Characteristics and clinical outcomes of patients with acute myeloid leukemia with inv(3)(q21q26.2) or t(3;3)(q21;q26.2)

Guillaume Richard-Carpentier,[1,2] Caitlin R. Rausch,[3] Koji Sasaki,[2] Danielle Hammond,[2] Kiyomi Morita,[2] Koichi Takahashi,[2] Guilin Tang,[4] Rashmi Kanagal-Shamanna,[4] Kapil Bhalla,[2] Courtney D. Dinardo,[2] Gautam Borthakur,[2] Naveen Pemmaraju,[2] Elizabeth J. Shpall,[5] Amin Alousi,[5] Naval G. Daver,[2] Guillermo Garcia-Manero,[2] Marina Y. Konopleva,[2] Farhad Ravandi,[2] Hagop M. Kantarjian[2] and Tapan M. Kadia[2]

[1]Department of Medicine, Division of Medical Oncology and Hematology, University of Toronto, Princess Margaret Cancer Center, Toronto, Ontario, Canada; [2]Department of Leukemia, Division of Cancer Medicine, University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [3]Division of Pharmacy, University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [4]Department of Hematopathology, Division of Pathology and Laboratory Medicine, University of Texas, MD Anderson Cancer Center, Houston, TX, USA and [5]Department of Stem Cell Transplantation and Cellular Therapy, Division of Cancer Medicine, University of Texas, MD Anderson Cancer Center, Houston, Texas, USA

Correspondence: T. M. Kadia
tkadia@mdanderson.org

G. Richard-Carpentier
guillaume.richard-carpentier@uhn.ca

Received: October 18, 2022.
Accepted: March 13, 2023.
Early view: March 23, 2023.

https://doi.org/10.3324/haematol.2022.282030

Supplemental data

Characteristics and clinical outcomes of patients with acute myeloid leukemia with inv(3)(q21q26.2) or t(3;3)(q21;q26.2)

Guillaume Richard-Carpentier[1,2], Caitlin R. Rausch[3], Koji Sasaki[2], Danielle Hammond[2], Kiyomi Morita[2], Koichi Takahashi[2], Guilin Tang[4], Rashmi Kanagal-Shamanna[4], Kapil Bhalla[2], Courtney D. Dinardo[2], Gautam Borthakur[2], Naveen Pemmaraju[2], Elizabeth J. Shpall[5], Amin Alousi[5], Naval G. Daver[2], Guillermo Garcia-Manero[2], Marina Y. Konopleva[2], Farhad Ravandi[2], Hagop M. Kantarjian[2], Tapan M. Kadia[2]

[1] Department of Medicine, Division of Medical Oncology and Hematology, University of Toronto, Princess Margaret Cancer Centre, Toronto, Ontario, Canada
[2] Department of Leukemia, Division of Cancer Medicine, University of Texas, MD Anderson Cancer Center, Houston, Texas, USA
[3] Division of Pharmacy, University of Texas, MD Anderson Cancer Center, Houston, Texas, USA
[4] Department of Hematopathology, Division of Pathology and Laboratory Medicine, University of Texas, MD Anderson Cancer Center, Houston, Texas, USA
[5] Department of Stem Cell Transplantation and Cellular Therapy, Division of Cancer Medicine, University of Texas, MD Anderson Cancer Center, Houston, Texas, USA

Supplemental methods

Cytogenetic and molecular analysis

Somatic gene mutation data was obtained from single-gene assays targeting 9 genes prior to 2013 and amplicon-based targeted next-generation sequencing (NGS) from 2013 onwards. Prior to 2013, molecular results were obtained in 49 patients using single-gene assays for the following genes: *NPM1* and *FLT3* (PCR followed by capillary electrophoresis based fragment analysis, Limit of detection [LOD]: ~2.5%), *KRAS*, *NRAS*, *KIT* and *JAK2* (pyrosequencing, LOD: 5-10%) and *IDH1*, *IDH2* and *CEBPA* (Sanger sequencing, LOD: 10-20%). From 2013 onwards, molecular results were obtained using a 53-gene NGS panel in 4 patients (2013-2014), using a 28-gene NGS panel in 22 patients (2014-2017) and using a 81-gene NGS panel in 25 patients. Complementary gene mutation data from a 295-gene panel (SureSelect custom panel, Agilent Technologies, Santa Clara, CA, USA) was available for 7 patients included in a previous study evaluating the impact of somatic mutation clearance at remission in AML[1]. Only known pathogenic or likely pathogenic variants (inferred as somatic mutations using evidence from literature or online databases) were included for this study. Variant of unknown significance or of likely germline origin were excluded in our analyzes. Gene mutation testing was not performed in 8 patients presenting between 2000 and 2005.

