Genomic arrays identify high-risk chronic lymphocytic leukemia with genomic complexity: a multicenter study

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Supplementary Methods

TP53 mutation analysis and IGHV determination

In brief, exons 4-8 (in some centers also exons 1-3 and 9-10) of the *TP53* gene were sequenced in 1266/2293 patients. Sanger sequencing was used in most cases (>80%; **Supplemental Table 2**) while the remaining cases were evaluated by targeted next generation sequencing with a variant allele frequency cutoff of 10%. Patients carrying IGHV genes with <98% germline identity were classified as IG-mutated CLL (M-CLL); those with ≥98% as IG-unmutated CLL (U-CLL).

Genomic array analysis

DNA was extracted from whole blood samples or CD19-purified cells. DNA integrity and purity were routinely verified by gel electrophoresis and a260/a280 ratios, respectively. Features of array platforms included in this study are summarized in Haraksingh et al.(1) and array processing was performed according to the manufacturer's protocols. In general, the specific resolution of a particular platform is defined by the number and genomic distribution of the arrayed elements. Minimal resolution and sensitivity for platforms in this study are depicted in **Supplemental Table 3**. CNAs positioned in/overlapping with regions containing known germline copy-number variations (CNV, Database of Genomic Variants (DGV), http://projects.tcag.ca/variation) were discarded.(2) Any CNA greater than 5 Mb was included regardless of annotation in the DGV. CNAs were annotated against NCBI build GRCh37/hg19. Each genomic profile provided by the contributing centers was collated centrally and CNAs were classified as chromosomal aberrations related to a specific chromosome (loss or gain of the entire chromosome) or chromosome arm (e.g. loss 1p, gain 1p, loss 1q, gain 1q, etc). Putative chromothripsis was defined as ≥10 oscillating copy numbers involving 2 or 3 copy number states on one chromosome.(3)

ROC analysis

Receiver Operating Characteristic (ROC) curve analysis was used to assess the diagnostic accuracy of the total number of CNAs, measured at baseline(4) (date of array analysis), on overall survival. In order to detect the most appropriate threshold(s) reflecting genomic complexity, and to accommodate the time effect, time-dependent ROC analysis was applied by evaluating different time points from date of array analysis. In particular the years 5, 10, and 15 were considered and the most appropriate threshold for genomic complexity was detected in each case. The threshold/cutoff selection was based both on the (a) minimum distance criterion, and (b) the Youden index.(5, 6) The analysis was performed in R based on the

package “tdROC”, which calculates the time-dependent sensitivity, specificity and area under the curve using a nonparametric weighting adjustment.(7)

Maximally selected rank statistic

An alternative approach was applied in order to assess the diagnostic power of the total number of CNAs on overall survival, based on maximizing selected rank statistics(8). The most appropriate threshold was determined, resulting in two distinct groups. The maximally selected rank statistic approach was applied based on the R package “maxstat”.

Bootstrap

A bootstrapping procedure was applied to validate the stability of the detected thresholds. Particularly, 100 bootstrap samples, which were equal in size to the originally selected population, were randomly generated with replacement from the originally selected CLL population. Subsequently, for each bootstrap sample, the same procedure was applied, including the application of the time-dependent ROC analysis and the maximally selected rank statistic approach. The derived thresholds in each case were recorded resulting in the threshold distribution, which enabled us to evaluate the thresholds detected in the originally selected CLL population. The percentages observed for the original thresholds exhibited an average of 79% signifying their prevalence and validating the original selection.

Concordance index

The Harrell’s concordance index(9, 10) was calculated for each multivariable Cox model to assess the discriminatory ability of the Cox model.(11)

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Table S1. Demographics and biological features of the patients included in the study

N=2293	Whole cohort (N,%)	Untreated‡ (N,%)	Treated§ (N,%)
Male	1419, 67.9%	620, 66.2%	225, 69.0%
Female	672, 32.1%	316, 33.8%	101, 31.0%
Median age diagnosis	62.5 years	63.0 years	60.5 years
<55	363, 23.9%	222, 22.7%	102, 28.3%
>70	360, 23.7%	236, 24.1%	75, 20.8%
Binet A	794, 58.3%	597, 64.2%	146, 45.8%
Binet B	387, 28.4%	239, 25.7%	106, 33.2%
Binet C	181, 13.3%	94, 10.1%	67, 21.0%
M-CLL*	509, 50%	345, 54.6%	56, 36.4%
*TP53*abn†	238, 17.7%	82, 10.8%	66, 28%
del(11)(q22.3)	395, 17.2%	164, 16.8%	77, 21.3%
trisomy 12	293, 12.8%	118, 12.1%	49, 13.6%
del(13)(q14)	1184, 51.6%	528, 53.9%	195, 54.0%
Median follow up	33 months	44 months	15 months

Abbreviations: *M-CLL= CLL with mutated IGHV, †*TP53*abn= del(17)(p13.1) and/or *TP53* mutation, ‡"untreated"=untreated at date of sampling. §"treated"=treated at date of sampling. Percentages were calculated with respect to the number of patients with available data for the respective parameter in each of the 3 groups and not with respect to the total number of patients in the respective groups (whole cohort, untreated or treated).

Table S2. Sequencing methods used by participating centers

Center	Total nr	*TP53* sequencing method
Groningen UMC	NA	NA
Hospital del Mar Barcelona	NA	NA
University Hospital Brno	67	Sanger
Uppsala	364	Sanger
Karolinska Institute	216	Sanger
Southampton (Royal Bournemouth Hospital)	152	Sanger
Radboud UMC	206	Sanger/NGS
CHUV	NA	NA
Amsterdam UMC	56	Sanger
Pitie-Salpetriere	150	Sanger
MLL	38	Sanger/NGS
IUCT-Oncopole	14	NGS
SVHM	3	NGS

Table S3. Platform characteristics for genomic arrays used in this study

Center	Agilent oligonucleotide 180K	SurePrint G3 ISCA CGH+SNP	Affymetrix 250K SNP-array	Affymetrix SNP6.0	CytoScan HD array	Whole-Genome 2.7M	sensitivity	size resolution
Groningen UMC					138		10-20%	1 kb
Hospital del Mar Barcelona						74	10-25%	1 kb
University Hospital Brno					46	21	10-20%	1 kb
Uppsala			368				10-15%	1-10 kb
Karolinska Institute	216						10-15%	13 kb
Southampton (Bournemouth Hospital)				190			10-15%	1 kb
Radboud UMC					221		10-20%	1 kb
CHUV					480		10-15%	1 kb
Amsterdam UMC (AMC)	179						10-15%	13 kb
Pitie-Salpetriere	161						10-15%	13 kb
Amsterdam UMC (VUMC)					124		10-20%	1 kb
MLL		41					10-15%	25 kb
IUCT-Oncopole					22		10-20%	1 kb
SVHM					12		10-20%	1 kb

Table S4. Copy number alterations associated with del(11)(q22.3) (*ATM*), del(13)(q14), trisomy 12 and del(17)(p13.1) (*TP53*) and different CLL subgroups

