Eastern Cooperative Oncology Group performance status (ECOG PS) on overall survival. Patients with an ECOG PS of 0-1 are shown in green, patients with an ECOG PS of 2 are shown in orange, and patients with an ECOG PS of 3-4 are shown in red.

Supplemental Figure 3



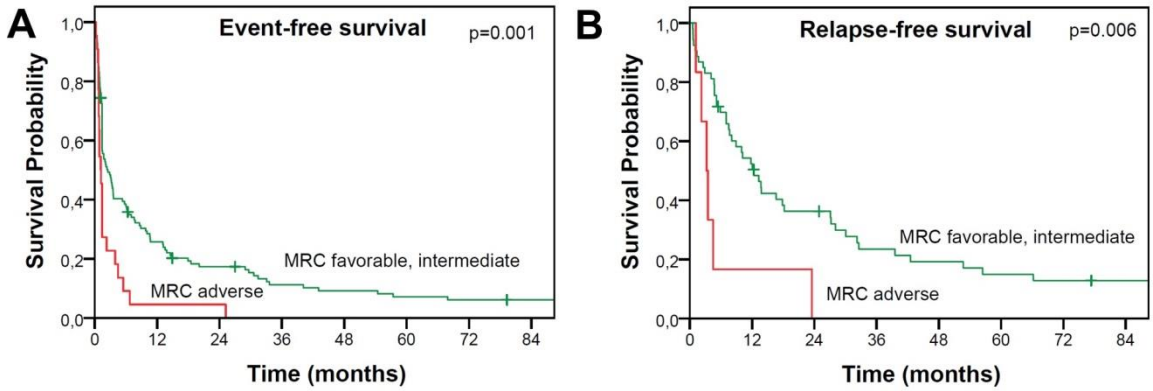
Supplemental Figure 3: Overall survival according to treatment arm (TAD induction vs. HAM induction)

A) Overall survival of patients randomized to TAD induction (red) vs. HAM induction (green).

B) Overall survival of MRC favorable or intermediate risk patients randomized to TAD induction (orange) vs. HAM induction (green).

C) Overall survival in MRC adverse risk patients risk randomized to TAD induction (orange) vs. HAM induction (green).

Supplemental Figure 4

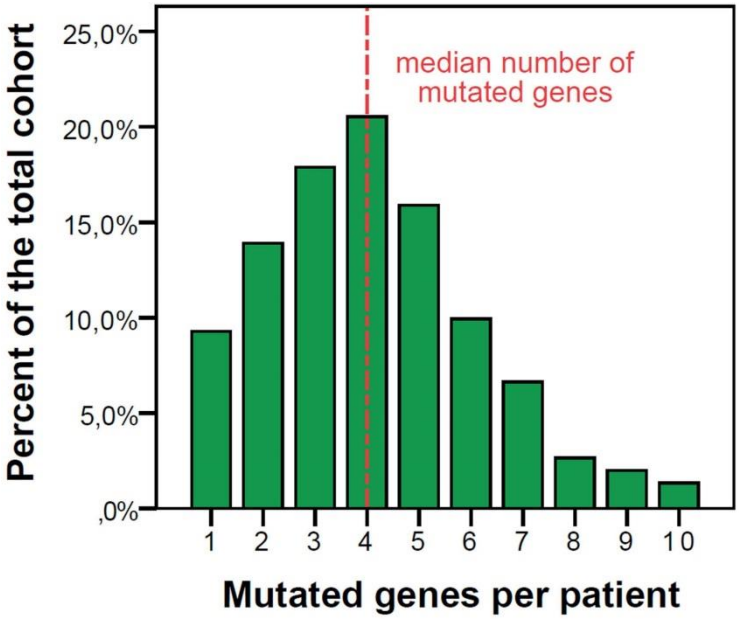


Supplemental Figure 4: Survival according to MRC risk classification

A) Event-free survival in MRC favorable and intermediate-risk (green) vs. MRC adverse-risk (red) patients.