References

1. Morita K, Kantarjian HM, Wang F, et al. Clearance of Somatic Mutations at Remission and the Risk of Relapse in Acute Myeloid Leukemia. *J Clin Oncol* 2018; 36: 1788-1797. 2018/04/28. DOI: 10.1200/JCO.2017.77.6757.

Supplementary Table 1. Frequency of somatic gene mutations

Gene mutation	Total (n = 108) n (%)	Newly diagnosed (n = 53) n (%)	Relapsed/Refractory (n = 55) n (%)	*p* value
Splicing factor	17/28 (61)	7/10 (70)	10/18 (56)	0.69
SF3B1	14/28 (50)	5/10 (50)	9/18 (50)	1.00
SRSF2	1/25 (4)	0/8 (0)	1/17 (6)	1.00
U2AF1	2/25 (8)	2/8 (25)	0/17 (0)	0.09
Signaling pathway	38/51 (75)	12/17 (71)	26/34 (76)	0.74
NRAS	23/94 (24)	6/43 (14)	17/51 (33)	0.03
PTPN11	14/51 (27)	6/17 (35)	8/34 (24)	0.51
KRAS	13/94 (14)	6/43 (14)	7/51 (14)	1.00
JAK2	5/65 (8)	3/26 (12)	2/39 (5)	0.38
***FLT3*-ITD**	5/95 (5)	1/44 (2)	4/51 (8)	0.37
***FLT3*-TKD D835**	4/94 (4)	1/44 (2)	3/50 (6)	0.62
KIT	3/81 (4)	3/32 (9)	0/49 (0)	0.06
NF1	2/51 (4)	1/17 (6)	1/34 (3)	1.00
CBL	1/51 (2)	1/17 (6)	0/34 (0)	0.33
Transcription factor	14/51 (27)	4/17 (24)	10/34 (29)	0.75
GATA2	7/47 (15)	0/13 (0)	7/34 (21)	0.17
RUNX1	6/49 (12)	4/15 (27)	2/34 (6)	0.06
CEBPA	3/72 (4)	1/26 (4)	2/43 (5)	1.00
Tumor suppressor	8/51 (16)	3/17 (18)	5/34 (15)	1.00
TP53	3/54 (6)	3/19 (16)	0/35 (0)	0.04
WT1	6/47 (13)	1/13 (8)	5/34 (15)	1.00
DNA methylation	8/51 (16)	3/17 (18)	5/34 (15)	1.00
DNMT3A	6/63 (10)	1/27 (4)	5/36 (14)	0.23
IDH1	1/74 (1)	1/32 (3)	0/42 (0)	0.43
IDH2	1/74 (1)	1/32 (3)	0/42 (0)	0.43
TET2	0/47 (0)	0/15 (0)	0/34 (0)	NA
Chromatin modifier	8/51 (16)	3/17 (18)	5/34 (15)	1.00
NPM1	3/85 (4)	2/41 (5)	1/44 (2)	0.61
ASXL1	7/47 (15)	3/13 (23)	4/34 (12)	0.38

Because of the different mutation testing assays and panels used over the years and in specific patients, the number of patients with available data for each genes or gene categories may vary (i.e. different denominator for calculation of mutation frequencies). For each gene categories, the denominator represents the number of patients for whom all genes from this category were tested or who had at least one mutation identified in one of these genes.