A

CLL subgroup	CNAs	ChisqTest.uncorrected.p.values	ChisqTest.corrected.p.values
del(11)(q22.3)	Loss.11q22.3	p<0,001	p<0,001
	TRIS.12	p<0,001	p<0,001
	Gain.2p	p<0,001	p<0,001
	Gain.8q	p<0,001	p<0,001
	Loss.8p	p<0,001	p<0,001
	Loss.18p	p<0,001	p<0,001
	Loss.4p	p<0,001	p<0,001
	Loss11q.other	p<0,001	p<0,001
	Loss.3q	p<0,001	p<0,001
	Gain.22q	p<0,001	p<0,001
	Loss.11p	p<0,001	p<0,001
	Loss.4q	p<0,001	p<0,001
	Gain.21q	p<0,001	0,002
	Loss.12p	p<0,001	0,002
	Gain.7p	p<0,001	0,002
	TRIS.22	p<0,001	0,002
	Gain.6p	0,001	0,003
	Loss.6q	0,002	0,003
	Gain.16q	0,002	0,016
	Loss.16q	0,002	0,016
	Loss.10	0,002	0,03
	Gain.14q	0,002	0,03
	Gain.20q	0,002	0,03
	Loss.13q14.mono	0,003	0,004
	Loss13q.other	0,005	0,009
	Loss.12q	0,005	0,022
	Loss.14q	0,009	0,014
	Loss.1q	0,009	0,016
	Gain.13q	0,011	0,024
	Gain.5p	0,011	0,052
	Loss.21q	0,013	0,037
	Gain.5q	0,015	0,033
	cth.2	0,023	0,133
	Gain.9q	0,023	0,133
	Loss.13	0,023	0,133
	Loss.Yp	0,023	0,133
	Gain.11p	0,025	0,062
	Gain.12p	0,025	0,062
	TRIS.19	0,028	0,055
	Loss.2	0,028	0,386
	cth.13	0,028	0,386
	Loss.16	0,028	0,386
	cth.22	0,028	0,386
	Loss.13q14	0,036	0,043
	Loss.20p	0,036	0,068
	TRIS.18	0,04	0,08
	Loss.2q	0,049	0,089
trisomy 12	Loss.13q14	p<0,001	p<0,001
	Loss.13q14.mono	p<0,001	p<0,001
	Loss.11q22.3	p<0,001	p<0,001
	TRIS.12	p<0,001	p<0,001
	Loss.13q14.bi	p<0,001	p<0,001
	Gain.2p	p<0,001	p<0,001
	Loss.14q	p<0,001	p<0,001
	TRIS.19	p<0,001	p<0,001
	TRIS.18	p<0,001	p<0,001
	Loss.8p	0,003	0,005
	TRIS.3	0,005	0,053
	TRIS.8	0,009	0,264
	Gain.9	0,009	0,264
	cth.13	0,009	0,264
	Gain.Y	0,009	0,264
	Loss.18p	0,01	0,017
	Loss.6q	0,013	0,02
	Gain.X	0,025	0,137
	Loss13q.other	0,035	0,067
	Gain.19p	0,035	0,116
	Gain.8q	0,04	0,056
	Loss.Y	0,041	0,073
del(13)(q14)	Loss.13q14	p<0,001	p<0,001
	Loss.13q14.mono	p<0,001	p<0,001
	TRIS.12	p<0,001	p<0,001
	Loss.13q14.bi	p<0,001	p<0,001
	Loss.14q	p<0,001	p<0,001
	Gain.17q	p<0,001	p<0,001
	Gain.13q	p<0,001	p<0,001
	Loss13q.other	p<0,001	0,001
	Loss.18p	0,005	0,007
	Loss.X	0,005	0,013
	Loss.9p	0,011	0,017
	Gain.Xq	0,015	0,035
	TRIS.21	0,021	0,062
	Gain.2p	0,026	0,032
	Gain.11p	0,028	0,056
	Loss.Y	0,03	0,045
	Loss.11q22.3	0,036	0,043
	Loss.1q	0,047	0,066
del(17)(p13.1)	Loss.17p13.1	p<0,001	p<0,001
	Gain.8q	p<0,001	p<0,001
	Loss.8p	p<0,001	p<0,001
	Loss.18p	p<0,001	p<0,001
	Loss.4p	p<0,001	p<0,001
	Loss.15q	p<0,001	p<0,001
	Gain.3q	p<0,001	p<0,001
	Loss.9p	p<0,001	p<0,001
	Loss.3p	p<0,001	p<0,001
	Loss.4q	p<0,001	p<0,001
	Loss13q.other	p<0,001	p<0,001
	Loss.6p	p<0,001	p<0,001
	Gain.17q	p<0,001	p<0,001
	Loss.2q	p<0,001	p<0,001
	Loss.20p	p<0,001	p<0,001
	Loss.10q	p<0,001	p<0,001
	Loss.9q	p<0,001	p<0,001
	Loss.18q	p<0,001	p<0,001
	Loss.2p	p<0,001	p<0,001
	Gain.15q	p<0,001	p<0,001
	Loss.19p	p<0,001	p<0,001
	Loss.10p	p<0,001	p<0,001
	Gain.11q	p<0,001	p<0,001
	Loss.5p	p<0,001	p<0,001
	cth.8	p<0,001	p<0,001
	Gain.3p	p<0,001	p<0,001
	Gain.5q	p<0,001	p<0,001
	Loss.5q	p<0,001	p<0,001
	Loss.17q	p<0,001	p<0,001
	Loss.Xp	p<0,001	p<0,001
	Gain.1p	p<0,001	p<0,001
	Loss.9	p<0,001	p<0,001
	cth.5	p<0,001	p<0,001
	Gain.13q	p<0,001	0,001
	Loss.21q	p<0,001	0,002
	cth.6	p<0,001	0,005
	Loss.13	p<0,001	0,005
	cth.17	p<0,001	0,005
	Loss.Yq	p<0,001	0,005
	cth.4	p<0,001	0,102
	Gain.9	p<0,001	0,102
	Loss.14	p<0,001	0,102
	Gain.17p	p<0,001	0,102
	cth.18	p<0,001	0,102
	Loss.18	p<0,001	0,102
	Loss.19	p<0,001	0,102
	Gain.11p	0,001	0,004
	Loss.7q	0,001	0,005
	Loss.1p	0,001	0,006
	Loss.11p	0,001	0,009
	Loss.16q	0,001	0,02
	Loss.14q	0,004	0,007
	Loss.3q	0,004	0,017
	Gain.5p	0,005	0,052
	Loss.Xq	0,005	0,052
	Gain.2q	0,006	0,032
	Loss.12p	0,006	0,032
	Gain.2p	0,007	0,012
	Loss.6q	0,012	0,023
	cth.3	0,014	0,096
	Gain.6q	0,021	0,337
	cth.7	0,021	0,337
	Gain.8p	0,021	0,337
	Gain.10p	0,021	0,337
	Gain.10q	0,021	0,337
	Loss.10	0,021	0,337
	cth.11	0,021	0,337
	Gain.14q	0,021	0,337
	Loss.16p	0,021	0,337
	Loss.19q	0,021	0,337
	Gain.9p	0,031	0,152
	Loss.12q	0,031	0,152
	Loss.Y	0,044	0,088

B

CLL subgroup	CNAs	ChisqTest.uncorrected.p.values	ChisqTest.corrected.p.values
previously treated	Loss.17p13.1	p<0,001	p<0,001
	Gain.8q	p<0,001	p<0,001
	Loss.3p	p<0,001	p<0,001
	Gain.21q	0,002	0,006
	Gain.15q	0,002	0,008
	Loss.10q	0,005	0,012
	Gain.5q	0,005	0,012
	Loss.6p	0,006	0,013
	Loss.2p	0,008	0,026
	Gain.12q	0,02	0,125
	Loss.9	0,02	0,125
	Gain.3p	0,02	0,125
	Loss.8p	0,026	0,039
	Loss.17q	0,03	0,108
	Loss.14q	0,032	0,046
	Loss.7q	0,036	0,071
Binet B/C	Loss.11q22.3	p<0,001	p<0,001
	Gain.2p	p<0,001	p<0,001
	Gain.8q	p<0,001	p<0,001
	Loss.6q	p<0,001	0,001
	Loss.8p	p<0,001	0,001
	Loss.6p	p<0,001	0,001
	Loss.13q14.bi	0,002	0,002
	Gain.21q	0,002	0,005
	Loss.1p	0,007	0,016
	Loss.17p13.1	0,009	0,013
	Loss.4p	0,017	0,026
	Gain.12p	0,018	0,063
	Loss.3p	0,019	0,034
	Loss13q.other	0,033	0,057
	Loss.21q	0,038	0,097
	Loss.12p	0,038	0,097
	Gain.19p	0,038	0,097
	Gain.9p	0,04	0,143
IGHV status	Loss.13q14	p<0,001	p<0,001
	Loss.11q22.3	p<0,001	p<0,001
	Loss.13q14.bi	p<0,001	p<0,001
	Loss.17p13.1	p<0,001	p<0,001
	Gain.2p	p<0,001	p<0,001
	Gain.8q	p<0,001	0,001
	Loss.14q	p<0,001	p<0,001
	Loss.6q	p<0,001	p<0,001
	Loss.8p	0,003	0,005
	Loss13q.other	0,003	0,006
	Loss.4p	0,004	0,007
	TRIS.19	0,004	0,013
	Loss.10q	0,008	0,023
	Gain.22q	0,008	0,023
	TRIS.12	0,01	0,013
	Loss.18p	0,01	0,016
	Loss.1q	0,011	0,021
	Loss.20p	0,012	0,024
	Loss.9p	0,02	0,038
	TRIS.18	0,033	0,075
	Loss.6p	0,034	0,07
	Loss.X	0,045	0,132
	Gain.12p	0,045	0,134
*TP53*abn (TP53 mut and/or del(17)(p13.1)	Loss.17p13.1	p<0,001	p<0,001
	Gain.8q	p<0,001	p<0,001
	Loss.8p	p<0,001	p<0,001
	Loss.18p	p<0,001	p<0,001
	Loss.4p	p<0,001	p<0,001
	Loss.15q	p<0,001	p<0,001
	Loss.9p	p<0,001	p<0,001
	Loss.Y	p<0,001	0,001
	Loss.3p	p<0,001	p<0,001
	Loss13q.other	p<0,001	p<0,001
	Loss.6p	p<0,001	p<0,001
	Gain.17q	p<0,001	p<0,001
	Loss.2q	p<0,001	p<0,001
	Loss.20p	p<0,001	p<0,001
	Loss.10q	p<0,001	p<0,001
	Gain.5q	p<0,001	p<0,001
	Loss.5q	p<0,001	0,001
	Loss.9q	p<0,001	p<0,001
	Loss.18q	p<0,001	p<0,001
	Loss.8q	p<0,001	0,001
	Loss.2p	p<0,001	p<0,001
	Gain.11p	p<0,001	0,002
	Gain.15q	p<0,001	p<0,001
	Loss.19p	p<0,001	p<0,001
	Loss.10p	p<0,001	0,001
	Gain.11q	p<0,001	p<0,001
	Loss.17q	p<0,001	0,002
	cth.3	p<0,001	p<0,001
	Gain.1p	p<0,001	0,003
	Loss.5p	p<0,001	p<0,001
	Loss.9	p<0,001	p<0,001
	cth.8	p<0,001	p<0,001
	Gain.3p	p<0,001	0,003
	cth.6	p<0,001	0,003
	Loss.4q	0,001	0,003
	Loss.6q	0,002	0,003
	Loss.11p	0,002	0,009
	Loss.13	0,002	0,033
	cth.17	0,002	0,033
	Loss.Yq	0,002	0,033
	cth.5	0,002	0,033
	Gain.3q	0,003	0,007
	Gain.13q	0,003	0,009
	Gain.Xq	0,003	0,018
	Loss.7q	0,006	0,015
	Loss.21q	0,006	0,024
	Loss.Xp	0,006	0,024
	Gain.7q	0,013	0,057
	Loss.3q	0,015	0,042
	Gain.5p	0,026	0,141
	Loss.16q	0,026	0,141
	Loss.14q	0,027	0,04
	Loss.1p	0,028	0,07
	Loss.11q22.3	0,03	0,037
	Gain.12q	0,031	0,396
	Gain.16q	0,031	0,396
	Loss.Yp	0,031	0,396
	cth.7	0,031	0,396
	Gain.8p	0,031	0,396
	Gain.10p	0,031	0,396
	Loss.10	0,031	0,396
	Gain.14q	0,031	0,396
	Loss.16p	0,031	0,396
	cth.1	0,031	0,396
	cth.4	0,031	0,396
	Gain.9	0,031	0,396
	Loss.14	0,031	0,396
	cth.14	0,031	0,396
	cth.16	0,031	0,396
	Gain.17p	0,031	0,396
	cth.18	0,031	0,396
	Loss.18	0,031	0,396
	Loss.19	0,031	0,396