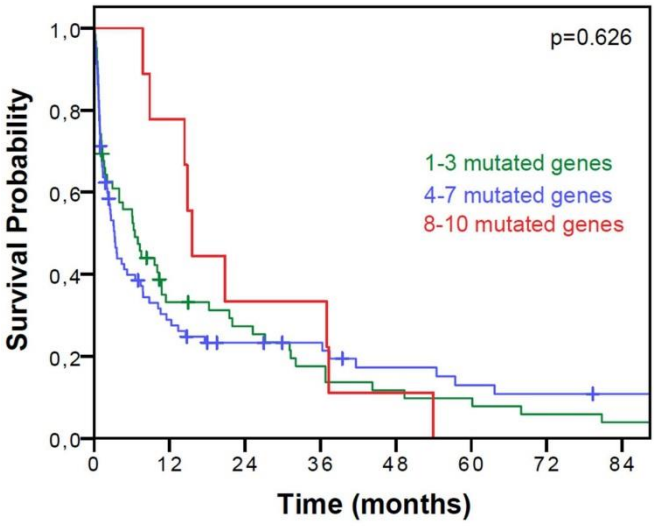
B) Relapse-free survival in MRC favorable and intermediate-risk (green) vs. MRC adverse-risk (red) patients.

Supplemental Figure 5



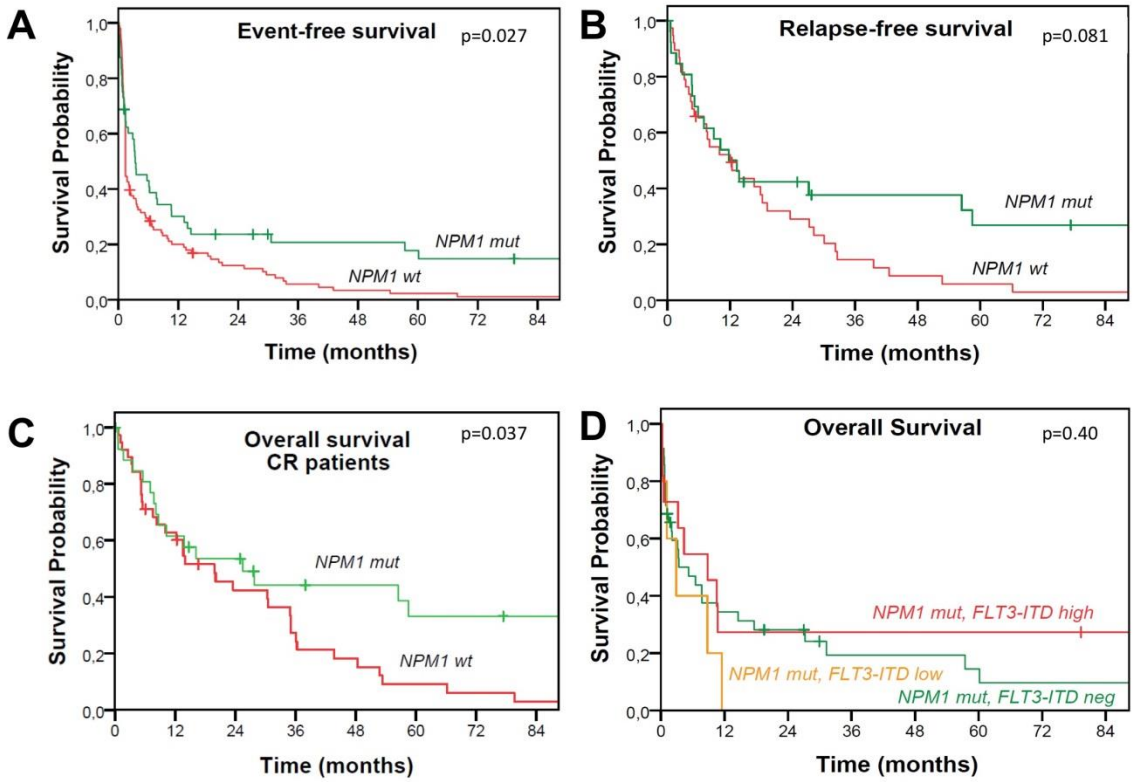
Supplemental Figure 5: Number of mutated driver genes per patient, shown as percentage of the entire cohort.

