

Genomic complexity and IGHV mutational status are key predictors of outcome of chronic lymphocytic leukemia patients with TP53 disruption

Julio Delgado,¹ Itziar Salaverria,² Tycho Baumann,¹ Alejandra Martínez-Trillos,² Eriong Lee,² Laura Jiménez,² Alba Navarro,² Cristina Royo,² Rodrigo Santacruz,¹ Cristina López,² Angel R. Payer,³ Enrique Colado,³ Marcos González,⁴ Lluís Armengol,⁵ Dolors Colomer,² Magda Pinyol,² Neus Villamor,² Marta Aymerich,² Ana Carrió,² Dolors Costa,² Guillem Clot,² Eva Giné,¹ Armando López-Guillermo,¹ Elías Campo,² and Sílvia Beà²

¹Department of Hematology, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona; ²Hematopathology Unit, Hospital Clínic, IDIBAPS, Barcelona; ³Department of Hematology, Hospital Central de Asturias, Oviedo; ⁴Department of Hematology, Hospital Clínic, Salamanca; and ⁵Genomics Laboratories, Barcelona, Spain

Correspondence: jdelgado@clinic.ub.es/sbea@clinic.cat doi:10.3324/haematol.2014.108365

Supplemental Table 1: Baseline characteristics and results of molecular studies according to the type of *TP53* disruption (*de novo* vs. acquired)

	Patients with <i>de novo</i> <i>TP53</i> disruption (n = 30)	Patients with acquired <i>TP53</i> disruption (n = 25)	P value (Fisher's exact or Mann- Whitney test)
Age at CLL diagnosis (y), median (range)	65 (30-98)	59 (41-82)	0.125
Age at detection of <i>TP53</i> disruption (y), median (range)	67 (30-98)	68 (43-82)	0.869
Sex, % male/female	50/50	60/40	0.588
Binet stage B or C, n (%)	10/29 (35)	17/23 (74)	0.006
CD38 expression \geq 30%, n (%)	13/25 (52)	15/22 (68)	0.373
ZAP70 expression \geq 20%, n (%)	16/26 (62)	15/24 (63)	1
Serum B2M, median (range)	2.9 (1.1-7.8)	4.4 (1.7-21.5)	0.016
Unmutated <i>IGHV</i> , n (%)	20/26 (77)	12/21 (57)	0.211
Cells with 17p deletion by FISH \geq 25%	14/25 (56)	7/18 (39)	0.358
Concomitant FISH abnormalities			
11q deletion, n (%)	3/27 (11)	3/18 (17)	0.670
13q deletion, n (%)	13/27 (48)	14/18 (78)	0.065
Trisomy 12, n (%)	2/27 (7)	3/18 (17)	0.375
17p aberration detected by CBA, n (%)	18/28 (64)	9/17 (53)	0.537
Complex karyotype by CBA, n (%)	16/28 (57)	7/17 (41)	0.365
<i>TP53</i> mutations, n (%)	23/30 (77)	20/25 (80)	1.0
<i>NOTCH1</i> mutations, n (%)	6/29 (21)	4/25 (16)	0.736
<i>SF3B1</i> mutations, n (%)	5/25 (20)	3/24 (13)	0.702
Copy number alterations, median (range)	3.5 (0-21)	4 (0-20)	0.833
17p alteration by CN-arrays, n (%)	15/24 (63)	14/19 (74)	0.523
Follow-up from detection of <i>TP53</i> disruption, median (range)	44 (13-130)	37 (15-80)	0.905

Abbreviations: CBA, chromosome banding analysis; CN, copy number; B2M, beta₂-microglobulin; FISH, fluorescent *in situ* hybridization, n, number; y, years.

Supplemental Table 2: Detailed description of cytogenetic, molecular and copy number results in our cohort of patients with 17p/TP53 disruption