Table S5. Overview of detected CNAs captured by FISH vs. genomic arrays for patients with simultaneous FISH and genomic array data

	del(11)(q22.3) (*ATM*)		trisomy 12		del(13)(q14)		del(17)(p13.1) (*TP53*)	
array								
	Freqs	Percent	Freqs	Percent	Freqs	Percent	Freqs	Percent
total	249	1	249	1	237	1	248	1
No	186	0.747	223	0.896	119	0.502	226	0.911
Yes	63	0.253	26	0.104	118	0.498	22	0.089
FISH								
total	249	1	249	1	237	1	248	1
No	171	0.687	217	0.871	98	0.414	225	0.907
Yes	78	0.313	32	0.129	139	0.586	23	0.093

Table S6. Minimal common regions of deletion or amplification

Chromosome arm	**[GRCh37] chromosomal regions**
del1q	1q21.1q21.2(144894611_149768855)
del1q	1q23.3q23.3(160751105_161479451)
dup2p	2p25.3p25.1(3721713_9073918)
dup2p	2p16.1p15(60932040_62206329)
dup2p	2p23.3p22.3(25342914_32841818)
dup3q	3q26.31q27.2(174773031-184972301)
del4p	4p15.2p15.1(27647757_28761977)
del6q	6q25.2q25.3(153946329_157482664)
del6q	6q21q21(107327737_110881818)
del8p	8p21.3p21.2(19101696_23304899)
dup8q	8q24.21q24.21(128286744_130836899)
del9p	9p24.3-p24.1(1404921-5932368)
del9p	9p21.3p21.3(22899648_23041037)
del9p	9p13.1p11.1(38916514_46746820)
del13q.other*	13q33.2q33.3(105570440_108304501)
del13q.other	13q21.2q21.33(62290433_70260961)
del13q.other	13q12.11q12.12(21375669_25254198)
dup13q	13q31.3q32.2(92210001_98472541)
del14q	14q21.1(39583972_44352416)
del14q	14q24.1q24.2(69704553_70051926)
del14q	14q32.13q32.33(95998766_104101254)
del15q	15q26.1q26.3(94308921_99056760)
del15q	15q15.1q15.1(40721923_40845473)
del15q	15q25.2q25.3(83734673_84867550)
del15q	15q21.3q21.3(54289217_54570517)
dup17q	17q22q24.3(53736288_67341400)
del18p	18p11.22p11.31(2641858_5824910)
del20p	20p12.3p12.3(6927825_7704212)x1

*del13q.other are deletions on 13q not containing the 13q14 region recurrently deleted in CLL

Table S7. Univariable Cox regression analysis for time to first treatment (TTFT)

Predictors	N=963	HR	95% HR CI	P-values
Male	920	1.34	1.11-1.62	0.003
>70 years	963	0.77	0.62-0.96	0.017
Binet B/C	915	4.74	3.95-5.69	<0.001
U-CLL*	628	4.68	3.79-5.80	<0.001
*TP53*abn†	749	1.57	1.18-2.08	0.002
del(11)(q22.3)	963	2.13	1.73-2.61	<0.001
GC‡ (3 categories)				
intermediate-GC‖ vs. low-GC§	963	1.67	1.32-2.12	<0.001
high-GC¶ vs. low-GC	963	2.81	2.04-3.86	<0.001
GC≥5	963	2.59	1.89-3.55	<0.001

Abbreviations: *U-CLL= CLL with unmutated IGHV, †*TP53*abn= del(17)(p13.1) (*TP53*) and/or *TP53* mutation, ‡GC=genomic complexity, GC categories: §low-GC=[0-2], ‖Intermediate-GC=[3-4], ¶High-GC=[≥5] CNAs detected by array

Table S8. Univariable Cox regression analysis for overall survival (OS)

Predictors	N=961	HR	95% HR CI	P-values
Male	918	1.38	1.10-1.75	0.006
>70 years	961	2.13	1.68-2.70	<0.001
Binet B/C	913	2.17	1.74-2.69	<0.001
U-CLL*	628	4.04	3.16-5.17	<0.001
*TP53*abn†	749	2.73	2.01-3.70	<0.001
del(11)(q22.3)	961	2.04	1.60-2.61	<0.001
GC‡ (3 categories)				
intermediate-GC‖ vs. low-GC§	961	1.67	1.24-2.25	0.001
high-GC¶ vs. low-GC	961	4.20	2.87-6.12	<0.001
GC≥5	961	3.90	2.68-5.67	<0.001

Abbreviations: *U-CLL= CLL with unmutated IGHV, †*TP53*abn= del(17)(p13.1) (*TP53*) and/or *TP53* mutation, ‡GC=genomic complexity, GC categories: §low-GC=[0-2], ‖Intermediate-GC=[3-4], ¶High-GC=[≥5] CNAs detected by array

Table S9. Multivariable analysis for time to first treatment (TTFT)

Multivariable analysis for time to first treatment (TTFT)			
N=528	**HR**	**95% HR CI**	**P-values**
Male	1.05	0.83-1.32	0.682
>70 years	1.10	0.83-1.46	0.496
Binet B/C	3.88	3.04-4.94	<0.001
U-CLL*	3.23	2.50-4.19	<0.001
*TP53*abn†	1.16	0.80-1.67	0.435
del(11)(q22.3)	1.24	0.95-1.61	0.11
GC‡≥5	2.00	1.28-3.14	0.002