Supplemental Figure 6



Supplemental Figure 6: Overall survival of patients who harbored 1-3 (green), 4-7 (purple) or 8-11 (red) driver gene mutations.

Supplemental Figure 7



Supplemental Figure 7: Survival according to *NPM1* mutation status and *FLT3*-ITD allelic ratio

A) Event free survival of *NPM1* mutated patients (green) compared to *NPM1* wildtype patients (red).

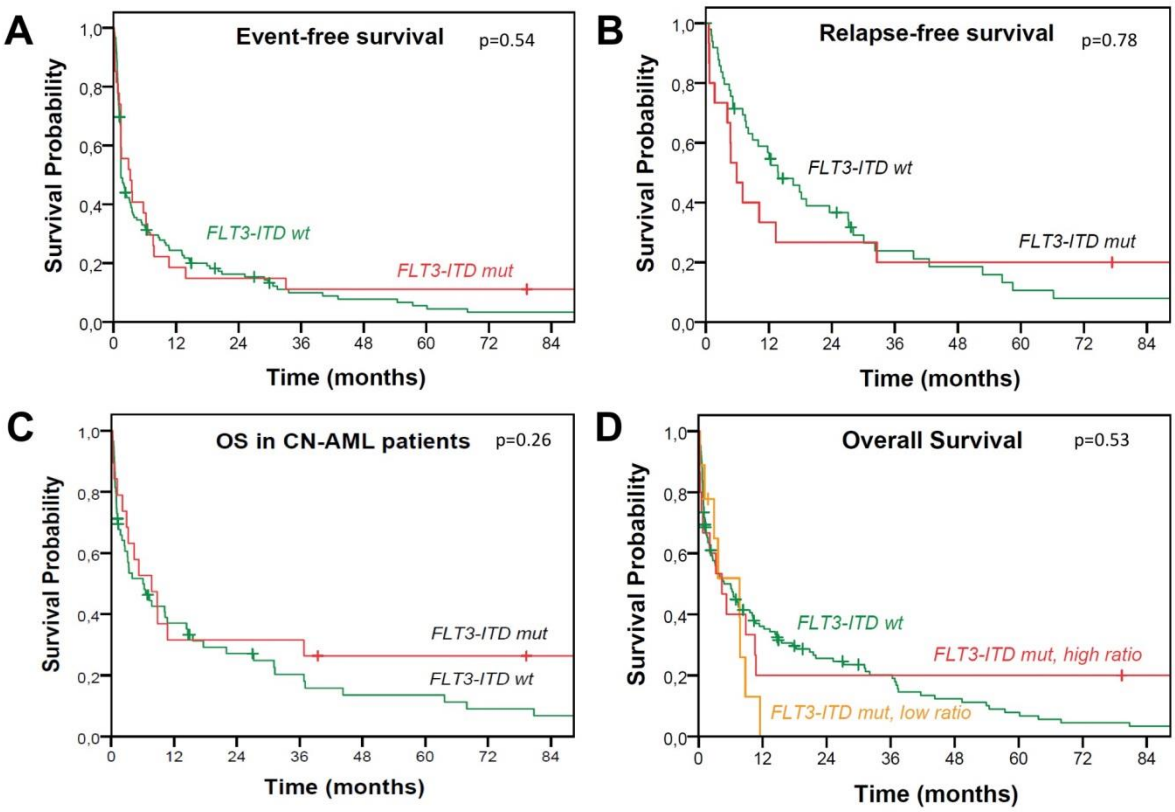
B) Relapse-free survival of *NPM1* mutated patients (green) compared to *NPM1* wildtype patients (red).

C) Overall survival (OS) of *NPM1* mutated patients (green) compared to *NPM1* wildtype patients (red) who achieved CR (calculated from the day of achieving CR).