Patient code	% of cells with 17p- by FISH	Additional FISH abnormalities	IGHV	TP53 gene	Chromosome banding analysis	Complex karyotype	Acquired deletion
002	35	+12	Unmutated	WT	N/A	N/A	Yes
007	0	13q-	Mutated	Mutated	46,XY[20]	No	No
030	22	13q-	Unmutated	Mutated	44,XY,add(8)(p23),del(13)(q14q21),-14,add(17)(p13),-21,+mar[cp8]/46,XY[2]	Yes	Yes
047	41	13q-, +12	Mutated	Mutated	46,XY,t(1;19;15)(q23;p13;p11),+12,del(13)(q14q21),del(17)(p12),-17[cp13]	Yes	Yes
050	0	13q-	N/A	Mutated	N/A	N/A	Yes
075	98	-	N/A	Mutated	N/A	N/A	Yes
076	6	-	Unmutated	Mutated	46,XY,t(1;6)(p32;p23)[10]/46,XY[2]	No	No
088	14	13q-, 11q-	Mutated	WT	44,XY,del(2)(q?),add(3)(p26),-8,del(11)(q14q23),add(12)(q24),del(13)(q13q31),add(16)(p13),del(17)(p11.2),add(18)(q23)[cp7]/46,XY[5]	Yes	Yes
092	0	13q-	N/A	Mutated	47,XY,+12[3]/46,XY[21]	No	No
094	40	13q-	Unmutated	Mutated	NA	No	Yes
096	N/A	+12	Unmutated	WT	46,XX,del(6)(q23q25),del(17)(p11.2)[7]/47,XX,+12[2]/47,XX,+12,add(7)(q33)[1]/46,XX[3]	Yes	No
102	N/A	13q-, +12	Unmutated	Mutated	46,XX,-11,+12,del(13)(q14q21),i(17)(q10)[1]/46,XX[17]	Yes	Yes
108	0	13q-, 11q-	Unmutated	Mutated	46,XX,del(11)(q22q23),del(13)(q14q14)[8]/46,XX[19]	No	No
163	N/A	N/A	Unmutated	Mutated	47,XX,+12[9]/46,XX[41]	No	No
177	64	-	Unmutated	Mutated	N/A	N/A	No
192	79	13q-	Mutated	Mutated	46,XX,t(13;14)(q14.3;q32),del(17)(p12)[9]/46,XX[8]	No	No
279	0	13q-	Unmutated	Mutated	46,XX[20]	No	Yes
287	10	13q-, +12	Mutated	Mutated	47,XY,+12[1]/46,XY[19]	No	Yes
294	75	13q-	Unmutated	Mutated	42-44,X,-Y[4],add(1)(q42)[4],-3[4],add(11)(p15)[4],der(13)t(13;?)(q13;?)[2],-14[4],del(17)(p12)[4],-20[2],+mar1[3],+mar2[1][cp4]/46,XY[16]	Yes	No
296	12	13q-, +12, 11q-	Unmutated	WT	47,XY,+12[2]/47,idem,del(11)(q22q23)[2]/47,idem,t(9;13)(q31;q14.3)[3]/46,idem,dic(8;17)(p11;p11)[2]/46,XY[11]	Yes	No
306	13	13q-, 11q-	Unmutated	WT	46,XY,del(2)(p23),add(3)(p24),del(6)(q22q24),add(17)(p13)[cp18]/46,XY[4]	Yes	No
344	10	13q-	Mutated	Mutated	46,XX[20]	No	Yes
390	40	13q-, +12	Unmutated	Mutated	46,XY,del(13)(q14q21)[6]/46,XY[14]	No	No
418	N/A	N/A	Unmutated	Mutated	45,XX,-15,t(15;17)(q?;?),del(17)(p13)[?]	Yes	No
511	0	+12	Unmutated	Mutated	47,XY,+12[6]/46,XY[14]	No	Yes

524	98	-	Unmutated	Mutated	45,XX,del(13)(q14q21),-16,-17,-18,+mar1,+mar2[11]	Yes	No
526	96	13q-	Unmutated	Mutated	43-45,XX,del(3)(q25q27)[7],add(5)(p15.2)[3],add(6)(q26)[7],-10[12],der(12)[7],der(14)t(10;14)(q11.2;p11.2)[12],-15[5],-17[3],del(20)(q11.2)[2],+mar1[4],+mar2[1],+mar3[1][cp12]	Yes	No
576	0	13q-	Mutated	Mutated	N/A	N/A	Yes
587	53	13q-	Mutated	Mutated	45,XY,ins(3;5)(q25;q11.2q31),-5,del(14)(q24)[1]/46,XY[36]	Yes	Yes
612	N/A	N/A	Unmutated	Mutated	46,XY,del(10)(q22q26)[10]/46,XY[27]	No	Yes
618	93	-	Mutated	Mutated	45,XY,-8,der(17)t(8;17)(q12;p13)[8]/46,XY[6]	No	No
646	87	-	Unmutated	WT	46,XX[12]	No	No
656	81	11q-	Unmutated	Mutated	92,XXXX,add(13)(p10)x2,del(17)(p13.1)x2[3]/92,idem,del(11)(q22q23)x2[6]/46,XX,del(17)(q13.1)[5]/46,XX[5]	Yes	No
672	6	-	Unmutated	Mutated	46,XY,del(6)(q22),del(16)(q22q24)[6]/46,XY,del(6)(q22)[6]46,XY,del(16)(q22q24)[3]/46,XY[26]	No	No
677	0	-	Unmutated	Mutated	45,X,-X[4]/46,X,add(X)(q28)[3],inv(6)(p25q13)[3],add(15)(p11)[1],i(17)(q10)[1][cp3]/46,XX,t(12;15)(q24;q13)[1]/46,XX[12]	Yes	No
686	22	13q-	Mutated	Mutated	N/A	N/A	Yes
701	3	-	Unmutated	Mutated	N/A	N/A	No
709	15	-	Mutated	Mutated	46,XX[20]	No	No
737	65	-	N/A	WT	45,XX,der(17)t(17;18)(q10;q10),-18[1]/44,idem,add(2)(q37),-20[9]/46,XX[10]	Yes	No
746	N/A	N/A	Mutated	WT	46,XX,del(17)(p13)	No	Yes
793	24	-	Unmutated	Mutated	45,X,-X[3]/46,XX,del(17)(p13)[1]/46,XX[16]	No	Yes
803	N/A	N/A	Unmutated	Mutated	N/A	N/A	Yes
812	11	13q-	Unmutated	Mutated	46,XX,t(7;11)(q21;p15),del(13)(q14q22),add(14)(q32)[6]/46,XX[14]	Yes	No
816	0	13q-	Mutated	Mutated	46,XY[20]	No	Yes
869	N/A	N/A	Unmutated	Mutated	N/A	N/A	Yes
878	48	13q-	Mutated	Mutated	45,XY,-4,der(17)t(4;17)(q12;p12)[18]/46,XY[2]	No	No
1183	33	-	Unmutated	WT	45-46,XY,del(6)(q15q23~25)[10],add(7)(p21)[2],add(8)(q24)[2],add(17)(p12)[7],-21[4],+?20[2][cp10]/46,XY[13]	Yes	No
1265	N/A	N/A	Unmutated	Mutated	N/A	N/A	Yes
1280	10	11q-	N/A	WT	46,XY,del(11)(q22q23)[12]/46,XY,del(11)(q22q23),del(17)(p13)[5]/46,XY[3]	No	Yes
1281	15	13q-	N/A	WT	45,XY,der(5),-13,[5]/45,idem,del(17)(p10)[3]/46,XY[21]	Yes	No
1286	49	13q-	N/A	Mutated	46,XY,del(13)(q14q21)[2]/46,idem,del(17)(p12)[5]/46,idem,der(13)t(13;17)(q14q23),der(17)del(17)(p12)t(13;17)(q14;q23)[5]/46,XY[8]	Yes	No