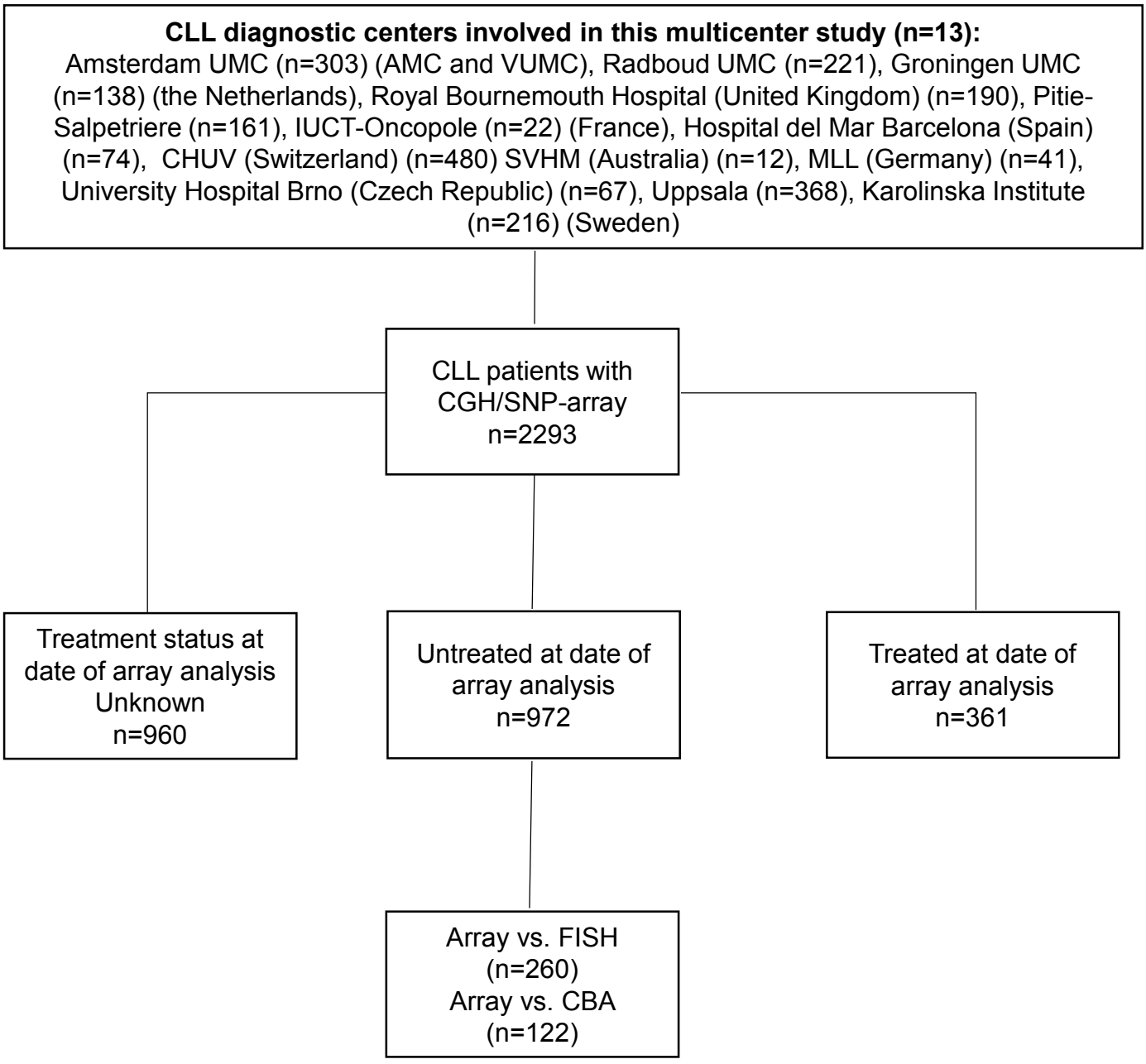
Abbreviations: *U-CLL= CLL with unmutated IGHV, †*TP53*abn= del(17)(p13.1) and/or *TP53* mutation, ‡GC≥5 =genomic complexity with ≥5 CNAs detected by array

Table S10. Multivariable analysis for overall survival (OS)

Multivariable analysis for overall survival (OS)			
N=528	**HR**	**95% HR CI**	**P-values**
Male	1.24	0.95-1.63	0.112
>70 years	2.49	1.87-3.33	<0.001
Binet B/C	1.49	1.15-1.94	0.003
U-CLL*	3.85	2.86-5.18	<0.001
*TP53*abn†	1.72	1.18-2.51	0.005
del(11)(q22.3)	0.98	0.72-1.32	0.87
GC‡≥5	2.18	1.35-3.54	0.002

Abbreviations: *U-CLL= CLL with unmutated IGHV, †*TP53*abn= del(17)(p13.1) and/or *TP53* mutation, ‡GC≥5 =genomic complexity with ≥5 CNAs detected by array

Figure S1. Diagram of the patients included in this study. For survival analysis only patients untreated at date of sampling were included to exclude the effects of prior treatment on survival.



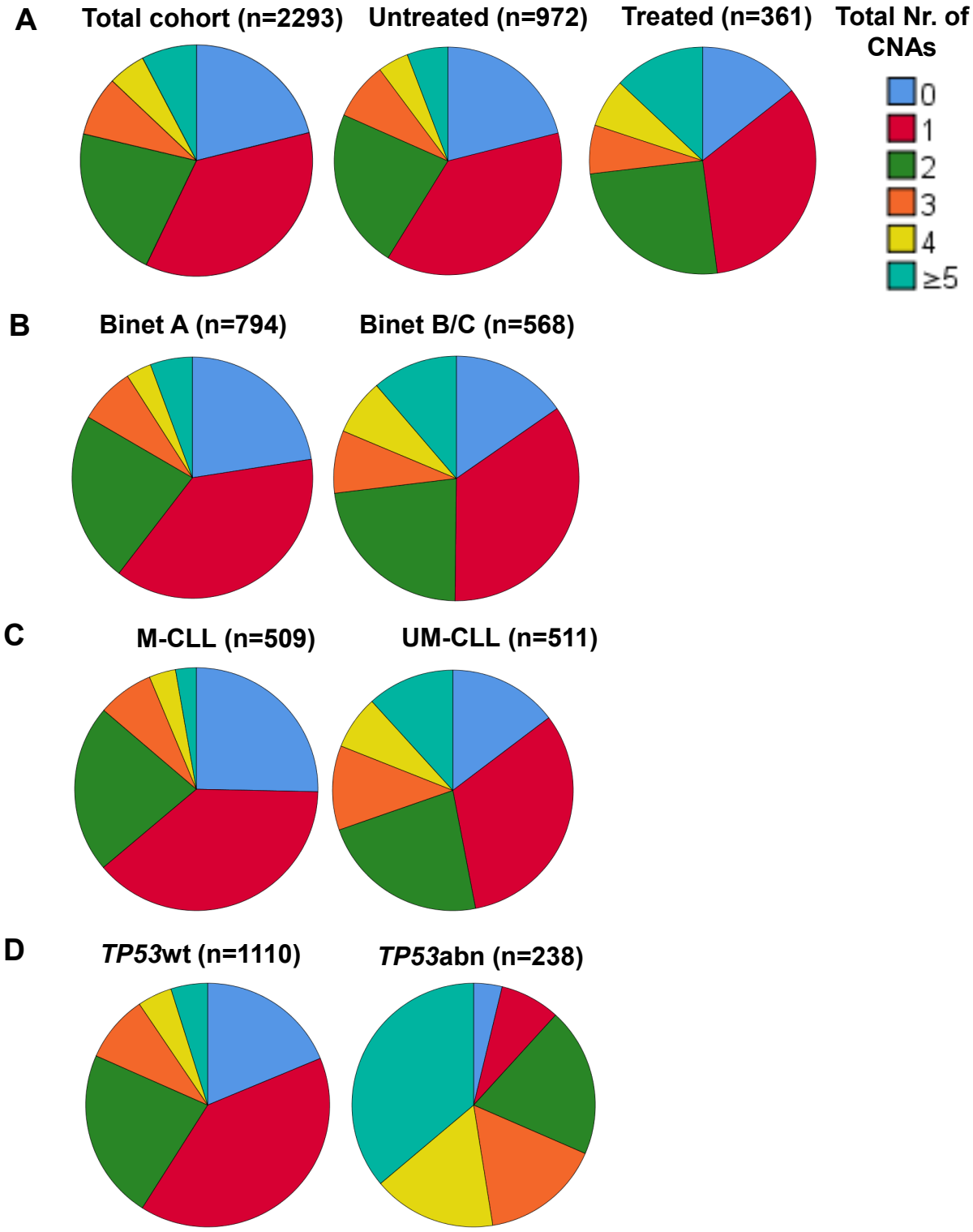
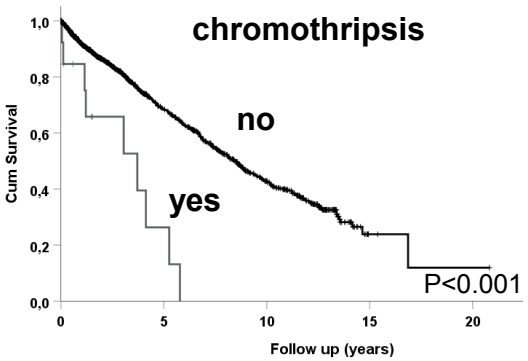


Figure S2. Overview of CNAs in different CLL subgroups. A-D) Pie charts representing the percentage of patients with a given number of CNAs detected by genomic array. Untreated and previously treated cases (A), different Binet subgroups (B), IGHV gene status (C) and *TP53* status (D) are shown

.

