A multicenter phase II trial of decitabine as first-line treatment for older patients with acute myeloid leukemia judged unfit for induction chemotherapy

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Supplementary Appendix

Design and Methods

Statistics

The effects of the following prognostic factors on objective response, best response, and on overall survival were analyzed: gender, age (<75, ≥75 years), performance status (ECOG 0, 1, 2+3), comorbidity index[1] (0, 1-2, ≥3), French-American-British subtype (M6, no M6), cytogenetics (favorable/intermediate, adverse, no metaphases/not assessed),[2] presence or absence of monosomal karyotype,[3] prior myelodysplastic syndrome (no, yes), white blood cell count (<5, 5-19.99, 20-49.99, ≥50 x 10^9/L), platelets (<50, ≥50×10^9/L), serum lactate dehydrogenase (<300, ≥300 U/L), hemoglobin (<10, ≥10 g/dL), bone marrow blasts (<50, ≥50%). The categorization of the factors was predefined independent of outcome. The effects of the factors were first analyzed in univariate analyses. Factors showing an effect with a *P*-value below 0.1 were included in multivariate analyses. In addition, the effects of two recently published prognostic scores from the MRC (the Wheatley score[4]) and ALFA (Malfuson score[5]) groups were analyzed. Both are used to predict the outcome of older acute myeloid leukemia patients in response to treatment: the Wheatley score applies the five parameters cytogenetic group, age, white blood cell count, performance status and type of acute myeloid leukemia (*de novo*, secondary), the Malfuson score applies the four parameters unfavorable cytogenetics, age ≥75 years, performance status ≥2, and white blood cell count ≥50×10^9/L. A more detailed analysis of the effect of duration of prior myelodysplastic syndrome was conducted in 109 patients with prior myelodysplastic syndrome of known duration. The effects of monosomal and complex karyotype were analyzed in 120 patients with abnormal cytogenetics.

Referencces

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Online Supplementary Table S1. Specification of infections captured by comorbidity scoring according to Sorror *et al.*[1]

		Requiring antimicrobial treatment n=51
Fungal infection		
	Candida mucositis (noral, esophageal)	N=5
	Pulmonary (aspergillosis)	N= 3
Bacterial infection		
	Pneumonia / bronchitis	N=18
	Abscess formation (dental, inguinal, etc.)	N=6
	GI Infection (*H. pylori*+ gastritis, diverticulitis, *D.diff*, etc.)	N=8
	Bacteremia	N=1
	Genito-urinary tract infection	N=1
	Arthritis	N=1
Viral infection	Herpes stomatitis	N=7
Fever of unknown origin		N= 5

Online Supplementary Table S2. Reasons for ineligibility for induction therapy, as determined at study entry by the treating physician. Low performance status, higher age and significant comorbidities were not further specified.

	All (n=227)(%)	<75 years (n=140) (%)	≥ 75 years (n=87) (%)
Low performance status	114 (50)	68 (49)	46 (53)
Higher age	42 (19)	15 (11)	27 (31)
Significant comorbidity	126 (56)	71(51)	55 (63)
Complex karyotype	13 (6)	10 (7)	3(3)
Refusal of the patient	132 (58)	81 (58)	51 (59)
One or more exclusion criteria for an AML study (induction treatment) fulfilled	41 (18)	29 (21)	12 (14)
Other	2 (1)	2 (1)	0 (0)
No reason given	9 (4)	8 (6)	1 (1)

Online Supplementary Table S3. Effect of patient and disease characteristics on complete (CR) and partial remissions (PR), univariate analyses.

Characteristic	CR/PR	Odds Ratio	95%- Confidence Interval	*P* value
All patients	26%			
Gender				0.33
male	24%	1.00	-	
female	30%	0.74	[0.41, 1.36]	
Age (years)				0.042
< 75	31%	1.00	-	
≥ 75	18%	1.97	[1.03, 3.77]	
Performance status (ECOG)				0.0011
0	49%	1.00	-	
1	22%	3.36	[1.62, 6.94]	
2/3	17%	4.56	[1.79, 11.6]	
Comorbidity index				0.0097
0	43%	1.00	-	
1 – 2	18%	3.36	[1.54, 7.33]	
≥ 3	26%	2.09	[0.98, 4.44]	
French-American-British subtype				0.44
M6	36%	1.00	-	
no M6	26%	1.58	[0.50, 4.97]	
Cytogenetics				0.43
favorable / intermediate	27%	1.00	-	
adverse	29%	0.93	[0.48, 1.81]	
insufficent or no metaphases / not assessed	19%	1.63	[0.70, 3.79]	
Monosomal karyotype (MK)/complex karyotype (CK)				0.078
MK^+	37%	1.00	-	
MK^- / CK^+	12%	4.38	[0.87, 22.0]	
MK^- / CK^-	20%	2.33	[0.95, 5.72]	
Number of monosomies				0.038
MK^-	18%	1.00	-	
single MK^+	25%	0.67	[0.19, 2.37]	
multiple MK^+	45%	0.27	[0.10, 0.74]	
Prior myelodysplastic syndrome				0.20
no	28%	1.00	-	
< 8 months	17%	1.93	[0.84, 4.45]	
≥ 8 months	31%	0.86	[0.42, 1.77]	
White blood cells count ($\times 10^9$/L)				0.59
< 5	28%	1.00	-	
5-19.99	22%	1.41	[0.65, 3.08]	
20-49.99	31%	0.87	[0.38, 1.97]	
≥ 50	18%	1.79	[0.56, 5.69]	
Platelets count ($\times 10^9$/L)				0.22
< 50	23%	1.00	-	
≥ 50	30%	0.69	[0.38, 1.25]	
Serum lactate dehydrogenase (U/L)				0.29
< 300	29%	1.00	-	
≥ 300	23%	1.39	[0.76, 2.54]	
Hemoglobin (g/dL)				0.35
< 10	25%	1.00	-	
≥ 10	31%	0.73	[0.37, 1.42]	
Bone marrow blasts (%)				0.29
< 50	30%	1.00	-	
≥ 50	24%	1.38	[0.76, 2.51]	
Risk groups according to Wheatley *et al.*[4]				0.036
good	50%	1.00	-	
standard	35%	1.82	[0.51, 6.54]	
poor	22%	3.53	[1.07, 11.6]	
Risk groups according to Malfuson *et al.*[5]				0.93
good	26%	1.00	-	
poor	26%	1.03	[0.57, 1.86]	