Supplementary Table 2. Univariate analyses with logistic regression for ORR

Characteristic	All Patients		Newly diagnosed		Relapsed / Refractory	
	OR* [95% CI]	*p* value	OR* [95% CI]	*p* value	OR* [95% CI]	*p* value
Disease status (treated vs untreated)	0.16 [0.06 - 0.44]	< 0.01***	NA	NA	NA	NA
Diagnosis decade (2010 vs 2000)†	1.01 [0.93 - 1.11]	0.76	1.06 [0.95 - 1.19]	0.27	0.00 [0.00 – Inf]	1.00
Age (years)	1.00 [0.97 - 1.02]	0.89	0.97 [0.94 - 1.01]	0.15	0.99 [0.94 - 1.04]	0.58
Age ≥ 60 year-old	1.07 [0.45 - 2.54]	0.88	0.54 [0.18 - 1.62]	0.27	0.64 [0.07 - 6.26]	0.70
Sex (Male)	0.42 [0.18 - 1.01]	0.05**	0.53 [0.17 - 1.61]	0.26	0.36 [0.06 - 2.07]	0.25
WBC (x 10^9/L)	0.99 [0.96 - 1.01]	0.22	0.98 [0.95- 1.00]	0.08**	0.97 [0.88 - 1.07]	0.58
Hemoglobin (g/dL)	1.03 [0.79 - 1.33]	0.85	1.08 [0.79 - 1.46]	0.64	0.95 [0.47 - 1.89]	0.87
Platelets (x 10^9/L)	1.00 [1.00 - 1.00]	0.24	1.00 [1.00 - 1.00]	0.80	1.01 [1.00 - 1.02]	0.07**
Peripheral blood blasts (%)	0.98 [0.96 - 1.00]	0.02***	0.98 [0.95 - 1.00]	0.04***	0.99 [0.95 - 1.03]	0.61
Bone marrow blasts (%)	0.98 [0.96 - 1.00]	0.10	0.98 [0.96 - 1.01]	0.23	1.00 [0.96 - 1.04]	0.91
Secondary AML	0.37 [0.11 - 1.19]	0.09*	0.51 [0.15 - 2.46]	0.48	0.00 [0.00 - Inf]	1.00
Therapy-related AML	1.10 [0.39 - 3.10]	0.86	0.59 [0.18 - 1.90]	0.38	0.00 [0.00 - Inf]	1.00
Therapy intensity (low vs high)	0.72 [0.30 - 1.73]	0.47	1.70 [0.53 - 5.48]	0.38	0.36 [0.06 - 2.23]	0.27
Additional chromosomal abnormality	0.40 [0.15 - 1.05]	0.06**	0.45 [0.13 - 1.60]	0.22	0.38 [0.06 - 2.53]	0.31
Monosomy 7	0.52 [0.22 - 1.26]	0.15	0.53 [0.17 - 1.61]	0.26	0.50 [0.08 - 3.06]	0.45
Chromosome 7 abnormality	0.47 [0.20 - 1.11]	0.08**	0.54 [0.18 - 1.62]	0.27	0.29 [0.05 - 1.80]	0.18
≥ 2 additional abnormalities	0.57 [0.21 - 1.54]	0.27	1.23 [0.35 - 4.32]	0.75	0.00 [0.00 - Inf]	1.00
***FLT3*-ITD mutation**	2.04 [0.27 - 15.30]	0.49	NA	NA	3.20 [0.24 - 42.18]	0.38
***NRAS* mutation**	0.45 [0.13 - 1.51]	0.19	0.36 [0.06 - 2.21]	0.27	1.20 [0.19 - 7.64]	0.85
***KRAS* mutation**	0.76 [0.18 - 3.19]	0.71	0.80 [0.14 - 4.51]	0.80	0.00 [0.00 - Inf]	1.00
***PTPN11* mutation**	0.79 [0.20 - 3.21]	0.74	0.86 [0.10 - 7.51]	0.89	0.50 [0.05 - 5.22]	0.56
NRAS or KRAS mutation	0.53 [0.19 - 1.45]	0.21	0.60 [0.15 - 2.40]	0.47	0.71 [0.11 - 4.45]	0.72
NRAS, KRAS or PTPN11 mutation	0.42 [0.12 - 1.52]	0.19	0.20 [0.02 - 2.39]	0.20	0.50 [0.08 - 3.15]	0.46

Abbreviations: ORR, overall remission rate. OR, odds ratio; CI, confidence interval; WBC, white blood cell count; NA, not applicable; Inf, Infinite.