1287	59	13q-	Unmutated	Mutated	46,XY,del(17)(p-),+mar1,+mar2[cp6]	Yes	Yes
1292	92	13q-	Mutated	Mutated	44,XY,der(15)t(15;17)(p11;p11),-17,- 22,i(22)(q11)[7]/46,XY,dic(9;17)(p11;q11),- 17,der(22)t(9;22)(q11;p11),+mar[9]/46,XY[4]	Yes	No
1339	30	13q-,11q-	N/A	WT	46,XY,add(14)(q32)[1]/46,idem,del(11)(q22.3)[2]/46,idem,der(1)t(1;13)(q?q? ?),del(11)(q22.3),der(13)t(1;13)(q?p?),del(17)(p13.1)[2]/46,XY[8]	Yes	Yes
1345	N/A	N/A	Unmutated	Mutated	45,XX, add(1)(p36.3),-13,add(17)(13),-20,+mar[8]/46XX,[32]	Yes	No

Abbreviations: FISH, fluorescent *in situ* hybridization; WT, wild type; N/A, not available.

Supplemental Table 3: Copy number alterations and copy number loss of heterozygosity alterations in 42 patients with 17p/TP53 disruption

Pt code	DNA Sample	Chromosome region (NCBI36/hg18)	Event	Length (kb)	Cytoband	CN-array platform
002	002-0010-10TD	chr2:230,254,185-231,505,419	CN Loss	1251.234	q36.3 - q37.1	SNP 6.0
002	002-0010-10TD	chr17:48,658-22,142,713	CN Loss	22094.055	p13.3 - p11.1	SNP 6.0
002	002-0010-10TD	chr12:0-132349534	CN Gain	132349.535	p13.33-q24.33	SNP 6.0
002	002-0010-10TD	chr21:12,300,000-46,944,323	CN Gain	34644.324	q11.1 - q22.3	SNP 6.0
007	007-0020-01TD	chr13:49,560,000-50,300,000	CN Loss	740	q14.2	SNP 6.0
030	030-0067-04TDP	chr2:0-93,541,544	CN Gain	93541.545	p25.3 - q11.1	SNP 6.0
030	030-0067-04TDP	chr8:0-43,905,972	CN Loss	43905.973	p23.3 - p11.1	SNP 6.0
030	030-0067-04TDP	chr13:46,460,050-49,341,360	CN Loss	2881.311	q14.2 - q14.3	SNP 6.0
030	030-0067-04TDP	chr13:49,341,361-50,388,227	Homozygous Deletion	1046.867	q14.3	SNP 6.0
030	030-0067-04TDP	chr13:50,388,228-51,936,576	CN Loss	1548.349	q14.3	SNP 6.0
030	030-0067-04TDP	chr17:0-20,960,328	CN Loss	20960.329	p13.3 - p11.2	SNP 6.0
047	047-0084-06TD	chr5:90,198,784-112,925,573	CN Loss	22726.789	q14.3 - q22.2	SNP 6.0
047	047-0084-06TD	chr13:47,740,866-51,881,152	CN Loss	4140.286	q14.2 - q14.3	SNP 6.0
047	047-0084-06TD	chr17:48,658-22,841,728	CN Loss	22793.07	p13.3 - q11.1	SNP 6.0
047	047-0084-06TD	chr17:22,842,626-23,567,037	CN Loss	724.411	q11.1 - q11.2	SNP 6.0
047	047-0084-06TD	chr17:26,128,608-29,353,270	CN Loss	3224.662	q11.2 - q12	SNP 6.0
047	047-0084-06TD	chr17:31,891,335-32,780,236	CN Loss	888.901	q12	SNP 6.0
047	047-0084-06TD	chr17:46,795,287-52,121,598	CN Loss	5326.311	q21.33 - q22	SNP 6.0
047	047-0084-06TD	chr17:64,689,659-69,743,048	CN Loss	5053.389	q24.3 - q25.1	SNP 6.0
047	047-0084-06TD	chr12:0-132,349,534	CN Gain	132349.535	p13.33 - q24.33	SNP 6.0
047	047-0084-06TD	chr11:60,210,471-134,452,384	CNN-LOH	74241.914	q12.2 - q25	SNP 6.0
050	050-0116-01TD	chr13:48,792,824-49,385,078	CN Loss	592.255	q14.2 - q14.3	SNP 6.0
050	050-0116-01TD	chr13:49,385,078-50,472,903	Homozygous Deletion	1087.826	q14.3	SNP 6.0
092	092-0181-01DVT	chr12:16001-132289534	CN Gain	133851.896	p13.33 - q24.33	custom 8x60k array
094	094-02-01DVT	chr5:63001-1688135	CN Gain	1635.136	p15.33	custom 8x60k array
094	094-02-01DVT	chr5:1688135-16166045	CN Loss	14477.911	p15.33 - p15.1	custom 8x60k array