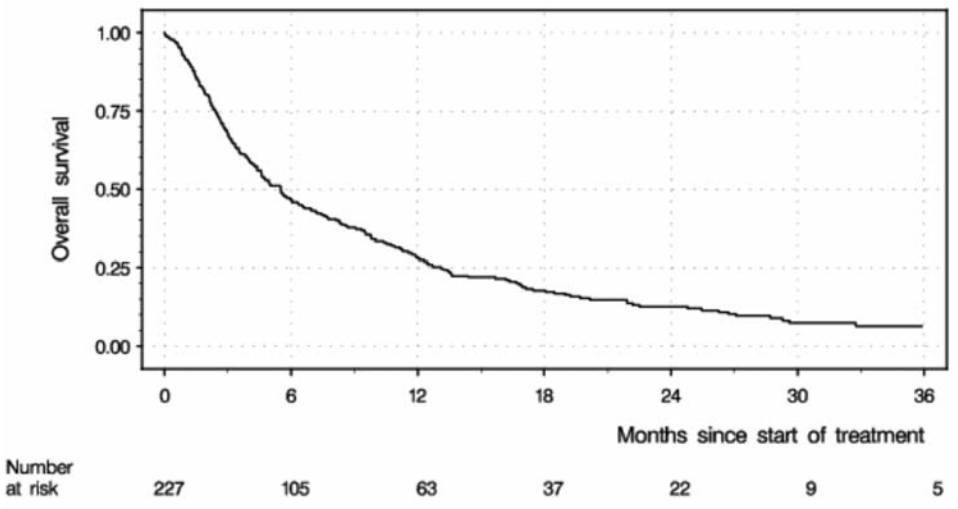
Online Supplementary Table S4. Features of the 30 patients who achieved a complete remission.

Center	PatID	Age/sex	PS	HCT-CI	Prior MDS	MDS duration (months)	%BM blasts	WBC	Cytogenetics	Overall survival (months)
FR-002	2	76/f	1	1	No		90	1200	52,XX,+del(1)(q24),del(5)(q13q33),del(7)(q21q32), +11,+13,+14,+16,-17,+21,+22 [7]	6.5
FR-007	7	74/m	1	3	Yes	32	43	600	46,XY [15]	38.7
FR-009	9	69/f	1	4	No		89	74 800	46,XX [20]	26.3
FR-010	10	73/m	1	3	Yes	20	63	1100	46,XY [5]	25.4
H-002	24	64/m	0	3	Yes	n.a.	70	2200	46,XY [15]	42.1
UL-004	33	74/m	1	4	No		31	5600	46,XY [20]	24.8
UL-011	42	77/f	1	1	Yes	4	78	29 900	46,XX,del(9)(q13q22),del(11)(q11q23) [3]	8.2
D-004	46	69/f	0	1	No		49	1100	53-54,XX,+1,-4,-5,+6,+8,+8,+11,+13,-14,+18,+18, +3mar [18]/46,XX [4]	28.7
D-003	47	67/f	0	4	No		36	2800	46,XX [22]	18.0
UL-013	48	75/m	0	0	No		86	4200	46,XY [5]	16.3
HA-001	51	82/f	1	0	No		50	21 450	46,XX,del(5)(q13q33),der(16)del(16)(p11)del(16)(q22),-17,der(20)t(17;20)(q11;q11),+der(20) [17]	10.4
UL-020	65	65/f	0	1	Yes	6	35	15 400	46,XX,del(5)(q13q33) [9]	32.7
UL-024	76	70/f	1	0	Yes	2	43	5200	46,XX [12]	40.8+
UL-033	94	75/m	0	0	No		95	2000	no metaphases	8.7
UL-037	103	68/m	1	0	No		54	2300	~41,XY,add(1)(q32),-3,-5,-7,-12,del(16)(q22),-17, -18,del(20)(q11q13),+mar,dmin [12]	16.9
H-005	108	60/m	1	1	Yes	2	50	4200	41-45,XY,del(3)(q14),del(4)(q26),-5,-7,add(15)(q26),+mar[cp9]/46,XY[7]	33.9+
D-017	116	70/m	0	0	Yes	29	32	1500	46,XY [22]	29.2
UL-040	117	72/m	1	3	No		45	1400	47,XY,+8 [6]	6.0
HA-009	123	79/f	2	1	No		41	1100	not done	12.4
DD-003	124	74/f	1	1	No		38	2340	47,XX,+4 [17]/46,XX [4]	31.4+
VS-003	128	73/m	2	4	No		90	800	47,XY,+13 [5]/45,X,-Y [2]	26.7
UL-049	133	64/m	1	1	Yes	16	36	12 300	46,XY,del(5)(q?15q?35) [7]	16.1
UL-055	151	63/m	0	2	Yes	14	71	1400	46,XY [12]	28.8+
UL-056	154	76/f	0	4	No		48	1400	47,XX,+8 [3]/47,XX,+13 [5]	9.0
UL-065	155	76/m	1	3	Yes	84	36	4200	45,XY,-7 [12]	28.4+
UL-067	181	70/m	1	1	No		40	1700	43-45,XY,add(1)(q10),add(4)(p12),-5,add(6)(q13), -7,add(9)(q34),add(12)(p11),-15,-17,-20,+2-4mar [9]	18.9
D-030	222	72/m	0	0	No		40	3500	43-49,XY,der(3),del(5)(q),2-5der(8),-14,-15,-17, -18,-20,+21,+mar [cp8]	12.6
D-031	223	61/f	1	3	No		95	1700	46,XX [1]/45,X,-X,?der(5;7)(p10,p10),-17,add(18) (q?22),-21,+mar,+mar [22]	11.8
UL-085	232	66/m	1	0	Yes	30	40	800	46,XY [10]	18.5+
UL-086	233	71/m	2	0	No		100	58 400	45,X,-Y [12]	19.0+