***** Lower OR means lower odds of achieving CR

† No patient with relapsed/refractory AML with *MECOM*-R AML between 2000-2009 achieved CR (0/9 = 0%) compared to 17% (6/35) between 2010-2019.

*** Significant *p* values at a level of 0.05.

** *p* values between 0.05 and 0.10

Supplementary Table 3. Univariate analyses for OS (clinical characteristics)

Characteristic	All Patients		Newly diagnosed		Relapsed / Refractory	
	HR [95% CI]	*p* value	HR [95% CI]	*p* value	HR [95% CI]	*p* value
Disease status (untreated vs treated)	1.16 [0.76 - 1.75]	0.49	NA	NA	NA	NA
Diagnosis decade (2010 vs 2000)	0.99 [0.95 - 1.04]	0.70	0.99 [0.93 - 1.05]	0.65	0.98 [0.90 - 1.06]	0.58
Age (years)	1.01 [1.00 - 1.03]	0.04***	1.02 [1.00 - 1.04]	0.08**	1.02 [0.99 - 1.04]	0.17
Age ≥ 60 year-old	1.41 [0.93 - 2.14]	0.11	1.27 [0.71 - 2.28]	0.42	1.91 [0.87 - 4.16]	0.11
Sex (Male)	1.06 [0.69 - 1.62]	0.80	1.06 [0.59 - 1.93]	0.84	1.20 [0.59 - 2.44]	0.62
WBC (x 10^9/L)	1.02 [1.01 - 1.02]	< 0.01***	1.02 [1.01 - 1.03]	< 0.01***	1.02 [1.01 - 1.04]	< 0.01***
WBC ≥ 20 x 10^9/L	2.19 [1.34 - 3.59]	< 0.01***	1.85 [0.96 - 3.56]	0.06**	7.19 [2.54 - 20.39]	< 0.01***
Hemoglobin (g/dL)	1.04 [0.89 - 1.21]	0.67	0.96 [0.78 - 1.19]	0.73	1.17 [0.89 - 1.52]	0.26
Platelets (x 10^9/L)	1.00 [1.00 - 1.00]	0.39	1.00 [1.00 - 1.00]	0.83	1.00 [0.99 - 1.00]	0.14
Peripheral blood blasts (%)	1.01 [1.00 - 1.02]	< 0.01***	1.01 [1.00 - 1.02]	0.04***	1.01 [1.00 - 1.02]	0.04***
Bone marrow blasts (%)	1.01 [1.00 - 1.02]	0.15	1.01 [1.00 - 1.02]	0.21	1.01 [1.00 - 1.02]	0.45
Secondary AML	1.81 [1.31 - 2.91]	0.01***	1.90 [0.91 - 3.99]	0.09**	1.65 [0.81 - 3.34]	0.17
Therapy-related AML	1.09 [0.64 - 1.86]	0.74	1.19 [0.63 - 2.25]	0.58	0.90 [0.27 - 2.97]	0.86
Therapy intensity (low vs high)	0.88 [0.57 - 1.36]	0.57	0.60 [0.32 - 1.13]	0.11	0.90 [0.27 - 2.97]	0.86

Abbreviations: OS, overall survival, HR, hazard ratio; CI, confidence interval; WBC, white blood cell count; NA, not applicable; Inf, Infinite.

*** Significant *p* values at a level of 0.05.

** *p* values between 0.05 and 0.10

Supplementary Table 4. Univariate analyses for OS (genetic characteristics)