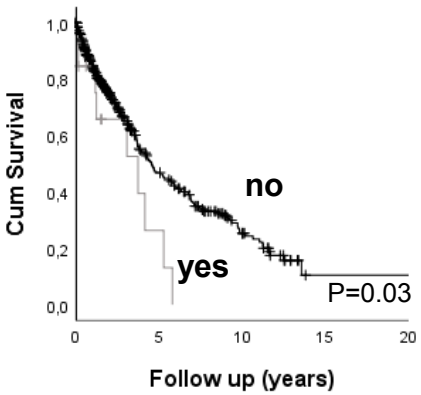
A



No. of events	Median (95% CI)
508/1419	no 8.5 (7.7-9.2)
9/13	yes 3.7 (0.6-6.8)

B

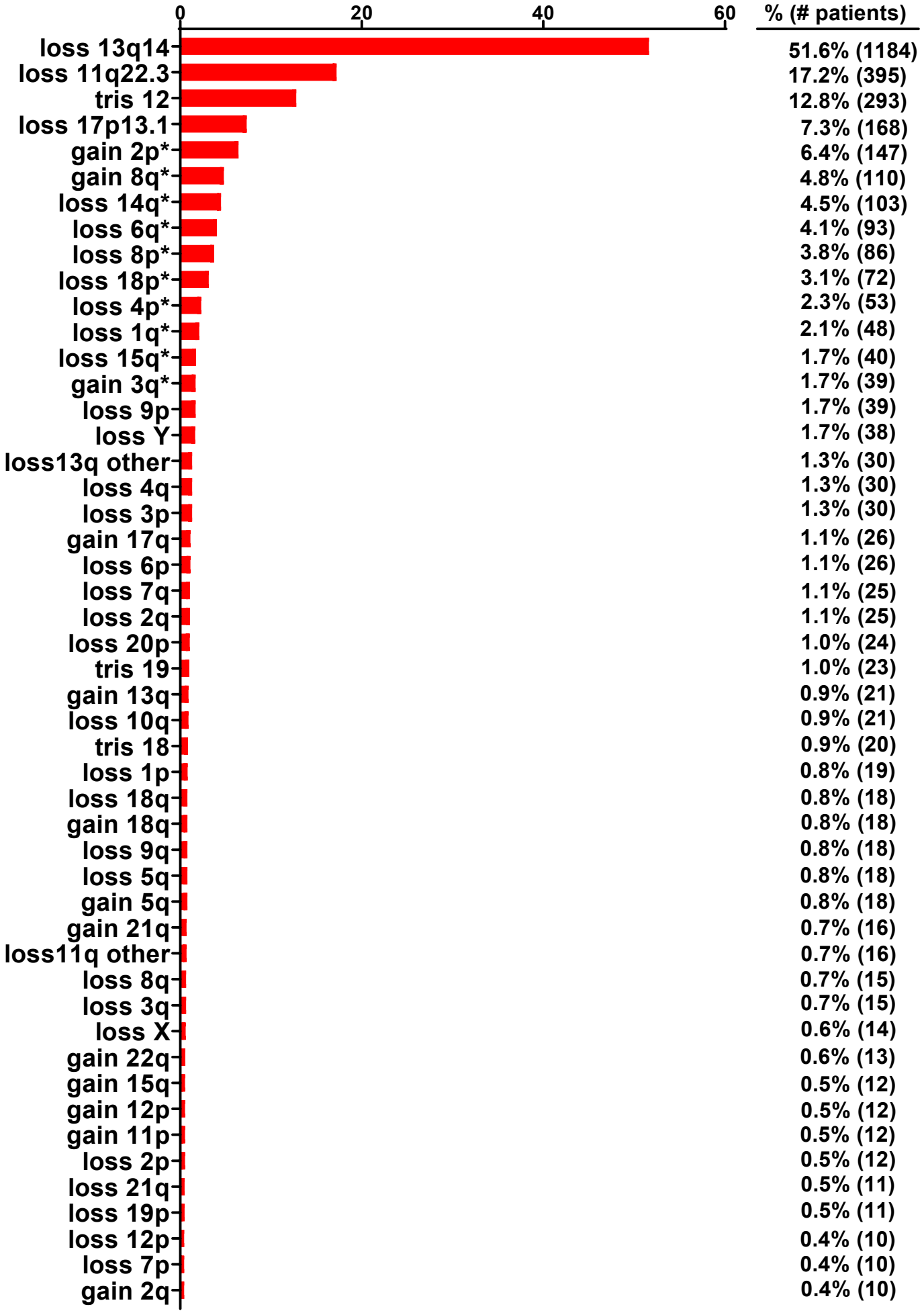
***TP53*abn/del11q22.3 (*ATM*) cases**



No. of events	Median (95% CI)
380/393	no 4.5 (3.6-5.5)
9/13	yes 3.7 (0.6-6.8)

Figure S3. Kaplan-Meier plots representing the effect of putative chromothripsis events on overall survival in all evaluable (A) and in TP53abn/del(11q22.3) (ATM) cases (B). Analyses performed on all patients of which survival data were available (irrespective of treatment information; n=1432 or n=406, respectively)

Figure S4. Overview of CNAs in this study observed in at least 10 patients



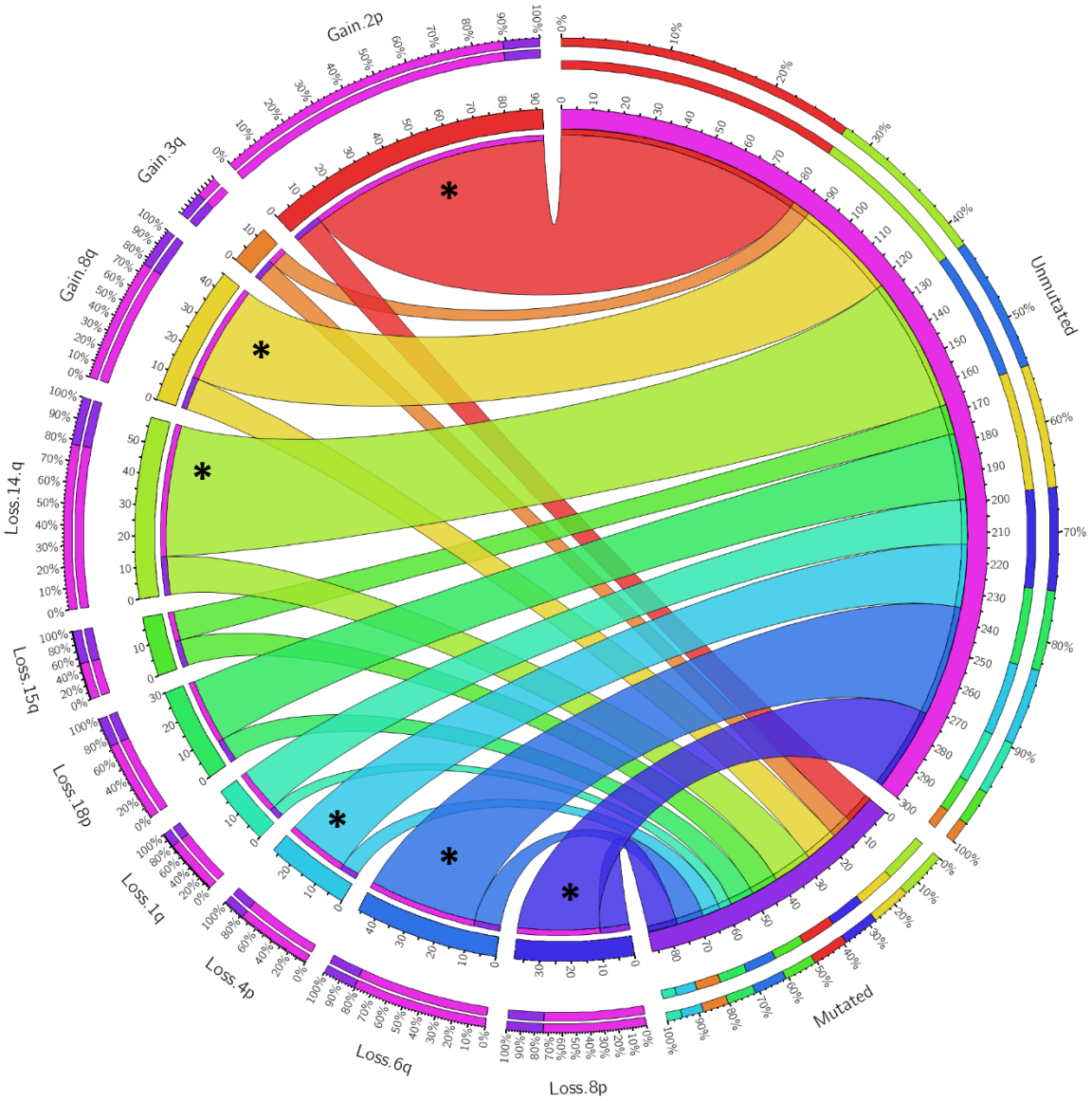


Figure S5. Correlation of CNAs detected by genomic arrays with IGHV gene status. Circos plot comparing the correlation of the 10 most frequently observed CNAs other than del(11)(q22.3) (*ATM*), trisomy 12, del(13)(q14) and del(17)(p13.1) (*TP53*) normally detected by FISH in this study, with IGHV gene status. Significant correlations with a corrected $p<0.01$ are indicated with an asterisk (*).