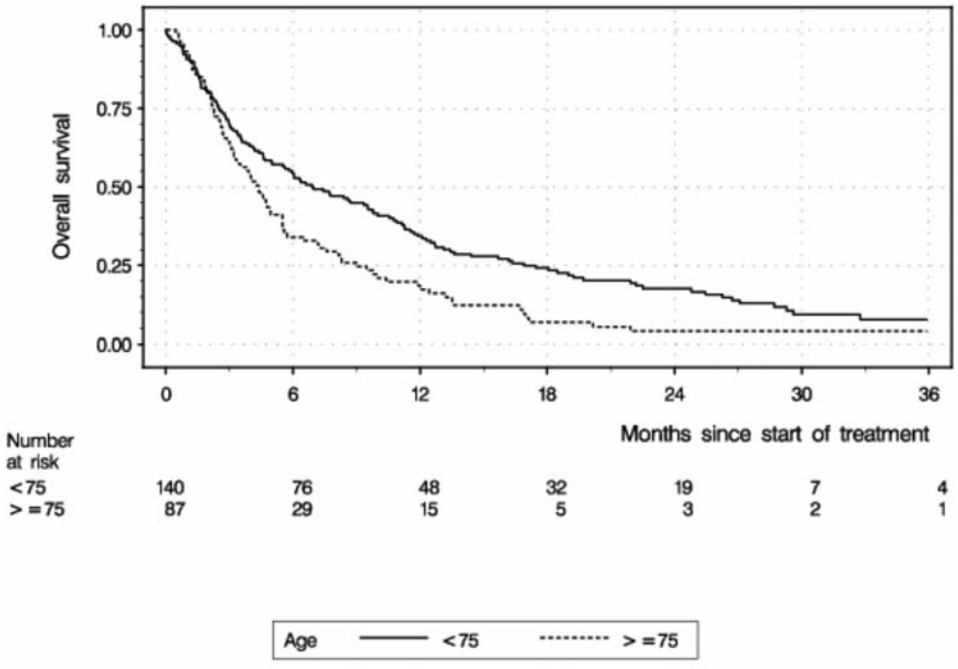
*Complete remission was attained after one cycle in six patients, after two cycles in 13 patients, after three cycles in four patients, and after four cycles in seven patients. *as determined by matrix comparative genomic hybridization. For overall survival, + indicates that the patient is still alive. PS: performance status; HCT-CI: hematopoietic cell transplantation comorbidity index; BM: bone marrow; MDS: myelodysplastic syndrome, WBC: white blood cell count.*

Online Supplementary Table S5. Effects of prognostic factors on overall survival, univariate analyses.