D) Overall survival of *NPM1* mutated/*FLT3*-ITD negative patients (green) compared to *NPM1* mutated/*FLT3*-ITD mutated patients with high allelic ratio (≥0.5; red) or low allelic ratio (<0.5; orange).

Abbreviations: “Mut” denotes mutated and “wt” wildtype.

Supplemental Figure 8



Supplemental Figure 8: Survival and *FLT3*-ITD mutations

A) Event-free survival of *FLT3*-ITD mutated patients (red) compared to *FLT3*-ITD wildtype patients (green).

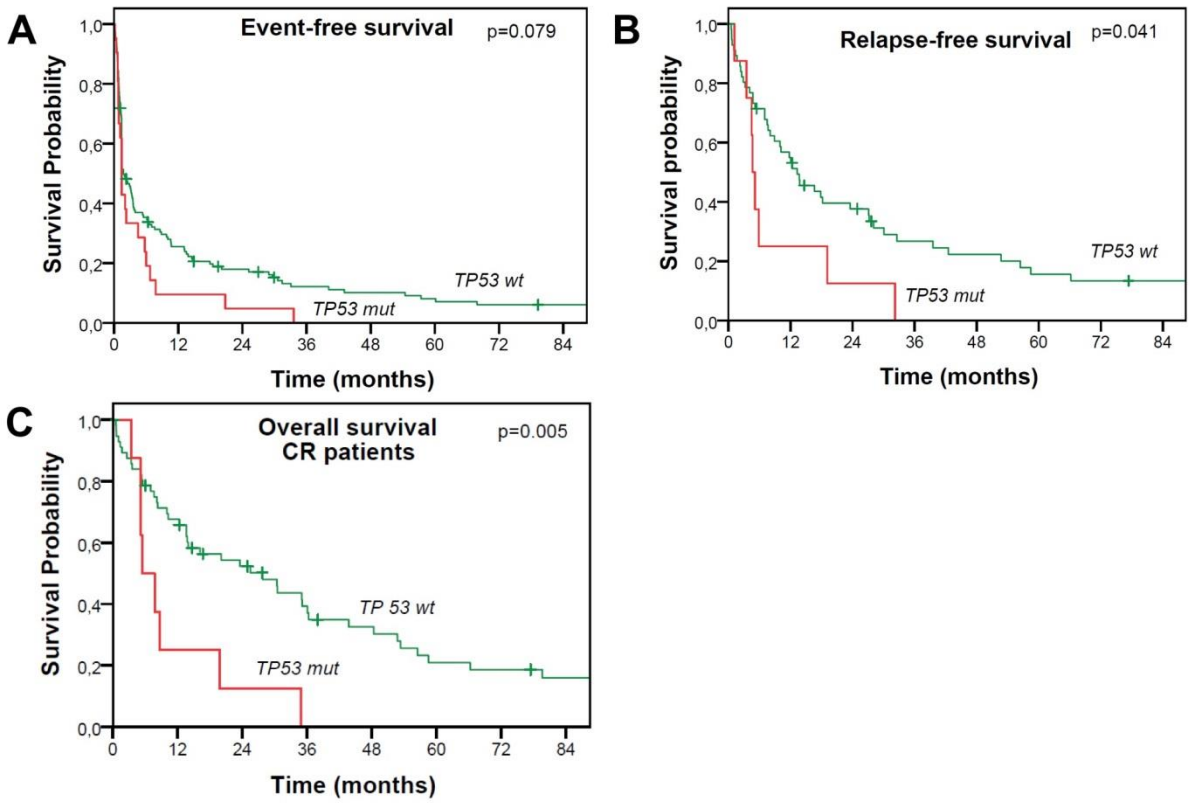
B) Relapse-free survival of *FLT3*-ITD mutated patients (red) compared to *FLT3*-ITD wildtype patients (green).