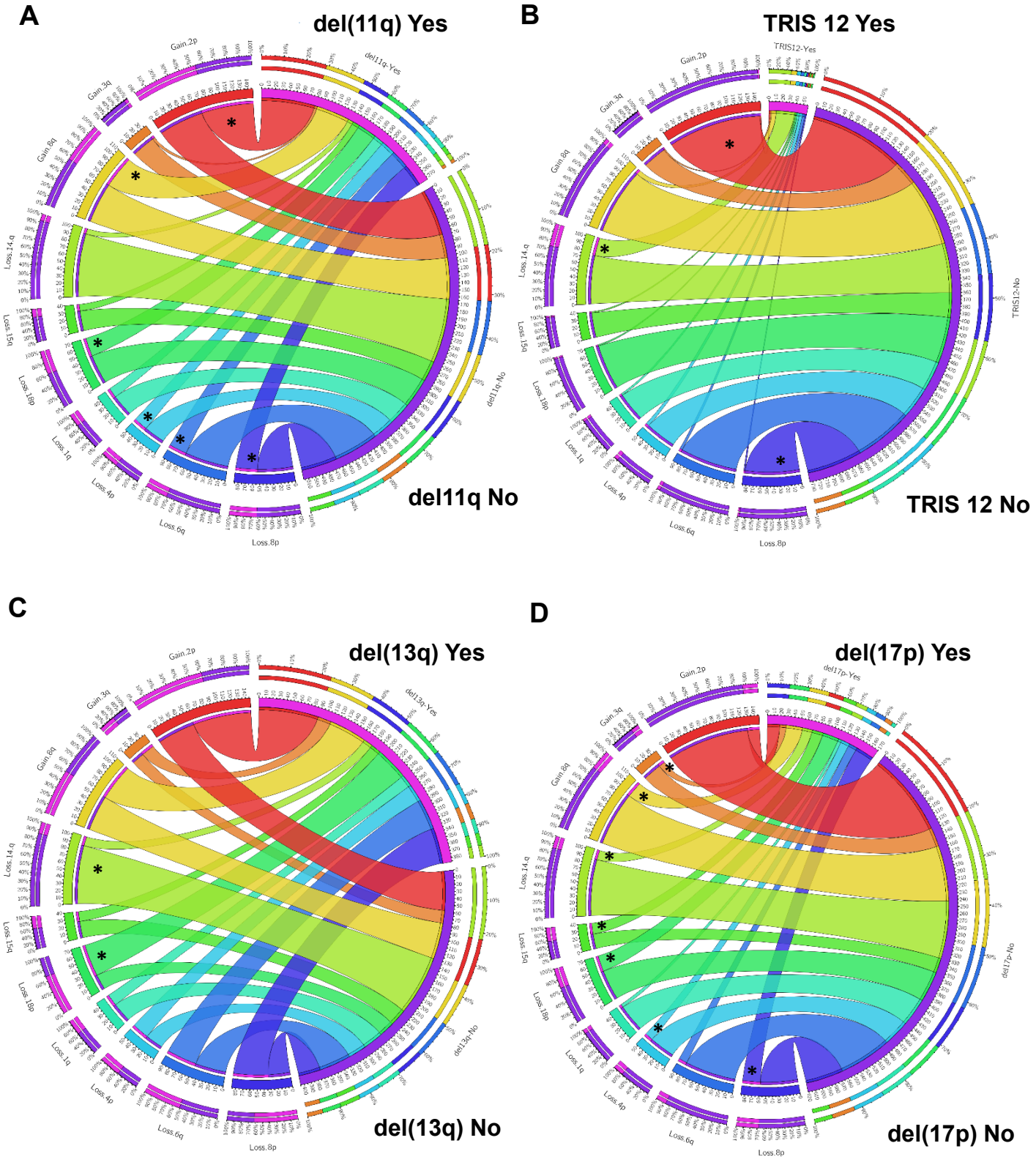


Figure S6. Correlation of CNAs detected by genomic array with CNAs normally analyzed by FISH. Circos plots comparing the correlation of del(11q) (A), trisomy 12 (B), del(13q) (C) and del(17p) (D) status with 10 CNAs not captured by CLL FISH probes. Significant correlations with a corrected $p<0.01$ are indicated with an asterisk (*).

Figure S7. Kaplan-Meier plots representing the effect of different CNAs on overall survival

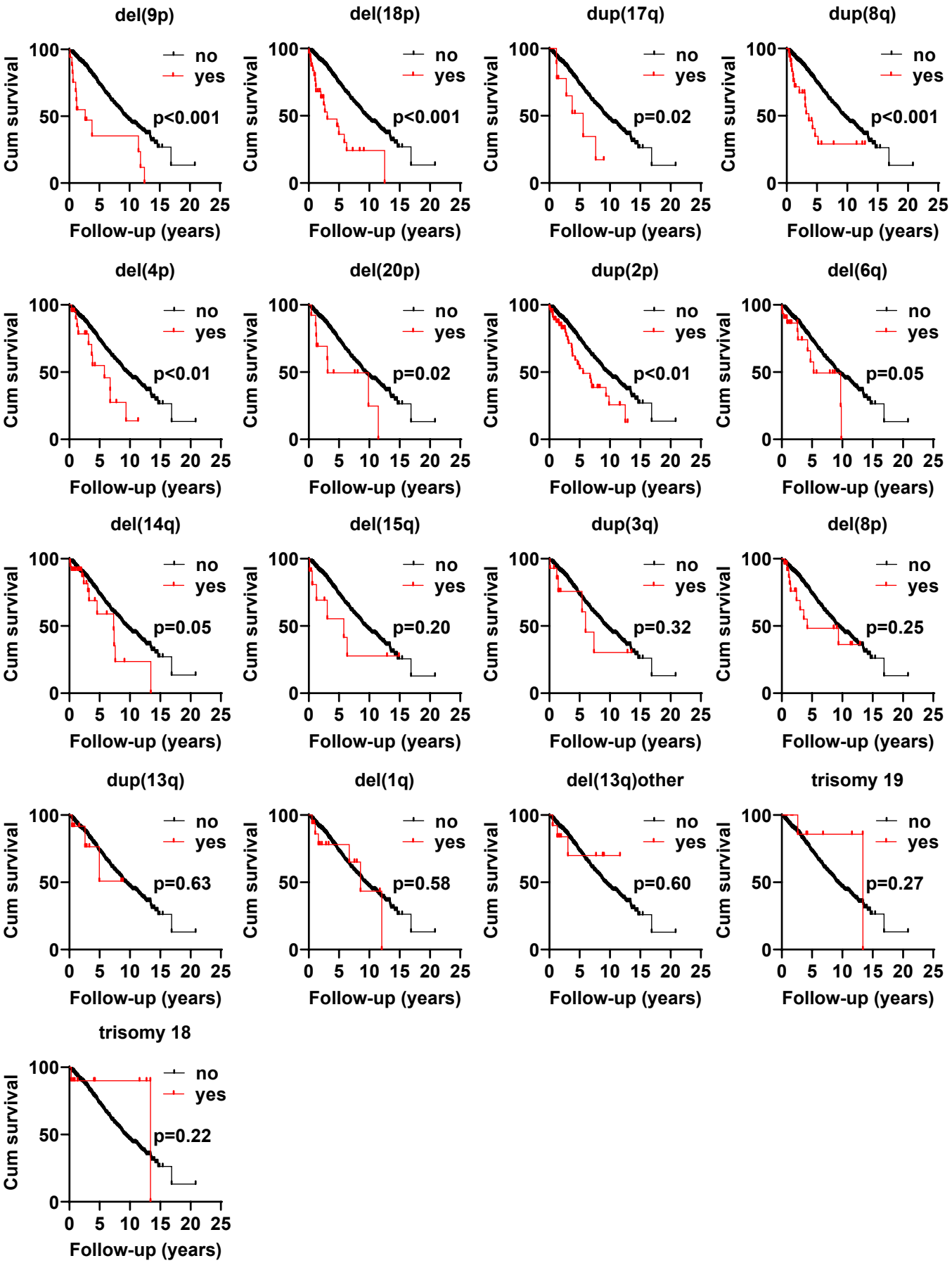
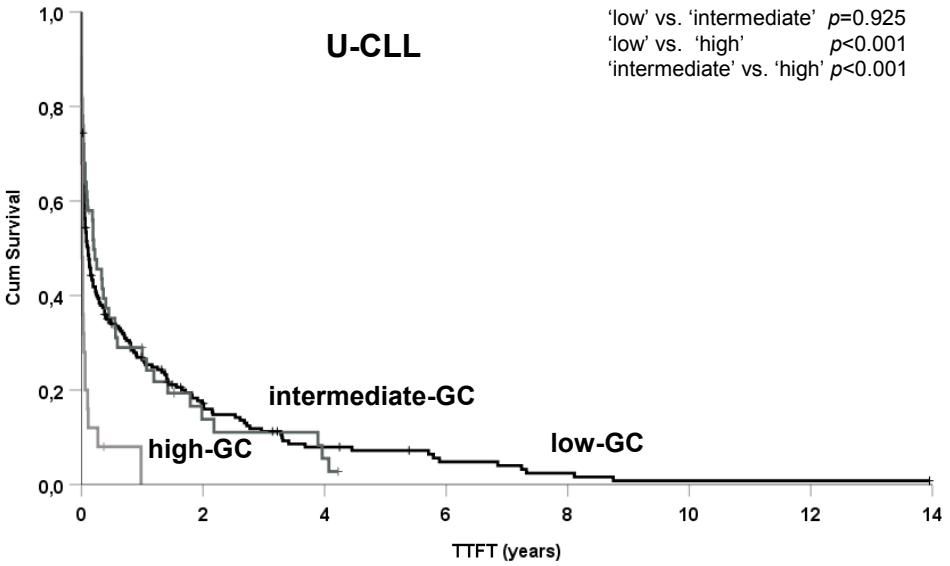