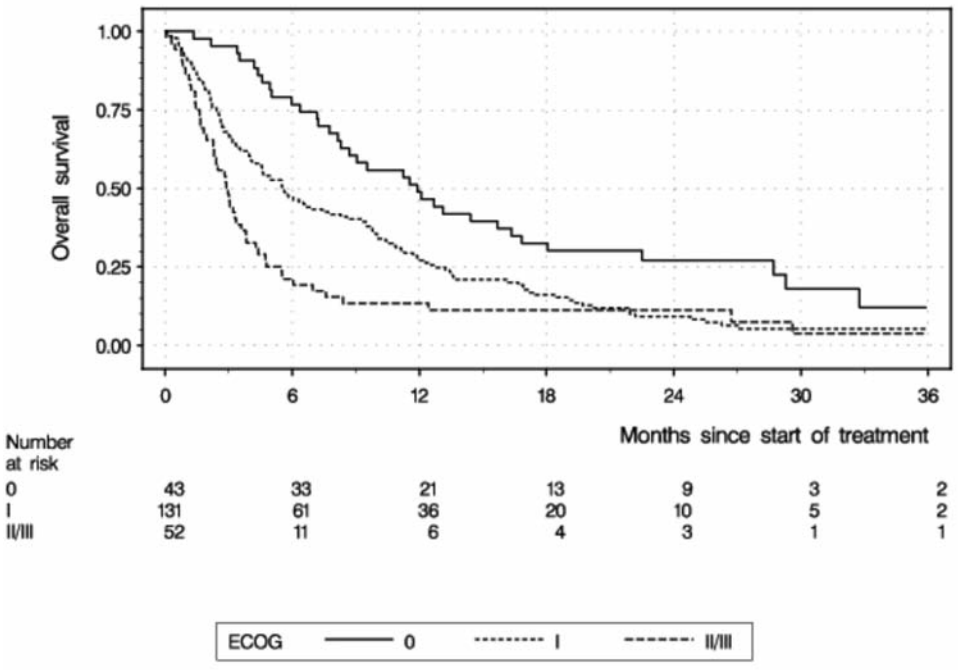
Characteristic	1-year survival rate	Hazard ratio	95%- Confidence Interval	*P* value
All patients	28%			
Gender				0.50
male	28%	1.00	-	
female	28%	0.91	[0.69,1.20]	
Age (years)				0.0038
< 75	34%	1.00	-	
≥ 75	17%	1.52	[1.15,2.02]	
Performance status (ECOG)				<0.0001
0	49%	1.00	-	
I	27%	1.82	[1.25,2.66]	
II/III	13%	2.91	[1.87,4.52]	
Comorbidity index				0.051
0	45%	1.00	-	
1-2	24%	1.57	[1.07,2.30]	
≥ 3	23%	1.52	[1.04,2.24]	
French-American-British subtype				0.20
M6	41%	1.00	-	
no M6	24%	1.48	[0.82,2.66]	
Cytogenetics				0.19
favorable / intermediate	30%	1.00	-	
adverse	21%	1.33	[0.98,1.82]	
insufficient or no metaphases / not assessed	33%	1.07	[0.74,1.55]	
Monosomal karyotype (MK)/complex karyotype (CK)				0.46
MK^+	21%	1.00	-	
MK^- / CK^+	18%	1.43	[0.80,2.55]	
MK^- / CK^-	19%	1.05	[0.70,1.59]	
Number of monosomies				0.50
MK^-	19%	1.00	-	
single MK^+	13%	1.12	[0.65,1.92]	
multiple MK^+	27%	0.78	[0.48,1.27]	
Prior myelodysplastic syndrome				0.22
no	24%	1.00	-	
< 8 months	25%	0.94	[0.67, 1.32]	
≥ 8 months	36%	0.73	[0.51,1.04]	
White blood cell count ($\times 10^9$/L)				0.0041
< 5	34%	1.00	-	
5-19.99	27%	1.21	[0.85,1.72]	
20-49.99	17%	1.80	[1.22,2.65]	
≥ 50	14%	1.91	[1.19,3.07]	
Platelets count $\times 10^9$/L				0.068
< 50	21%	1.00	-	
≥ 50	37%	0.77	[0.58,1.02]	
Serum lactate dehydrogenase (U/L)				0.0008
< 300	34%	1.00	-	
≥ 300	19%	1.62	[1.22,2.15]	
Hemoglobin (g/dL)				0.28
< 10	27%	1.00	-	
≥ 10	30%	0.84	[0.61,1.16]	
Bone marrow blasts (%)				0.31
< 50	32%	1.00	-	
≥ 50	25%	1.15	[0.87,1.53]	
Risk groups according to Wheatley *et al.*[4]				0.0005
good	58%	1.00	-	
standard	40%	1.58	[0.77,3.27]	
poor	22%	2.68	[1.36,5.26]	
Risk groups according to Malfuson *et al.*[5]				0.013
good	33%	1.00	-	
poor	21%	1.42	[1.08,1.87]	



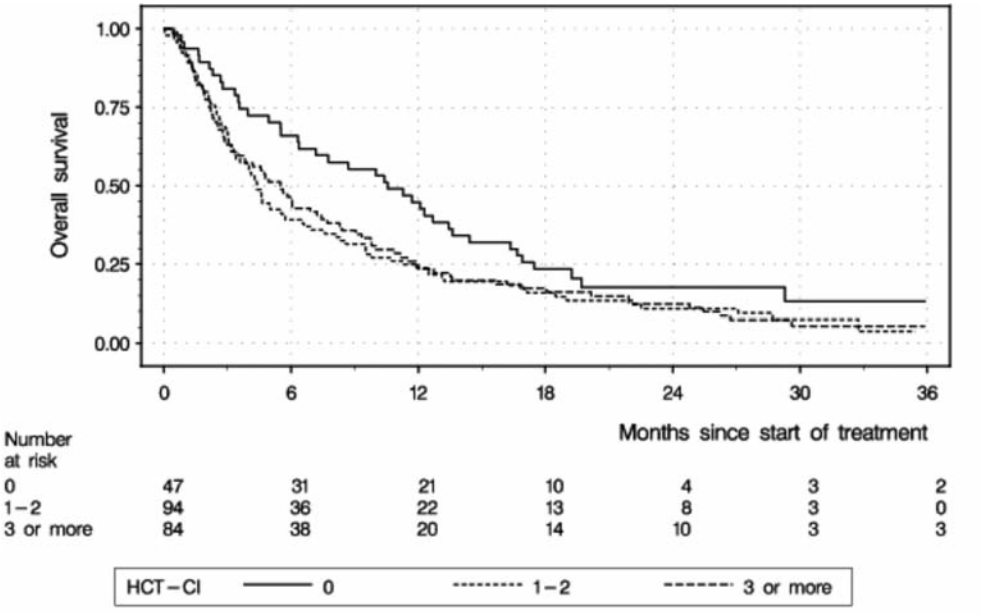
Online Supplementary Figure S1. Kaplan-Meier overall survival estimate of all patients (n=227): median survival 5.5 months; 1-year survival rate 28%.



