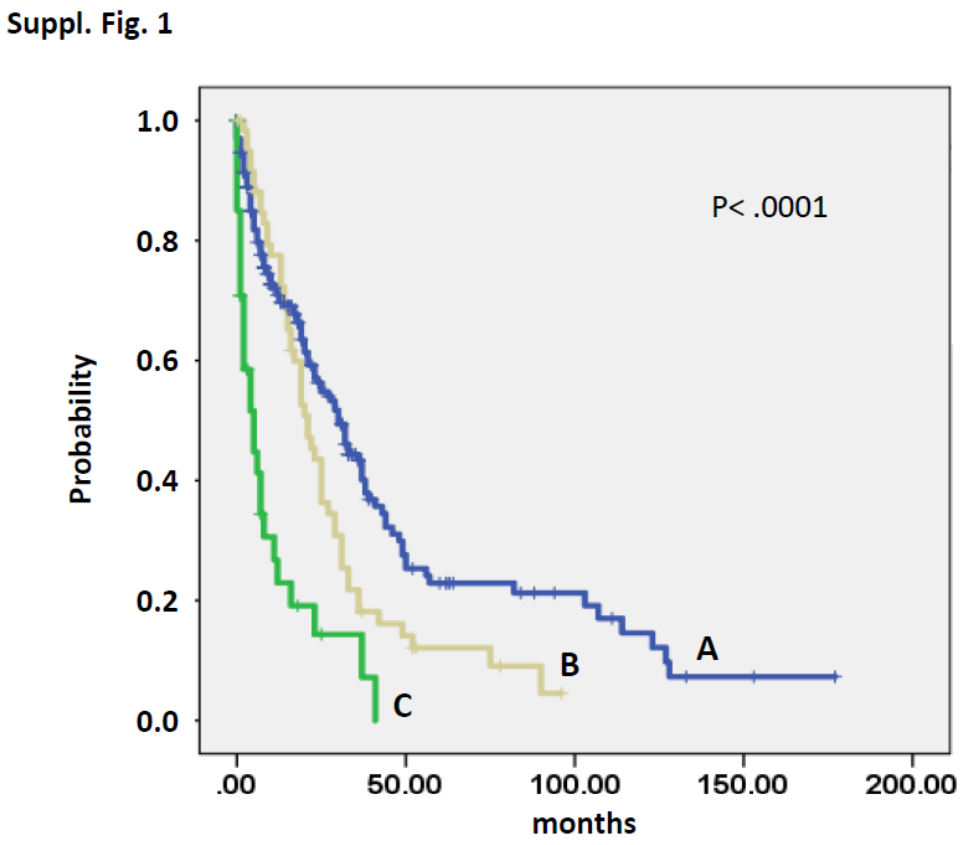
Supplementary figure 1. Kaplan-Meier survival curves of the 3 patient cohorts. Patients were divided into 3 cohorts based on criteria recently proposed by an international consortium:[28] patients without evidence of progression (cohort A, n=236), patients who developed disease progression (transformation and/or disease-related death) during follow up (cohort B, n=61), and patients who had already transformed to sAML at the time of sampling (cohort C, n=40). Median survival was 30 months in cohort A, 21 months in cohort B, and 5 months in cohort C, respectively.



Supplementary table 1. Laboratory values of the 3 patient cohorts: patients without evidence of progression (cohort A), patients who developed disease progression (transformation and/or disease-related death) during follow up (cohort B), and patients who had already transformed to secondary AML at the time of sampling (cohort C).

Parameters	Cohort A, N=236	Cohort B, N=61	Cohort C, N=40
WBC x 10^9/L; median (range)	12.2 (2.5-139)	17.9 (3.6-94)	27.8 (4.1-205)
Hb g/dL; median (range)	11.0 (4.3-14.9)	11.1 (6.4-15.3)	9.8 (4.1-14.1)
Platelet x 10^9/L; median (range)	115 (5-726)	89 (7-695)	56 (17-397)
PB Blast %; median (range)	0 (0-17)	0 (0-13)	2.0 (0-94)
Monocyte %; median (range)	22 (3-60)	24 (4-74)	26 (0-74)

Supplementary table 2. Frequencies of other than RASopathy gene mutations in the 3 patient cohorts: patients without evidence of progression (cohort A), patients who developed disease progression (transformation and/or disease-related death) during follow up (cohort B), and patients who had already transformed to secondary AML at the time of sampling (cohort C). NGS analysis was performed as described in Patients and Methods. Details regarding gene panel, library preparation and data processing have been reported previously.[27] In case of conflicting results for the pathogenicity of a variant, the underlying data were manually rechecked. Variants were considered (likely) benign unless they satisfied all of the following conditions: the mutation occurred in a protein coding region, the mutation function was not synonymous, the annotation from ClinVar was not benign, and the change was not found at a frequency of 1% or higher in a population. Clearly pathogenic variants and variants of unknown significance were retained as potential mutations. Only mutations with allele frequencies of at least 20% were considered as positive, and only mutations with a frequency of at least 10% in the total cohort are shown.