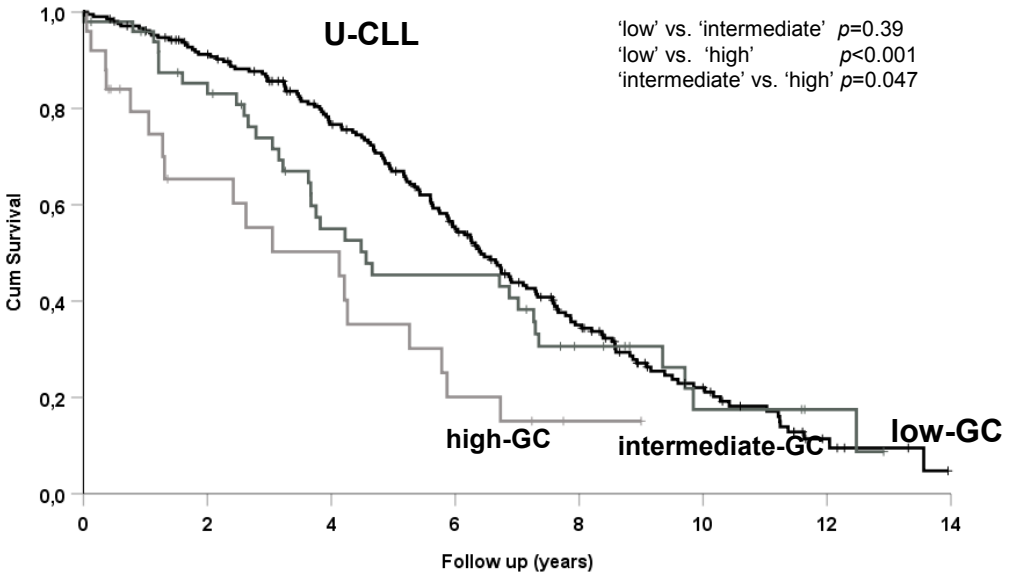
Figure S8. Kaplan-Meier plots representing the effect of GC subgroups on time to first treatment (A) and overall survival (B) in unmutated IGHV gene (U-CLL) cases.

A Time to first treatment



	No. of events	Median (95% CI)
low-GC [0-2 CNAs]	194/211	0.11 (0.05-0.2)
intermediate-GC [3-4 CNAs]	45/50	0.20 (0.03-0.4)
high-GC [≥5 CNAs]	14/25	0.01 (0.0-0.02)

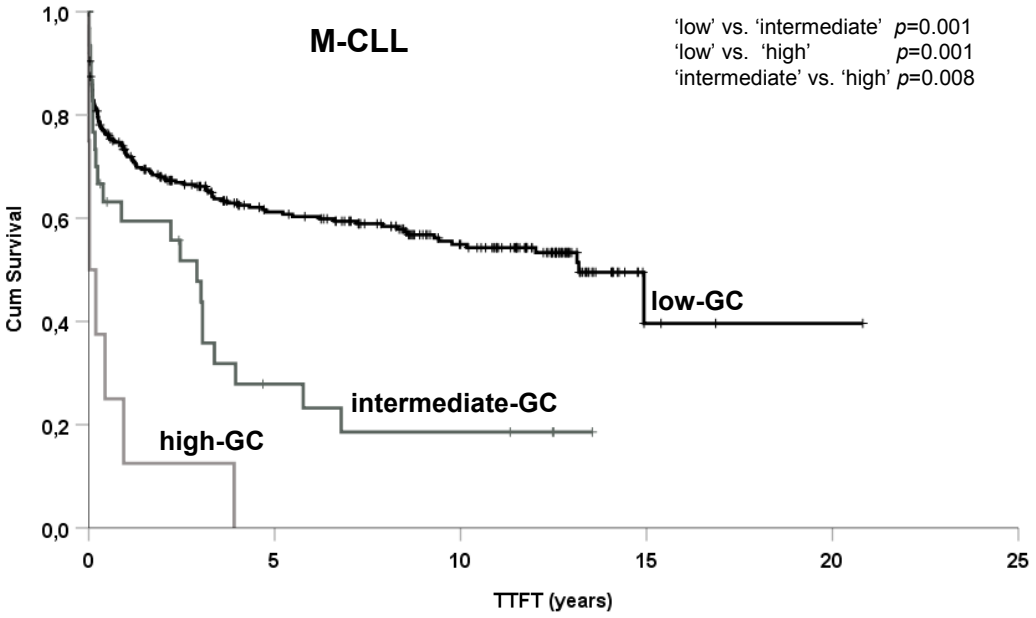
B Overall Survival



	No. of events	Median (95% CI)
low-GC [0-2 CNAs]	164/212	6.4 (5.8-7.0)
intermediate-GC [3-4 CNAs]	34/50	4.6 (1.0-8.2)
high-GC [≥5 CNAs]	18/25	4.1 (1.9-6.4)

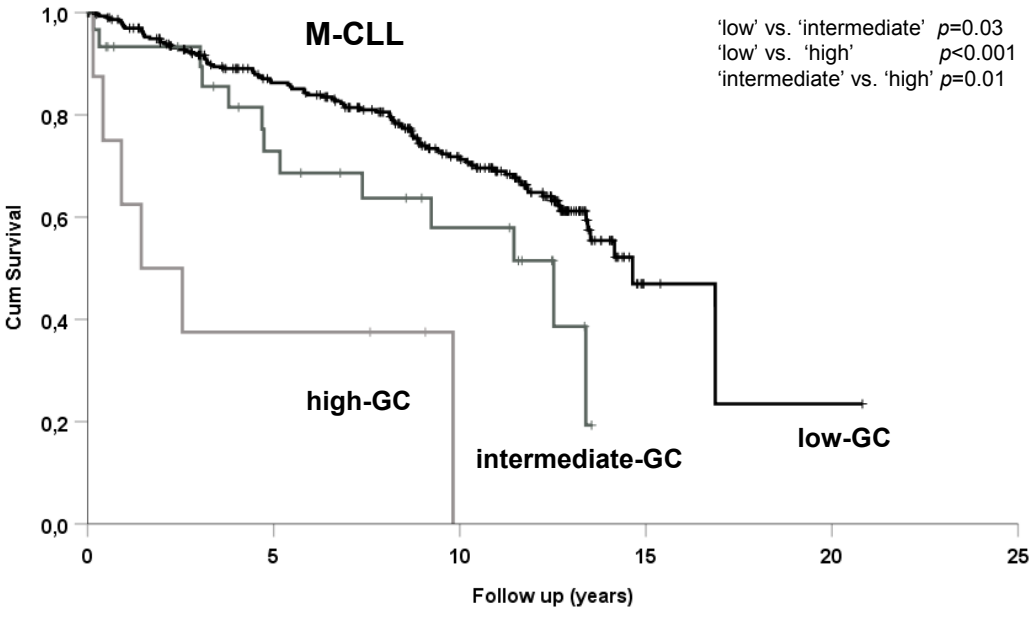
Figure S9. Kaplan-Meier plots representing the effect of GC subgroups on time to first treatment (A) and overall survival (B) in mutated IGHV gene (M-CLL) cases.