094	094-02-01DVT	chr5:16166045-21777019	CN Gain	5628.218	p15.1 - p14.3	custom 8x60k array
094	094-02-01DVT	chr5:21777019-22752437	CN Loss	975.419	p14.3	custom 8x60k array
094	094-02-01DVT	chr5:22752437-23676346	CN Gain	923.91	p14.3 - p14.2	custom 8x60k array
094	094-02-01DVT	chr5:23676346-24599623	CN Loss	923.278	p14.2	custom 8x60k array
094	094-02-01DVT	chr5:24599623-29321939	CN Gain	4722.317	p14.2 - p13.3	custom 8x60k array
094	094-02-01DVT	chr5:29321939-30256856	CN Loss	934.918	p13.3	custom 8x60k array
094	094-02-01DVT	chr5:30256856-33101101	CN Gain	2844.246	p13.3	custom 8x60k array
094	094-02-01DVT	chr12:16001-34747961	CN Gain	35800.001	p13.33 - q11	custom 8x60k array
094	094-02-01DVT	chr17:1-22078701	CN Loss	22154.575	p13.3 - p11.2	custom 8x60k array
094	094-02-01DVT	chr17:47919657-49389588	CN Loss	1469.932	q22	custom 8x60k array
094	094-02-01DVT	chr17:49749870-78654742	CN Gain	28800.34	q22 - q25.3	custom 8x60k array
096	096-0189-01DVT	chr5:121595727-180837866	CN Gain	59347.433	q23.2 - q35.3	custom 8x60k array
096	096-0189-01DVT	chr7:118446327-158821424	CN Loss	40479.573	q31.31 - q36.3	custom 8x60k array
096	096-0189-01DVT	chr12:16001-132289534	CN Gain	133851.896	p13.33 - q24.33	custom 8x60k array
102	102DVT04	chr1:1423477-39899512	CN Loss	38693.312	p36.33- p34.2	custom 8x60k array
102	102DVT04	chr1:39899512-41444688	Amplification	1545.177	p34.2	custom 8x60k array
102	102DVT04	chr1:41444688-46521718	CN Gain	5077.031	p34.2 - p34.1	custom 8x60k array
102	102DVT04	chr4:128886668-137194571	CN Loss	8307.904	q28.1 - q28.3	custom 8x60k array
102	102DVT04	chr9:89964200-140273252	CN Gain	50439.052	q22.1 - q34.3	custom 8x60k array
102	102DVT04	chr13:46216961-62538075	CN Loss	16321.115	q14.2 - q21.31	custom 8x60k array
102	102DVT04	chr13:63198479-114127980	CN Gain	50869.401	q21.31 - q34	custom 8x60k array
102	102DVT04	chr14:81601429-84446020	CN Loss	2844.592	q31.1 - q31.3	custom 8x60k array
102	102DVT04	chr14:96465783-99202275	CN Loss	2736.493	q32.2	custom 8x60k array
102	102DVT04	chr14:102373302-105405849	CN Loss	3031.256	q32.32 - q32.33	custom 8x60k array
102	102DVT04	chr16:45058242-49431076	CN Gain	4372.835	q11.2 - q12.1	custom 8x60k array
102	102DVT04	chr16:63315965-66933334	CN Gain	3617.37	q21 - q22.1	custom 8x60k array
102	102DVT04	chr16:71619117-76081598	CN Gain	4462.482	q22.3 - q23.1	custom 8x60k array
102	102DVT04	chr16:78467845-86841445	CN Gain	8373.601	q23.2 - q24.2	custom 8x60k array
102	102DVT04	chr16:86841445-87921813	CN Loss	1110.369	q24.2 - q24.3	custom 8x60k array