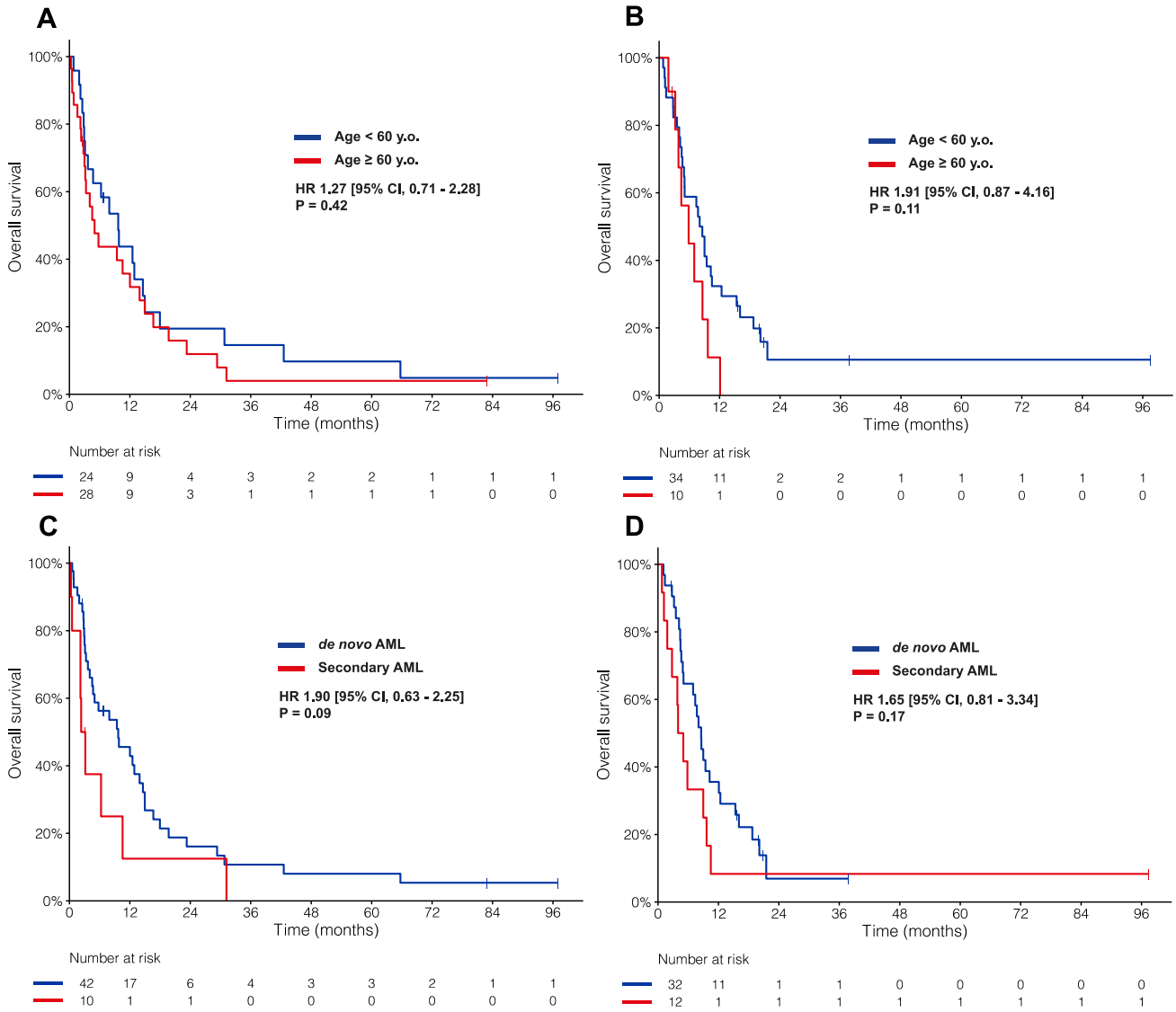
Characteristic	All Patients		Previously Untreated		Previously Treated	
	HR [95% CI]	p value	HR [95% CI]	p value	HR [95% CI]	p value
Type of *MECOM*-r (inv(3) as reference)	0.90 [0.54 - 1.51]	0.69	0.71 [0.31 - 1.59]	0.40	0.96 [0.45 - 2.03]	0.91
Additional chromosomal abnormality	0.80 [0.49 - 1.29]	0.35	0.69 [0.36 - 1.32]	0.26	0.96 [0.42 - 2.20]	0.93
Monosomy 7	0.87 [0.57 - 1.32]	0.51	1.17 [0.64 - 2.14]	0.60	0.54 [0.28 - 1.03]	0.06**
Chromosome 7 abnormality	0.81 [0.53 - 1.22]	0.31	0.92 [0.51 - 1.65]	0.78	0.71 [0.37 - 1.36]	0.30
≥ 2 additonal abnormalities	1.25 [0.80 - 1.94]	0.33	1.14 [0.59 - 2.23]	0.69	1.41 [0.73 - 2.75]	0.31
Monosomal karyotype	0.95 [0.63 – 1.43]	0.80	1.26 [0.70 – 2.27]	0.45	0.63 [0.33 – 1.19]	0.15
***FLT3*-ITD mutation**	1.06 [0.42 - 2.62]	0.91	0.56 [0.08 - 4.13]	0.57	1.05 [0.32 - 3.50]	0.94
***DNMT3A* mutation**	3.09 [1.17 - 8.16]	0.03***	Inf [0.00 - Inf]	1.00	2.45 [0.67 - 8.95]	0.17
***NRAS* mutation**	1.22 [0.73 - 2.05]	0.45	2.39 [0.97 - 5.85]	0.06**	0.79 [0.37 - 1.66]	0.53
***KRAS* mutation**	2.37 [1.20 - 4.68]	0.01***	1.72 [0.65 - 4.55]	0.28	6.58 [2.07 - 20.94]	< 0.01***
***PTPN11* mutation**	0.65 [0.31 - 1.33]	0.24	1.63 [0.44 - 6.00]	0.46	0.40 [0.15 - 1.11]	0.08**
***NRAS* or *KRAS* mutation**	1.47 [0.92 - 2.35]	0.11	2.05 [0.96 - 4.37]	0.06**	1.20 [0.60 - 2.39]	0.60
***NRAS*, *KRAS* or *PTPN11* mutation**	1.24 [0.64 - 2.39]	0.52	3.22 [0.83 - 12.48]	0.09	0.72 [0.30 -1.76]	0.47
***SF3B1* mutation**	1.85 [0.73 - 4.73]	0.20	1.56 [0.26 - 9.43]	0.63	1.97 [0.60 - 6.50]	0.27
***ASXL1* mutation**	2.62 [1.07 - 6.42]	0.04***	11.92 [1.05 - 134.9]	0.045***	1.79 [0.52 - 6.17]	0.361
***GATA2* mutation**	1.83 [0.73 - 4.57]	0.19	NA	NA	2.80 [1.00 - 7.83]	0.05**
***WT1* mutation**	1.03 [0.39 - 2.71]	0.95	0.00 [0.00 - Inf]	1.00	1.19 [0.39 - 3.64]	0.76
***RUNX1* mutation**	0.48 [0.17 - 1.36]	0.17	0.13 [0.02 - 1.06]	0.06**	0.44 [0.06 - 3.32]	0.43
***JAK2* mutation**	2.51 [0.97 - 6.47]	0.06**	2.90 [0.80 - 10.47]	0.11	2.69 [0.59 - 12.35]	0.20
***TP53* mutation**	0.65 [0.15 - 2.76]	0.56	0.69 [0.15 - 3.23]	0.64	NA	NA
***FLT3*-TKD mutation**	0.38 [0.09 - 1.54]	0.18	0.56 [0.08 - 4.13]	0.57	0.30 [0.04 - 2.24]	0.24
***KIT* mutation**	0.53 [0.13 - 2.19]	0.38	0.57 [0.13 - 2.44]	0.45	NA	NA
***NPM1* mutation**	2.04 [0.63 - 6.62]	0.24	2.63 [0.60 - 11.53]	0.20	1.74 [0.23 - 13.26]	0.59
***CEBPA* mutation**	2.36 [0.70 - 7.92]	0.16	2.74 [0.34 - 22.33]	0.35	3.40 [0.72 - 16.06]	0.12