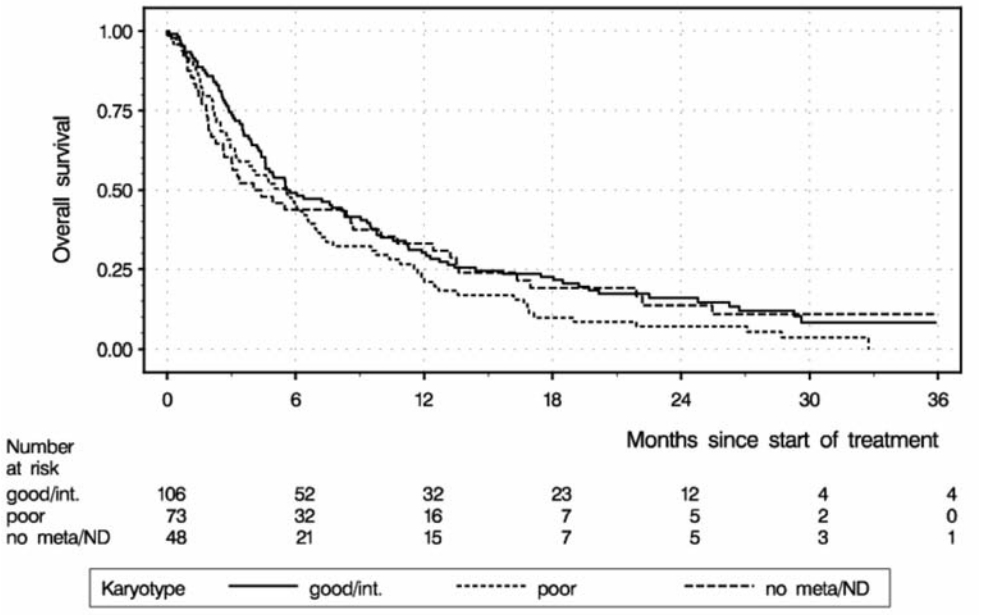
Online Supplementary Figure S2. Kaplan-Meier overall survival estimate by age: <75 years (n=140, solid line), ≥75 years (n=87, dotted line).



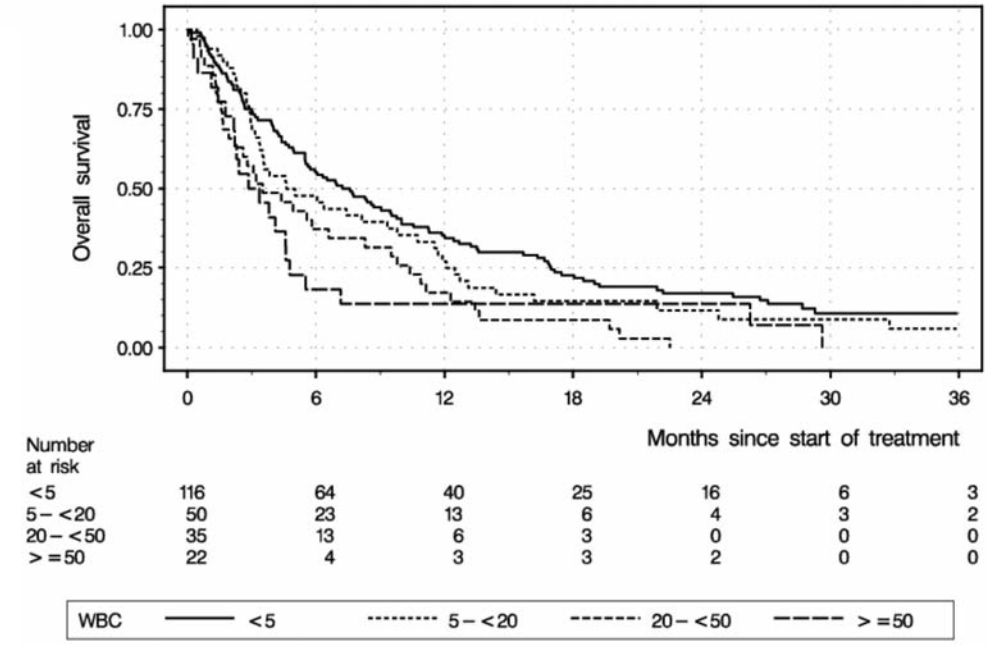
Online Supplementary Figure S3. Kaplan-Meier overall survival estimate by performance status ECOG 0 (n=43, solid line), 1 (n=131, dotted line), 2 (n=52, broken line).



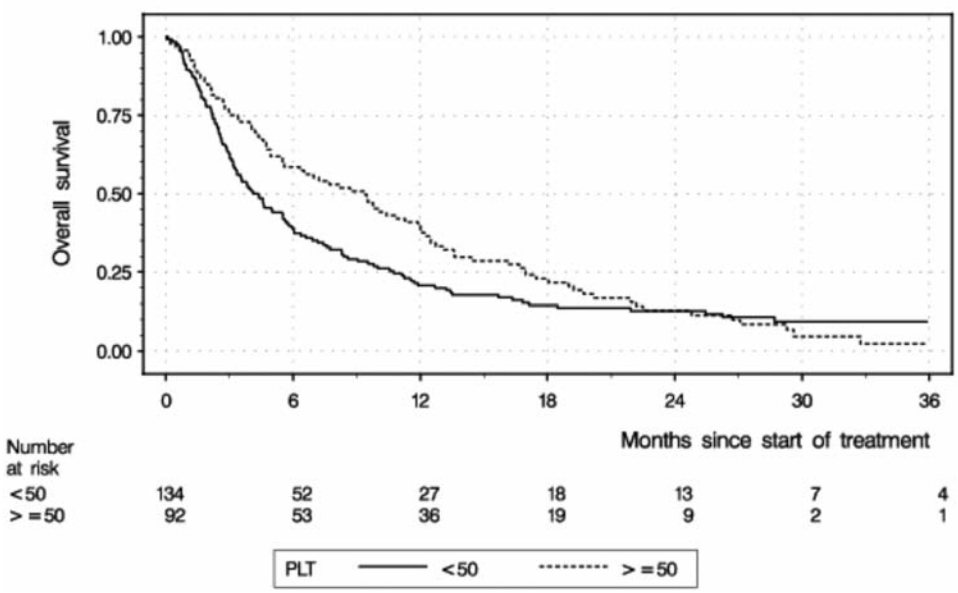
Online Supplementary Figure S4. Kaplan-Meier overall survival estimate by comorbidities, scored according to the hematopoietic cell transplantation-comorbity index[1]: no comorbidities (n=47, solid line), one or two (n=94, dotted line), or three or more comorbidities (n=84, broken line).