102	102DVT04	chr17:1-17918031	CN Loss	17977.307	p13.3 - p11.2	custom 8x60k array
102	102DVT04	chr17:17918032-20419026	CN Gain	2501.128	p11.2	custom 8x60k array
163	163-01-1DVT	chr3:35001-49954750	CN Loss	49979.747	p26.3 - p21.31	custom 8x60k array
163	163-01-1DVT	chr3:65935337-69422722	CN Gain	3379.736	p14.1	custom 8x60k array
163	163-01-1DVT	chr3:72,836,240-99,504,696	CN Loss	26668.457	p13 - q12.1	custom 8x60k array
163	163-01-1DVT	chr12:16001-132289534	CN Gain	133851.896	p13.33 - q24.33	custom 8x60k array
163	163-01-1DVT	chr17:1-17117514	CN Loss	17176.79	p13.3 - p11.2	custom 8x60k array
177	177-01-9TD	chr3:165,654,906-166,902,609	CN Loss	1247.704	q26.1	SNP 6.0
177	177-01-9TD	chr3:49,282,753-54,293,371	CN Loss	5010.619	p21.31 - p21.1	SNP 6.0
177	177-01-9TD	chr3:20,482,126-28,386,865	CN Loss	7904.74	p24.3 - p24.1	SNP 6.0
177	177-01-9TD	chr17:0-19,083,459	CN Loss	19083.46	p13.3 - p11.2	SNP 6.0
177	177-01-9TD	chr3:59,636,680-90,532,433	CN Loss	30895.754	p14.2 - p11.1	SNP 6.0
192	192-01-4TD	chr13:45,811,253-50,420,317	CN Loss	4609.064	q14.12 - q14.3	SNP 6.0
192	192-01-4TD	chr17:72,804-18,478,029	CN Loss	18405.225	p13.3 - p11.2	SNP 6.0
192	192-01-4TD	chr17:18,693,178-21,952,980	CN Gain	3259.802	p11.2	SNP 6.0
279	279-01-4TD	chr13:47,601,534-51,783,511	CN Loss	4181.977	q14.2 - q14.3	SNP 6.0
279	279-01-4TD	chr17:0-19,503,203	CNN-LOH	19503.204	p13.3 - p11.2	SNP 6.0
287	287-01-4TD	chr13:49,386,312-50,610,584	CN Loss	1224.272	q14.3	SNP 6.0
287	287-01-4TD	chr1:215,738,655-215,784,216	CN Gain	45.561	q41	SNP 6.0
287	287-01-4TD	chr2:6,819-38,155	CN Gain	31.336	p25.3	SNP 6.0
287	287-01-4TD	chr12:0-132,349,534	CN Gain	132349.535	p13.33 - q24.33	SNP 6.0
294	294-05-01TD	chr1:245,222,728-247,249,719	CN Loss	2026.992	q44	SNP 6.0
294	294-05-01TD	chr2:203,531,899-216,647,168	CN Gain	13115.27	q33.2 - q35	SNP 6.0
294	294-05-01TD	chr2:217,558,834-225,499,672	CN Loss	7940.839	q35 - q36.2	SNP 6.0
294	294-05-01TD	chr2:230,534,650-231,598,025	CN Loss	1063.376	q36.3 - q37.1	SNP 6.0
294	294-05-01TD	chr2:232,164,077-235,973,602	CN Gain	3809.526	q37.1 - q37.2	SNP 6.0
294	294-05-01TD	chr4:161,120,640-164,136,919	CN Loss	3016.28	q32.1 - q32.2	SNP 6.0
294	294-05-01TD	chr8:69,015,495-69,581,450	CN Loss	565.956	q13.2	SNP 6.0
294	294-05-01TD	chr8:72,456,804-73,335,936	CN Gain	879.133	q13.3	SNP 6.0

294	294-05-01TD	chr8:93,951,262-108,725,331	CN Gain	14774.07	q22.1 - q23.1	SNP 6.0
294	294-05-01TD	chr8:125,161,561-130,449,225	CN Gain	5287.665	q24.13 - q24.21	SNP 6.0
294	294-05-01TD	chr8:137,536,755-146,274,826	CN Gain	8738.072	q24.23 - q24.3	SNP 6.0
294	294-05-01TD	chr9:22,335,401-26,162,762	CN Loss	3827.362	p21.3 - p21.2	SNP 6.0
294	294-05-01TD	chr9:69,267,323-140,193,110	CN Loss	70925.788	q12 - q34.3	SNP 6.0
294	294-05-01TD	chr11:105,089,642-126,708,871	CN Gain	21619.23	q22.3 - q24.2	SNP 6.0
294	294-05-01TD	chr11:126,709,177-134,452,384	CN Gain	7743.208	q24.2 - q25	SNP 6.0
294	294-05-01TD	chr13:46,215,611-54,589,609	CN Loss	8373.999	q14.2 - q21.1	SNP 6.0
294	294-05-01TD	chr13:56,676,375-57,651,934	CN Loss	975.56	q21.1 - q21.2	SNP 6.0
294	294-05-01TD	chr17:0-16,102,745	CN Loss	16102.746	p13.3 - p11.2	SNP 6.0
294	294-05-01TD	chr20:0-16,503,962	CN Loss	16503.963	p13 - p12.1	SNP 6.0
296	296-04-3TD	chr13:49,200,000-50,460,000	CN Loss	1260	q14.3	SNP 6.0
306	306-01-4TD	chr3:862,859-951,157	CN Loss	88.298	p26.3	SNP 6.0
306	306-01-4TD	chr4:61,352-36,388,604	CN Loss	36327.252	p16.3 - p14	SNP 6.0
306	306-01-4TD	chr5:135,788,823-180,632,469	CN Gain	44843.646	q31.2 - q35.3	SNP 6.0
306	306-01-4TD	chr7:125,081,362-158,778,583	CN Gain	33697.221	q31.33 - q36.3	SNP 6.0
306	306-01-4TD	chr8:75,979,898-146,250,965	CN Gain	70271.067	q21.11 - q24.3	SNP 6.0
306	306-01-4TD	chr11:116,094,610-134,452,384	CNN-LOH	18357.775	q23.3 - q25	SNP 6.0
306	306-01-4TD	chr11:86,264,325-115,268,435	CN Loss	29004.11	q14.2 - q23.2	SNP 6.0
344	344-01-7TD	chr13:49,452,162-50,290,680	CN Loss	838.518	q14.3	SNP 6.0
390	390-02-01DVT	No alterations		0		custom 8x60k array
418	418-02-01DVT	chr13:49469299-49998957	CN Loss	529.659	q14.2 - q14.3	custom 8x60k array
418	418-02-01DVT	chr13:50097453-50203143	CN Loss	105.691	q14.3	custom 8x60k array
418	418-02-01DVT	chr15:18355495-41925205	CN Loss	24042.433	q11.1 - q15.3	custom 8x60k array
418	418-02-01DVT	chr15:43755995-46824835	CN Loss	3068.841	q21.1	custom 8x60k array
418	418-02-01DVT	chr15:51775454-56370382	CN Loss	4594.929	q21.3	custom 8x60k array
418	418-02-01DVT	chr15:57682924-61534170	CN Loss	3851.486	q22.2 - q22.31	custom 8x60k array
418	418-02-01DVT	chr17:1-19038621	CN Loss	19098.029	p13.3 - p11.2	custom 8x60k array
511	511-01-1DVT	chr3:190320824-198686294	CN Loss	8363.768	q28 - q29	custom 8x60k array