C) Overall survival of *FLT3*-ITD mutated patients (red) compared to *FLT3*-ITD wildtype patients (green) in cytogenetic normal (CN) AML patients.

D) Overall survival of *FLT3*-ITD mutated patients with high allelic ratio (≥0.5, red) compared to patients with low allelic ratio (<0.5, orange) and *FLT3*-ITD wildtype patients (green).

Abbreviations: “Mut” denotes mutated and “wt” wildtype.

Supplemental Figure 9



Supplemental Figure 9: Survival and *TP53* mutations

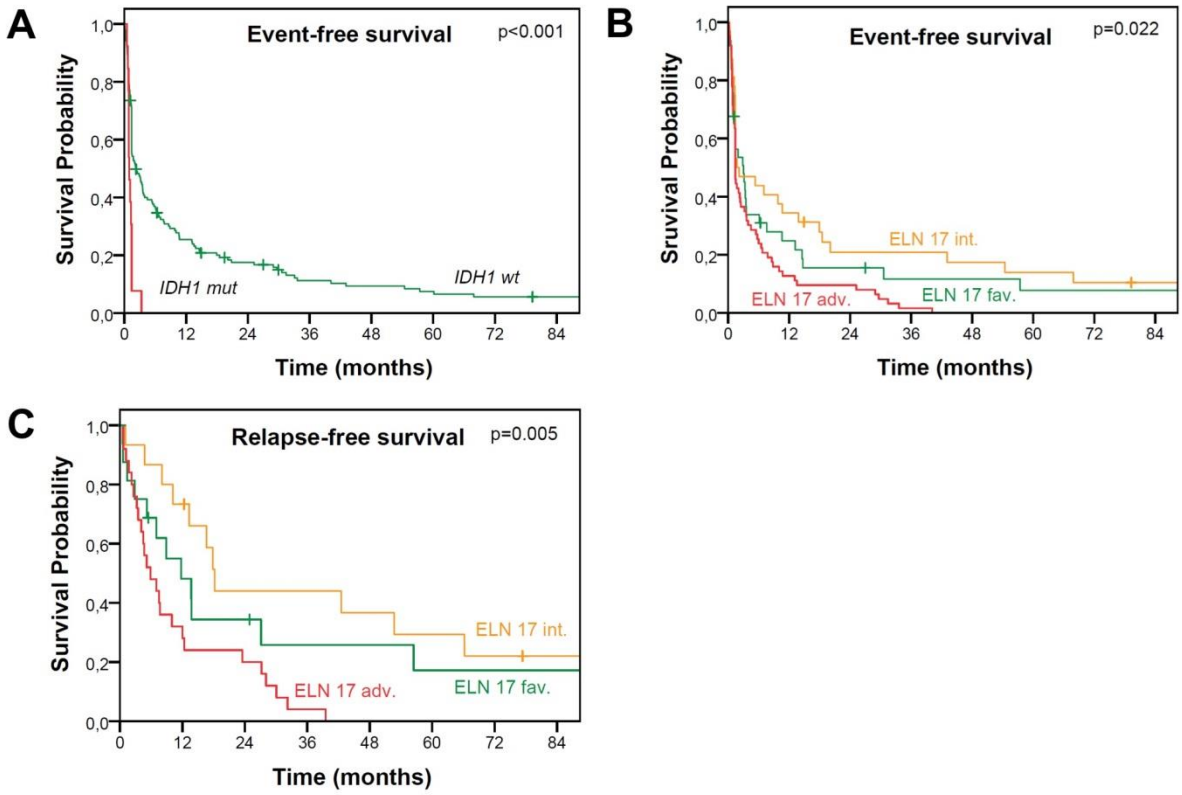
A) Event-free survival in *TP53* mutated patients (red) compared to *TP53* wildtype patients (green).

B) Relapse-free survival in *TP53* mutated patients (red) compared to *TP53* wildtype patients (green).

C) Overall survival in *TP53* mutated patients (red) compared to *TP53* wildtype patients (green) who achieved CR (calculated from the day of achieving CR).