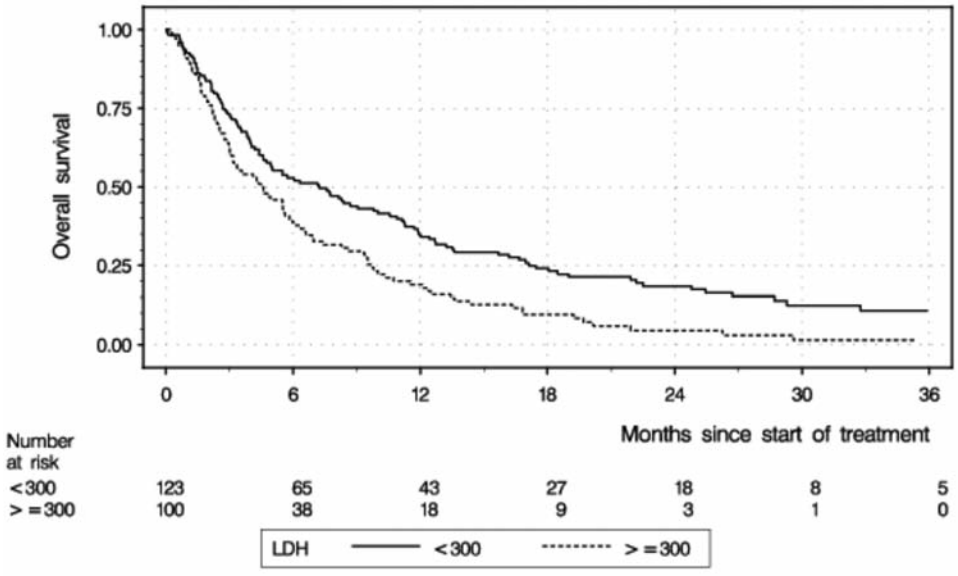
Online Supplementary Figure S5. Kaplan-Meier overall survival estimate by cytogenetics: favorable or intermediate-risk cytogenetics (n=106, solid line), adverse cytogenetics (n=73, dotted line); or cytogenetics not available due to insufficient or no metaphases or no cytogenetics attempted (n=48, broken line).



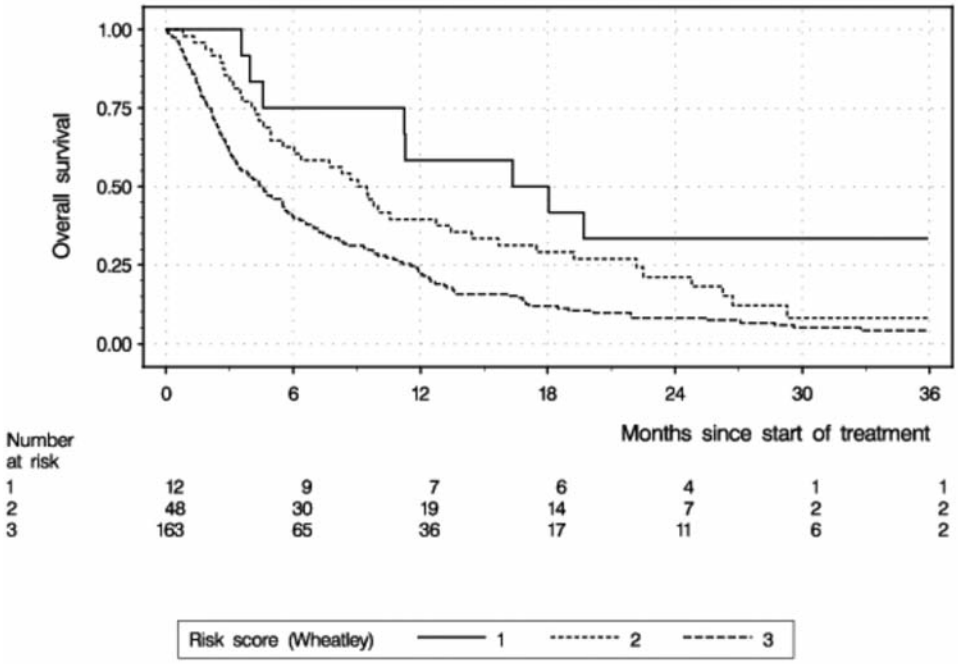
Online Supplementary Figure S6. Kaplan-Meier overall survival estimate by WBC counts: $<5x10^9$/L (n=116, solid line), 5-19.99x10^9/L (n=50, dotted line), 20-49.99x10^9/L (n=35, dashed line), ≥50x10^9/L (n=22, broken line).