511	511-01-1DVT	chr12:16001-8656017	Amplification	8764.751	p13.33 - p13.31	custom 8x60k array
511	511-01-1DVT	chr12:8656018-132289534	CN Gain	125087.145	p13.31 - q24.33	custom 8x60k array
511	511-01-1DVT	chr17:1-22095197	CN Loss	22171.071	p13.3 - p11.2	custom 8x60k array
576	576-01-4TD	chr5:85,178,432-94,316,551	CN Loss	9138.119	q14.3 - q15	SNP 6.0
576	576-01-4TD	chr13:45,717,672-50,437,033	CN Loss	4719.361	q14.12 - q14.3	SNP 6.0
576	576-01-4TD	chr16:80,610,220-88,677,188	CN Loss	8066.968	q23.3 - q24.3	SNP 6.0
576	576-01-4TD	chr21:27,328,821-46,920,425	CN Gain	19591.604	q21.3 - q22.3	SNP 6.0
576	576-01-4TD	chr3:187,275,439-188,933,527	CN Gain	1658.088	q27.2 - q27.3	SNP 6.0
587	587-03-01DVT	chr3:142903248-150750190	CN Loss	7846.943	q23 - q25.1	custom 8x60k array
587	587-03-01DVT	chr3:168600442-172793795	CN Gain	4193.354	q26.1 - q26.31	custom 8x60k array
587	587-03-01DVT	chr3:176029893-180077791	CN Gain	4047.899	q26.31 - q26.32	custom 8x60k array
587	587-03-01DVT	chr3:194005866-197377649	CN Gain	3370.081	q29	custom 8x60k array
587	587-03-01DVT	chr4:1-38908319	CN Loss	39231.925	p16.3 - p14	custom 8x60k array
587	587-03-01DVT	chr5:49672789-123356048	CN Loss	73691.118	q11.1 - q23.2	custom 8x60k array
587	587-03-01DVT	chr5:142876713-156029322	CN Loss	13200.225	q31.3 - q33.3	custom 8x60k array
587	587-03-01DVT	chr5:172560000-178004610	CN Gain	5444.611	q35.1 - q35.3	custom 8x60k array
587	587-03-01DVT	chr14:67923256-105118709	CN Loss	37194.162	q24.1 - q32.33	custom 8x60k array
587	587-03-01DVT	chr17:1-19061493	CN Loss	19120.901	p13.3 - p11.2	custom 8x60k array
618	618-1503-04TD	chr8:151,272-43,647,263	CN Loss	43495.991	p23.3 - p11.1	SNP 6.0
618	618-1503-04TD	chr17:47,346-22,052,669	CN Loss	22005.323	p13.3 - p11.2	SNP 6.0
656	656-02-1DVT	chr15:39897245-100338915	CN Gain	60421.44	q15.1 - q26.3	custom 8x60k array
656	656-02-1DVT	chr17:1-21507201	CN Loss	21583.538	p13.3 - p11.2	custom 8x60k array
656	656-02-1DVT	chr21:15922942-32809228	CN Loss	16886.287	q21.1 - q22.11	custom 8x60k array
656	656-02-1DVT	chr21:32809228-34479739	CN Gain	1670.513	q22.11	custom 8x60k array
656	656-02-1DVT	chr21:34479739-46944323	CN Loss	12572.027	q22.11 - q22.3	custom 8x60k array
677	677-07-01TD	chr17:0-19,016,888	CN Loss	19016.889	p13.3 - p11.2	SNP 6.0
677	677-07-01TD	chr17:19,080,352-20,721,169	CN Gain	1640.818	p11.2	SNP 6.0
677	677-07-01TD	chr17:25,799,221-78,774,742	CN Gain	52975.522	q11.2 - q25.3	SNP 6.0
709	709-06-01TD	chr17:0-22,145,688	CN Loss	22145.689	p13.3 - p11.1	SNP 6.0