Abbreviations: OS, overall survival, HR, hazard ratio; CI, confidence interval; WBC, white blood cell count; NA, not applicable; Inf, Infinite.

*** Significant p values at a level of 0.05.

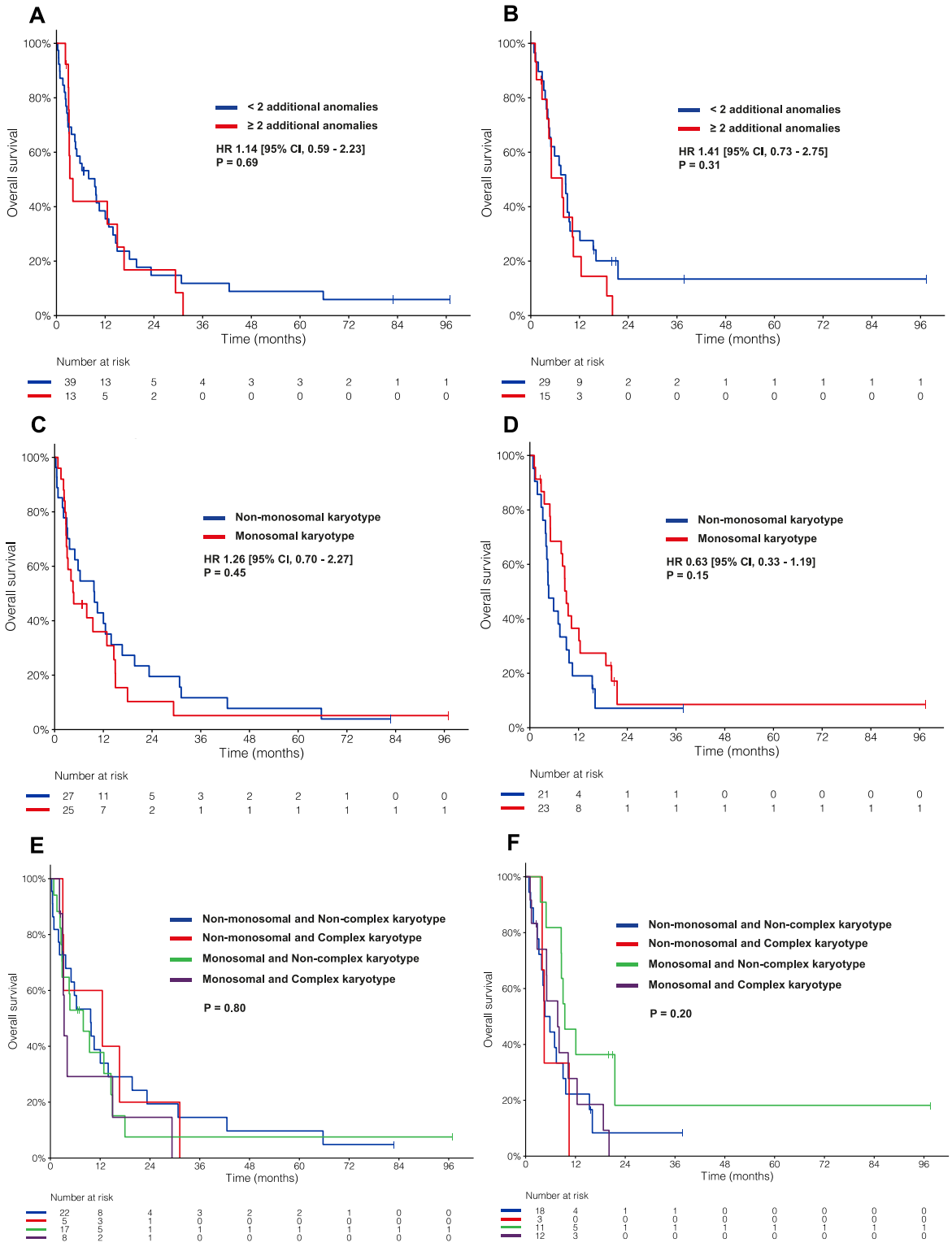
** p values between 0.05 and 0.10

Supplementary Figure 1. Overall survival according to baseline characteristics
OS according to age in A) ND patients and B) R/R patients. OS according in *de novo* versus secondary AML in C) ND patients and D) R/R patients.



Supplementary Figure 2. OS according to karyotype

OS according to complex karyotype in A) ND patients and B) R/R patients. OS according to monosomal karyotype in C) ND patients and D) R/R patients. OS according to both monosomal and/or complex karyotype in E) ND patients and F) R/R patients.



Supplementary Figure 3. OS according to treatment intensity

OS according to treatment intensity in A) ND patients and B) R/R patients. High-intensity treatment was defined as regimens including anthracyclines and/or high-dose cytarabine (≥ 1 g/m^2).