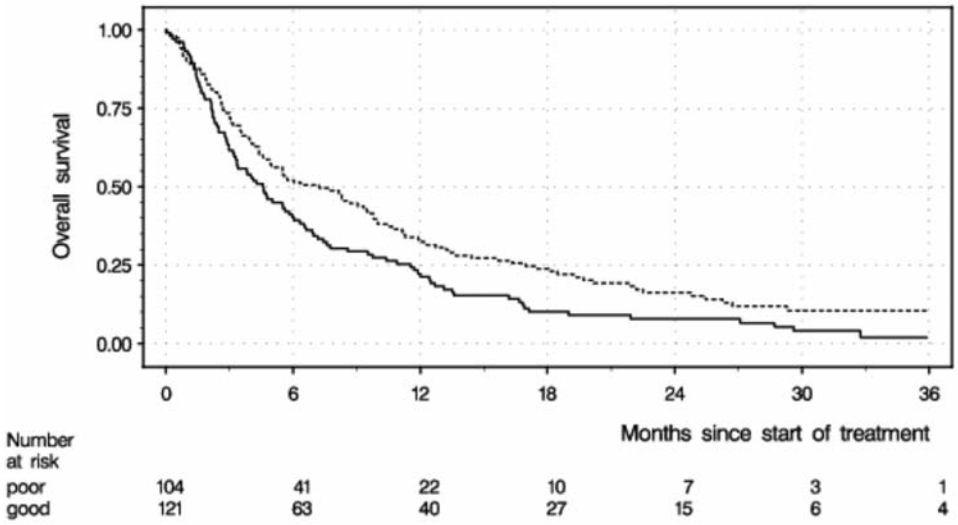
Online Supplementary Figure S7. Kaplan-Meier overall survival estimate by platelet counts: <50x10^9/L (n=134, solid line), ≥50x10^9/L (n=92, dotted line).



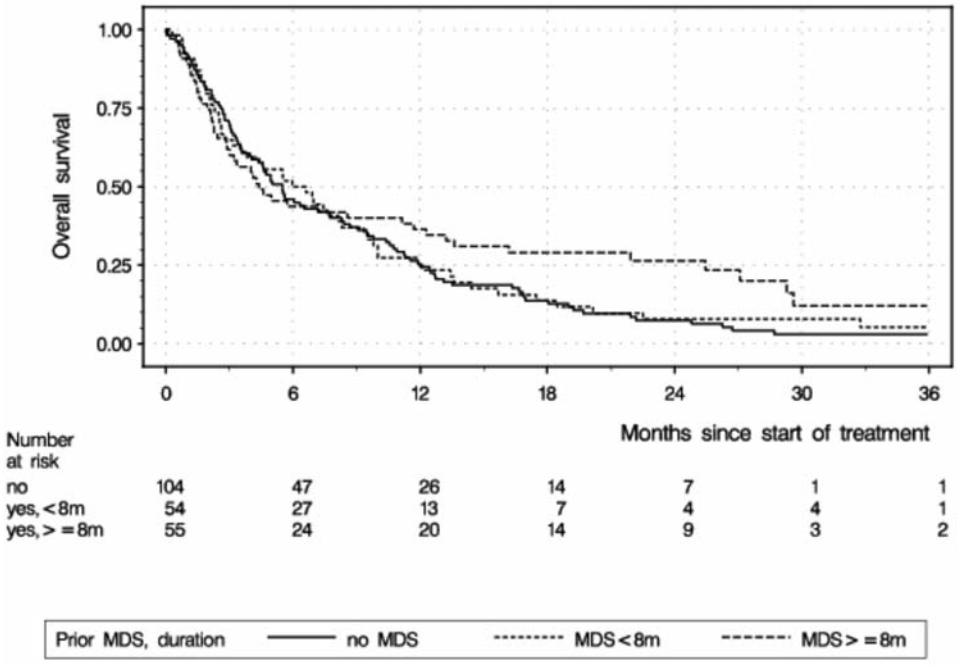
Online Supplementary Figure S8. Kaplan-Meier overall survival estimate by serum lactate dehydrogenase levels: <300 U/L (n=123, solid line), ≥300 U/L (n=100, dotted line).



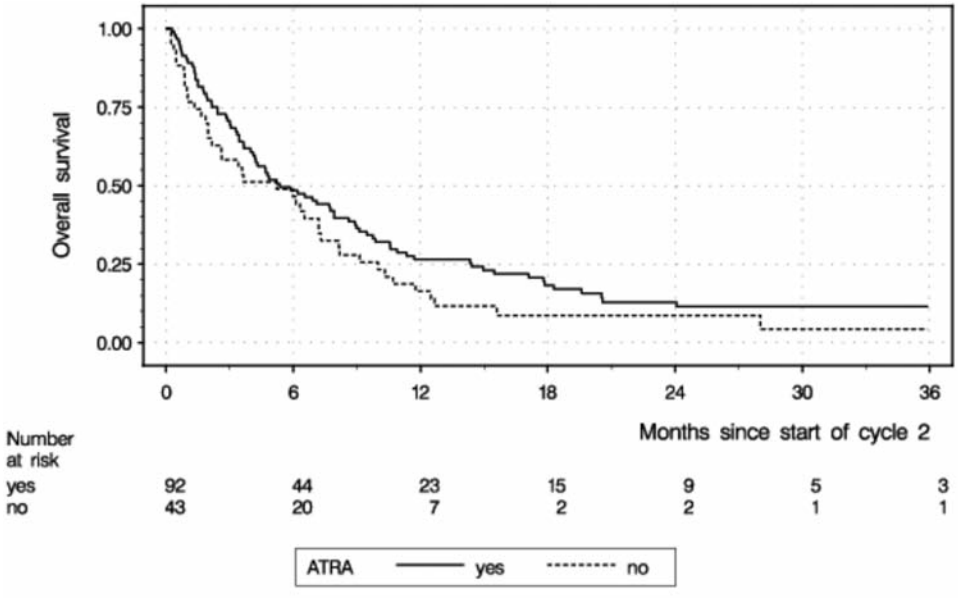
Online Supplementary Figure S9. Kaplan-Meier overall survival estimate by Wheatley score:[4] 1 point (n=12, solid line), 2 points (n=48, dotted line), 3 points (n=163, broken line).