709	709-06-01TD	chr18:0-12,779,105	CN Loss	12779.106	p11.32 - p11.21	SNP 6.0
793	793-01-01DVT	chr6:110946409-111397533	CN Loss	451.125	q21	custom 8x60k array
793	793-01-01DVT	chr6:112101862-116299885	CN Loss	4198.024	q21 - q22.1	custom 8x60k array
793	793-01-01DVT	chr8:1-6693102	CN Loss	6705.693	p23.3 - p23.1	custom 8x60k array
793	793-01-01DVT	chr8:59885000-66799521	CN Loss	6914.522	q12.1 - q13.1	custom 8x60k array
793	793-01-01DVT	chr8:110805092-119819257	CN Loss	9014.161	q23.2 - q24.12	custom 8x60k array
793	793-01-01DVT	chr12:16001-132289534	CN Gain	133851.896	p13.33 - q24.33	custom 8x60k array
793	793-01-01DVT	chr14:68343233-106360585	CN Loss	38076.061	q24.1 - q32.33	custom 8x60k array
793	793-01-01DVT	chr17:1-20319446	CN Loss	20378.855	p13.3 - p11.2	custom 8x60k array
793	793-01-01DVT	chr18:35576459-56222497	CN Loss	20749.057	q12.3 - q21.32	custom 8x60k array
803	803-01-7TD	chr17:36,920,120-78,277,612	CN Gain	41357.492	q21.1-q25.3	SNP 6.0
803	803-01-7TD	chr6:83,443,472-127,299,379	CN Loss	43855.907	q14.1-q22.32	SNP 6.0
803	803-01-7TD	chr13:49,445,329-50,426,145	CN Loss	980.816	q14.3	SNP 6.0
803	803-01-7TD	chr17:514-21,453,603	CN Loss	21453.089	p13.3-p11.2	SNP 6.0
812	812-01-5TD	chr13:46,518,705-73,050,862	CN Loss	26532.157	q14.2-q22.1	SNP 6.0
816	816-01-1TD	chr2:2,774-91,669,499	CN Gain	91666.725	p25.3-p11.1	SNP 6.0
816	816-01-1TD	chr3:60,041,650-60,409,922	CN Loss	368.272	p14.2	SNP 6.0
816	816-01-1TD	chr17:0-20,791,513	CNN-LOH	20791.514	p13.3 - p11.2	SNP 6.0
869	869-01-2TD	chr5:168,382,054-180,857,866	CN Gain	12475.813	q35.1 - q35.3	SNP 6.0
869	869-01-2TD	chr3:89,132,917-89,280,511	CN Gain	147.595	p11.2	SNP 6.0
869	869-01-2TD	chr4:57,075,113-57,217,248	CN Loss	142.136	q12	SNP 6.0
869	869-01-2TD	chr11:101,703,556-101,935,029	CN Loss	231.474	q22.2	SNP 6.0
869	869-01-2TD	chr17:0-21,040,623	CN Loss	21040.624	p13.3 - p11.2	SNP 6.0
878	878-01-5TD	chr4:0-45,043,459	CN Loss	45043.46	p16.3 - p13	SNP 6.0
878	878-01-5TD	chr13:47,227,229-51,282,688	CN Loss	0	q14.2 - q14.3	SNP 6.0
878	878-01-5TD	chr13:49,507,665-50,533,842	Homozygous Deletion	1026.178	q14.3	SNP 6.0
878	878-01-5TD	chr17:0-20,947,424	CN Loss	20947.425	p13.3 - p11.2	SNP 6.0
1183	1183-01-04TD	chr21:28,461,644-46,944,323	CN Gain	18482.68	q21.3 - q22.3	SNP 6.0
1183	1183-01-04TD	chr8:113,873,279-128,751,921	CN Gain	14878.643	q23.3 - q24.21	SNP 6.0

1183	1183-01-04TD	chr4:55,257,694-55,363,922	CN Gain	106.229	q12	SNP 6.0
1183	1183-01-04TD	chr5:153,550,876-180,857,866	CN Gain	27306.991	q33.2 - q35.3	SNP 6.0
1183	1183-01-04TD	chr11:75,748-42,267,285	CN Gain	42191.538	p15.5 - p12	SNP 6.0
1183	1183-01-04TD	chr17:14,779,836-18,025,836	CN Gain	3246.001	p12 - p11.2	SNP 6.0
1183	1183-01-04TD	chr7:28,453,641-31,764,285	CN Gain	3310.645	p15.1	SNP 6.0
1183	1183-01-04TD	chr2:273,748-76,375,629	CN Gain	76101.882	p25.3 - p12	SNP 6.0
1183	1183-01-04TD	chr3:166,858,088-199,501,827	CN Gain	32643.74	q26.1 - q29	SNP 6.0
1183	1183-01-04TD	chr17:27,959,486-30,711,054	CN Gain	2751.569	q11.2 - q12	SNP 6.0
1183	1183-01-04TD	chr6:63,545,913-170,899,992	CN Loss	107354.08	q12 - q27	SNP 6.0
1183	1183-01-04TD	chr7:89,477-18,253,279	CN Loss	18163.803	p22.3 - p21.1	SNP 6.0
1183	1183-01-04TD	chr8:128,768,042-146,274,826	CN Loss	17506.785	q24.21 - q24.3	SNP 6.0
1183	1183-01-04TD	chr17:0-14,777,631	CN Loss	14777.632	p13.3 - p12	SNP 6.0
1183	1183-01-04TD	chr21:13,329,543-28,457,516	CN Loss	15127.974	q11.2 - q21.3	SNP 6.0
1265	1265-01-03TD	chr2:148,187,904-149,068,854	CN Loss	880.951	q22.3 - q23.1	SNP 6.0
1265	1265-01-03TD	chr2:200,697,449-229,889,239	CN Loss	29191.791	q33.1 - q36.3	SNP 6.0
1265	1265-01-03TD	chr3:108,880,100-121,733,466	CN Loss	12853.367	q13.12 - q13.33	SNP 6.0
1265	1265-01-03TD	chr4:14,870,807-37,608,056	CN Loss	22737.25	p15.33 - p14	SNP 6.0
1265	1265-01-03TD	chr4:44,293,818-45,637,745	CN Loss	1343.928	p13 - p12	SNP 6.0
1265	1265-01-03TD	chr4:60,995,625-65,934,591	CN Loss	4938.967	q13.1	SNP 6.0
1265	1265-01-03TD	chr9:2,133,734-81,398,000	CN Loss	79264.267	p24.3 - q21.31	SNP 6.0
1265	1265-01-03TD	chr9:92,969,628-95,407,494	CN Loss	2437.867	q22.2 - q22.31	SNP 6.0
1265	1265-01-03TD	chr9:101,707,986-133,951,077	CN Loss	32243.092	q31.1 - q34.13	SNP 6.0
1265	1265-01-03TD	chr11:73,051,422-73,465,000	CN Loss	413.579	q13.4	SNP 6.0
1265	1265-01-03TD	chr13:47,121,692-52,376,291	CN Loss	5254.6	q14.2 - q21.1	SNP 6.0
1265	1265-01-03TD	chr14:75,791,509-76,409,928	CN Gain	618.42	q24.3	SNP 6.0
1265	1265-01-03TD	chr15:73,475,399-74,566,967	CN Loss	1091.569	q24.2 - q24.3	SNP 6.0
1265	1265-01-03TD	chr16:66,965,085-88,827,254	CN Gain	21862.17	q22.1 - q24.3	SNP 6.0
1265	1265-01-03TD	chr17:0-16,367,018	CN Loss	16367.019	p13.3 - p11.2	SNP 6.0
1265	1265-01-03TD	chr17:16,367,018-16,943,167	CN Gain	576.15	p11.2	SNP 6.0