Abbreviations: “Mut” denotes mutated and “wt” wildtype.

Supplemental Figure 10



Supplemental Figure 10: Survival according to *IDH1* mutation status and ELN 2017 classification

A) Event-free survival in *IDH1* mutated (red) and *IDH1* wildtype (green) patients.

B) Event-free survival in favorable (green), intermediate (orange) and adverse risk (red) patients according to ELN 2017 classification.

C) Relapse-free survival in favorable (green), intermediate (orange) and adverse risk (red) patients according to ELN 2017 classification.

Abbreviations: “Mut” denotes mutated and “wt” wildtype.

Supplemental Table 1: Response rates (CR+CRi) and overall survival according to common gene mutations

Gene	CR rate		p	OS at 2 years		p
	mutated	wildtype		mutated	wildtype	
TET2	57%	41%	0.07	27%	24%	0.19
DNMT3A	53%	45%	0.40	27%	25%	0.58
NPM1	56%	44%	0.17	30%	23%	0.09
SRSF2	47%	48%	0.99	37%	21%	0.46
ASXL1	42%	49%	0.55	18%	27%	0.21
RUNX1	36%	50%	0.21	19%	27%	0.18
***FLT3*-ITD**	56%	46%	0.40	23%	26%	0.32
NRAS	48%	48%	0.99	17%	27%	0.80
IDH2	57%	46%	0.38	45%	22%	0.53
TP53	38%	49%	0.36	7%	28%	0.07
BCOR	45%	48%	0.82	27%	25%	0.69
***FLT3*-TKD**	50%	47%	0.99	22%	26%	0.91
IDH1	0%	52%	<0.001	0%	28%	<0.001
STAG2	62%	46%	0.39	42%	24%	0.13

Abbreviations: CR: complete remission; OS, overall survival, ITD: internal tandem duplication; TKD: tyrosine kinase domain mutation

Supplemental Table 2: Clinical characteristics of *IDH1* mutated compared to *IDH1* wildtype patients.

	***IDH1* wildtype**	***IDH1* mutated**	**p**
Median age (years)	76	78	0.08
Median BM blasts (%)	80	78	0.90
Median PB blasts (%)	24	57	0.60
Median WBC (G/l)	14.8	3	0.10
Median Platelets (G/l)	50	69	0.17

Footnote: The p-values were calculated by the Mann-Whitney U-Test.
Abbreviations: BM: bone marrow; PB: peripheral blood; WBC: White blood cell count

Supplemental Table 3: Clinical characteristics of the 13 *IDH1* mutated patients

Patient No.	Age	Sex	ECOG PS	Disease type	MRC	ELN 2017	VAF	Induction result	EFS (days)	OS (days)
1	78	f	1	de novo	int	fav	0.41	early death	21	21
2	81	f	1	de novo	int	int	0.23	refractory	42	78
3	77	f	1	sAML	adv	int	0.27	early death	26	26
4	75	m	1	de novo	int	adv	0.46	early death	15	15
5	75	m	1	de novo	int	fav	0.11	early death	42	42
6	79	m	2	sAML	int	adv	0.38	early death	26	26
7	78	f	1	tAML	int	fav	0.48	early death	33	33
8	79	f	1	sAML	int	int	0.38	refractory	42	218
9	78	m	-	de novo	int	adv	0.32	early death	26	26
10	79	f	3	de novo	int	adv	0.38	early death	38	38
11	79	m	2	de novo	int	int	0.5	early death	28	28
12	78	m	2	de novo	-	-	0.5	early death	24	24
13	75	f	1	de novo	int	-	0.43	unknown	99	99

Abbreviations: f: female; m: male; ECOG PS: Eastern Cooperative Oncology Group performance status; sAML: secondary AML; tAML: therapy-related AML; MRC: British Medical Research Council; ELN 2017: European LeukaemiaNet risk classification; fav: favorable-risk group; int: intermediate-risk group; adv: adverse-risk group; VAF, Variant allele frequency; EFS: Event-free survival; OS: Overall survival