Genes	**Cohort A**	**Cohort B**	**Cohort C**	**P**
SETBP1	33/198 (17%)	16/57 (28%)	15/58 (26%)	.090
TET2	145/198 (73%)	35/57 (61%)	39/58 (67%)	.202
EZH2	35/198 (18%)	9/57 (16%)	12/58 (21%)	.784
ASXL1	34/198 (17%)	17/57 (30%)	11/58 (19%)	.106
SRSF2	76/198 (38%)	19/57 (33%)	17/58 (29%)	.409
RUNX1	17/198 (9%)	11/57 (19%)	13/58 (22%)	.007
TP53	21/198 (11%)	8/57 (14%)	5/58 (9%)	.635

Supplementary table 3. Detailed informations (region, ENST, ENSP, variant allele frequency) of molecular aberrations detected in RASopathy genes in samples of patients with CMML derived AML.

Sample	Gene	Region	ENST	ENSP	VAF
1	*NRAS*	115258748	c.34G>A	p.Gly12Ser	25.44
2	*NRAS*	115258748	c.34G>C	p.Gly12Arg	47.89
3	*NRAS*	115258747	c.35G>A	p.Gly12Asp	90.63
4	*NRAS*	115258748	c.34G>A	p.Gly12Ser	30.58
5	*NRAS*	115258748	c.34G>C	p.Gly12Arg	38.77
6	*NRAS*	115258748	c.34G>C	p.Gly12Arg	31.90
7	*NRAS*	115258744	c.38G>A	p.Gly13Asp	49.92
8	*NRAS*	115258747	c.35G>A	p.Gly12Asp	47.69
9	*NRAS*	115258748	c.34G>T	p.Gly12Cys	70.17
10	*NRAS*	115258744	c.38G>T	p.Gly13Val	44.51
11	*NRAS*	115256521	c.190T>G	p.Tyr64Asp	32.78
12	*NRAS* *CBL*	115258747 119148922	c.35G>A c.1142G>C	p.Gly12Asp p.Cys381Ser	30.20 23.20
13	*NRAS* *NF1*	115258744 29663388	c.38G>A c.4979T>A	p.Gly13Asp p.Ile2015Asn	36.22 35.22
14	*NRAS*	115258747	c.35G>A	p.Gly12Asp	45.60
15	*NRAS*	115258744	c.38G>A	p.Gly13Asp	28.40
16	*KRAS*	25398285	c.34G>A	p.Gly12Ser	21.72
17	*KRAS*	25398284	c.35G>A	p.Gly12Asp	41,46
18	*KRAS*	25398285	c.34G>A	p.Gly12Ser	47.74
19	*KRAS*	25380279	c.179G>	p.Gly60Val	49.14
20	*KRAS*	25398285	c.34G>A	p.Gly12Ser	34.24
21	*KRAS*	25380283	c.183A>T	p.Gln61His	40.20
22	*KRAS*	25398285	c.34G>C	p.Gly12Arg	46.00
23	*KRAS*	25398284	c.35G>A	p.Gly12Asp	43.19
24	*KRAS*	25398266	c.53C>A	p.Ala18Asp	47.59
25	*KRAS*	25398284	c.35G>C	p.Gly12Ala	34.63
26	*KRAS* *NF1*	25380285 29496957	c.112-17440C>T c.528T>A	p.Thr58Ile p.Asp176Glu	55.06 37.34
27	*CBL*	119148991	c.1211G>A	p.Cys404Tyr	86.02
28	*CBL*	119148919	c.1139T>C	p.Leu380Pro	93.67
29	*CBL*	119148891	c.1111T>C	p.Tyr371His	89.49
30	*CBL*	119148925	c.1145A>G	p.Lys382Arg	74.40
31	*CBL*	119149246	c.1254C>G	p.Phe418Leu	92.30
32	*CBL*	119148991	c.1211G>A	p.Cys404Tyr	34.30
33	*CBL*	119148883	c.1103A>G	p.Tyr368Cys	32.21
34	*NF1*	29653035	c.4970A>G	p.Tyr1657Cys	87.90
35	*NF1*	29554236	c.4956C>A	p.Asn1673Lys	27.66
36	*NF1*	29496957	c.630T>A	p.Asp176Glu	49.44
37	*NF1*	29665757	c.6855>A	p.Tyr2285*	86.50
38	*PTPN11*	112940006	c.1658C>T	p.Thr553Met	52.86
39	*PTPN11*	112888165	c.181G>T	p.Asp61Tyr	34.83
40	*PTPN11*	112926910	c.1530G>T	p.Gln510His	50.43
41	*PTPN11*	112888202	c.218C>T	p.Thr73Ile	27.50