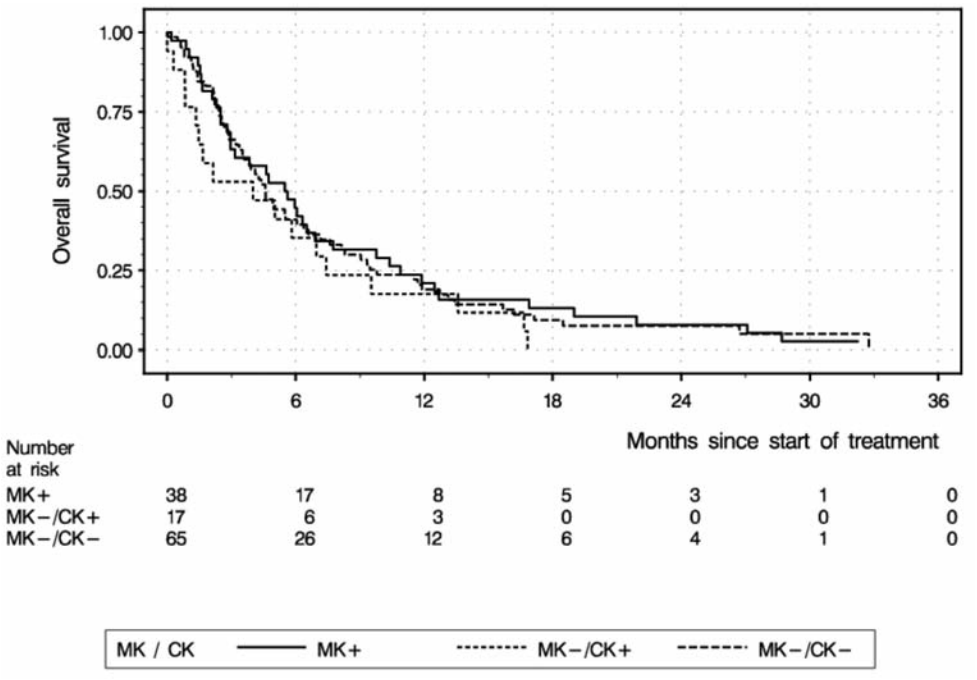
Online Supplementary Figure S10. Kaplan-Meier overall survival estimate by Malfuson score:[5] good risk (n=121, dotted line), poor risk (n=104, solid line).



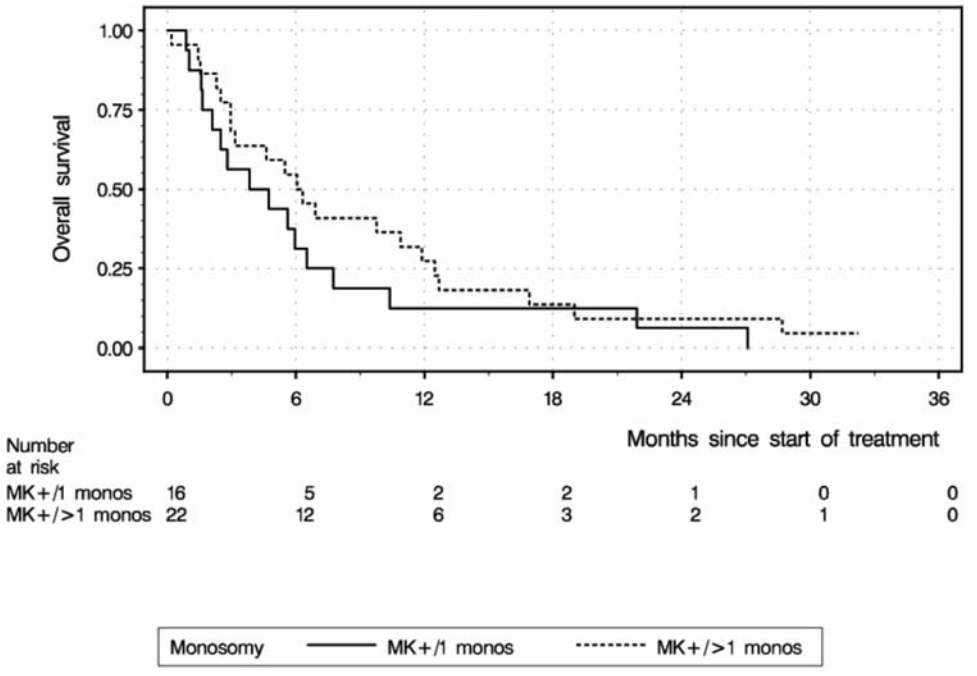
Online Supplementary Figure S11. Kaplan-Meier overall survival estimate by type of AML: *de novo* AML (n=104, solid line), secondary AML with prior MDS duration of less than 8 months (n=54, dotted line), or ≥8 months (n=55, broken line)



Online Supplementary Figure S12. Kaplan-Meier overall survival estimate of patients attaining an antileukemic effect[6] or stable disease after the first course of DAC and receiving DAC alone (n=43, broken line) or DAC and ATRA (n=92, solid line) during the second course of treatment.



Online Supplementary Figure S13. Kaplan-Meier overall survival estimate of patients with abnormal cytogenetics (n=120) according to the presence (n=38) or absence (n=82) of a monosomal karyotype (MK), as well as presence (n=54) or absence (n=66) of a complex karyotype (CK). MK^+ patients (37/38 MK^+ patients were also CK^+): solid line, MK^-/CK^+ patients (n=17, dotted line), MK^-/CK^- (n=65, broken line).



Online Supplementary Figure S12. Kaplan-Meier overall survival estimate of patients with abnormal cytogenetics by the presence of a single monosomy (n=16, solid line) or multiple monosomies (n=22, dotted line).