A Time to first treatment



	No. of events	Median (95% CI)
low-GC [0-2 CNAs]	129/303	13.2 (10.5-15.9)
intermediate-GC [3-4 CNAs]	22/31	2.9 (1.7-4.2)
high-GC [≥5 CNAs]	8/8	0.02 (0.0-0.2)

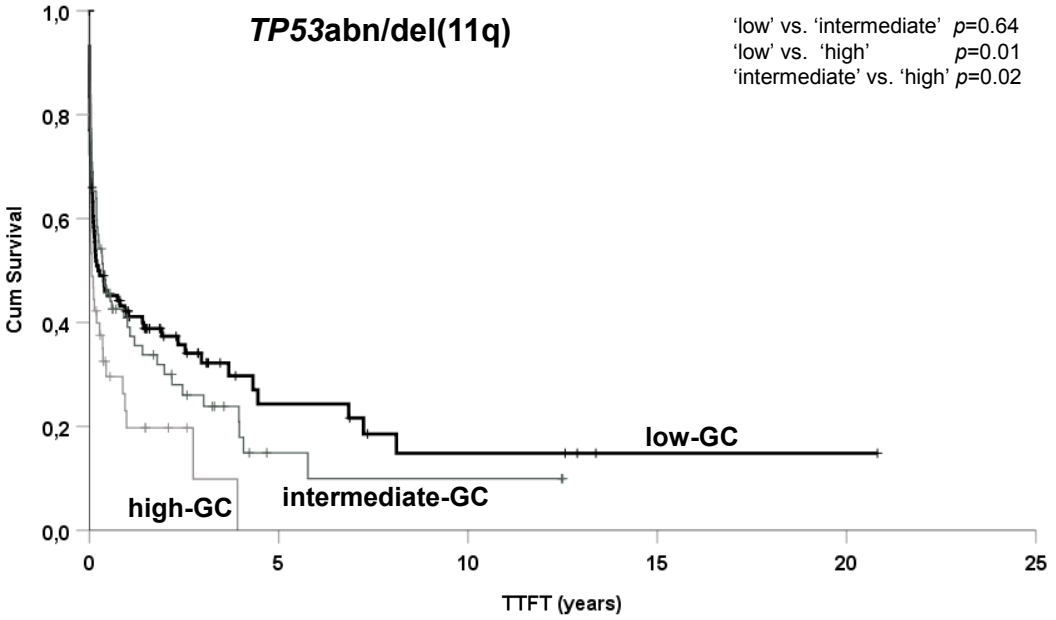
B Overall Survival



	No. of events	Median (95% CI)
low-GC [0-2 CNAs]	91/303	14.6 (13.2-16.1)
intermediate-GC [3-4 CNAs]	13/31	12.5 (7.9-17.2)
high-GC [≥5 CNAs]	6/8	1.4 (0.0-3.7)

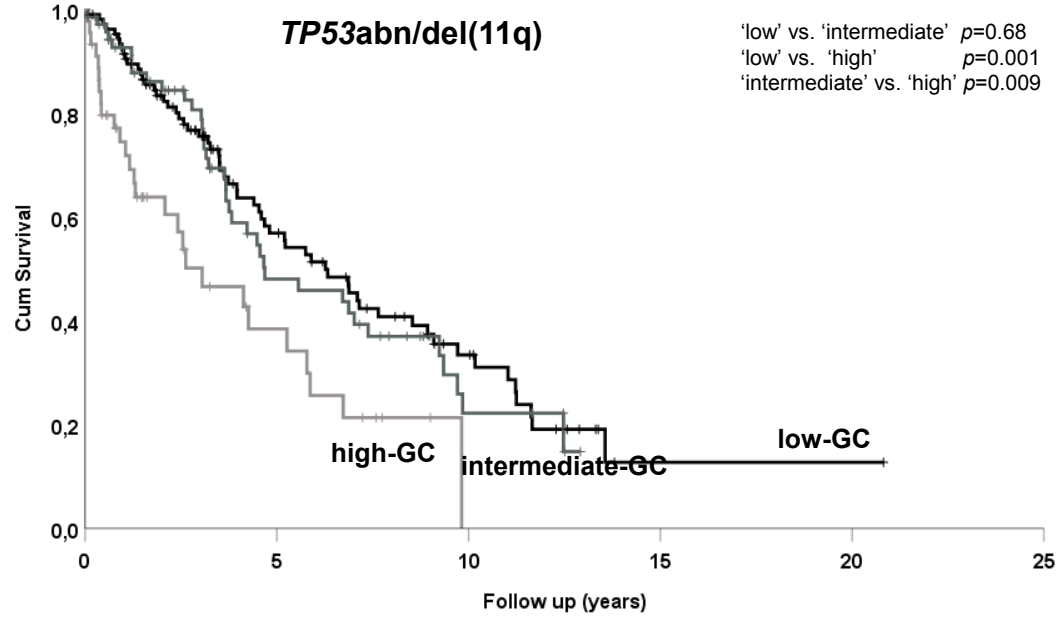
Figure S10. Kaplan-Meier plots representing the effect of GC subgroups on time to first treatment (A) and overall survival (B) in *TP53*abn/del(11q) positive cases.

A Time to first treatment



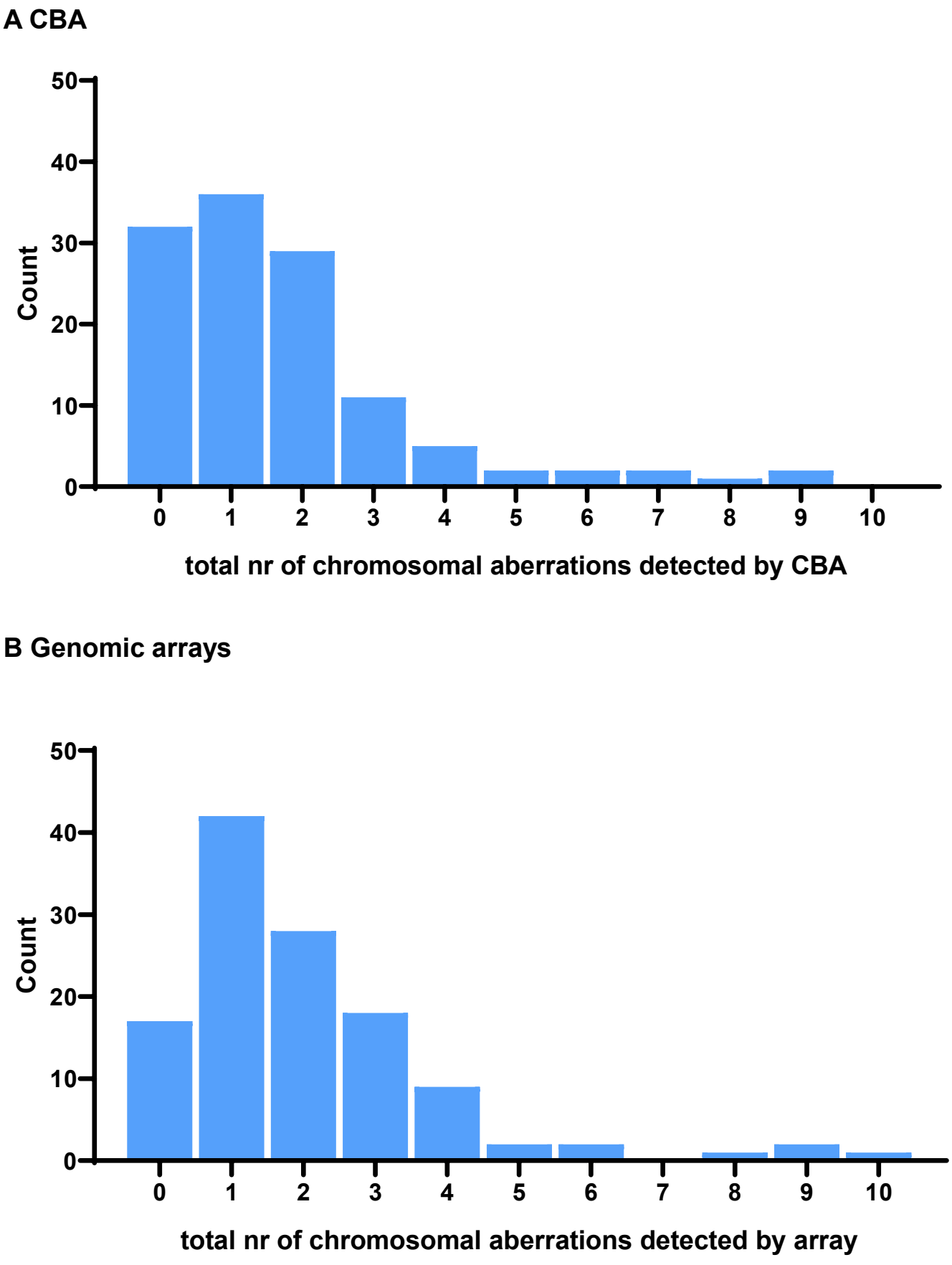
	No. of events	Median (95% CI)
low-GC [0-2 CNAs]	75/110	0.23 (0.0-0.7)
intermediate-GC [3-4 CNAs]	55/72	0.36 (0.05-0.7)
high-GC [≥5 CNAs]	36/45	0.06 (0.0-0.4)

B Overall survival



	No. of events	Median (95% CI)
low-GC [0-2 CNAs]	60/111	6.3 (4.5-8.1)
intermediate-GC [3-4 CNAs]	38/74	4.7 (2.1-7.3)
high-GC [≥5 CNAs]	27/46	3.1 (1.0-5.1)

Figure S11. Distribution of chromosomal abnormalities detected by CBA (A) and genomic arrays (B) in patients with simultaneous CBA and genomic array analyses available.



Supplemental excel file. A list of curated array profiles is provided online in the Supplemental excel file, separately uploaded.