1265	1265-01-03TD	chr20:23,149,307-25,919,692	CN Loss	2770.386	p11.21 - p11.1	SNP 6.0
1265	1265-01-03TD	chr22:41,712,345-44,120,300	CN Loss	2407.956	q13.2 - q13.31	SNP 6.0
1280	1280-01-01DVT	No alterations		0		custom 8x60k array
1281	1281-01-01DVT	chr5:18333210-39623419	CN Loss	21290.21	p15.1 - p13.1	custom 8x60k array
1281	1281-01-01DVT	chr5:44743748-46315492	CN Loss	1571.745	p12 - p11	custom 8x60k array
1281	1281-01-01DVT	chr5:49619946-68827087	CN Loss	19207.143	q11.1 - q13.2	custom 8x60k array
1281	1281-01-01DVT	chr5:159839194-160075628	CN Gain	236.435	q34	custom 8x60k array
1281	1281-01-01DVT	chr13:23914808-30519786	CN Gain	6604.979	q12.12 - q12.3	custom 8x60k array
1281	1281-01-01DVT	chr13:30519787-57439410	CN Loss	26919.623	q12.3 - q21.1	custom 8x60k array
1281	1281-01-01DVT	chr13:57439411-59947746	CN Gain	2508.336	q21.1 - q21.2	custom 8x60k array
1281	1281-01-01DVT	chr13:59947746-61270138	CN Loss	1322.393	q21.2 - q21.31	custom 8x60k array
1281	1281-01-01DVT	chr17:1-21142835	CN Loss	21202.243	p13.3 - p11.2	custom 8x60k array
1281	1281-01-01DVT	chr20:8001-20971194	CN Loss	21023.195	p13 - p11.23	custom 8x60k array
1286	1286-01-01DVT	chr13:49368641-49451867	CN Loss	83.227	q14.2	custom 8x60k array
1286	1286-01-01DVT	chr13:49451868-50324667	Homozygous Deletion	872.8	q14.2 - q14.3	custom 8x60k array
1286	1286-01-01DVT	chr13:50324667-50513979	CN Loss	189.313	q14.3	custom 8x60k array
1286	1286-01-01DVT	chr17:5944474-20106192	CN Loss	14161.851	p13.2 - p11.2	custom 8x60k array
1287	1287-021DVT	chr13:47808702-50415111	CN Loss	2606.41	q14.2 - q14.3	custom 8x60k array
1287	1287-021DVT	chr17:1-14510119	CN Loss	14569.395	p13.3 - p12	custom 8x60k array
1292	1292-01-02TD	chr9:69,962,638-140,273,252	CN Gain	70310.615	q12 - q34.3	SNP 6.0
1292	1292-01-02TD	chr12:7,903,690-19,610,100	CN Loss	11706.411	p13.31 - p12.3	SNP 6.0
1292	1292-01-02TD	chr13:48,773,936-49,436,563	CN Loss	662.628	q14.2 - q14.3	SNP 6.0
1292	1292-01-02TD	chr13:49,436,563-50,384,112	Homozygous Deletion	947.55	q14.3	SNP 6.0
1292	1292-01-02TD	chr13:50,384,112-50,858,008	CN Loss	473.897	q14.3	SNP 6.0
1292	1292-01-02TD	chr16:3,713,790-3,822,987	CN Loss	109.198	p13.3	SNP 6.0
1292	1292-01-02TD	chr17:0-21,068,483	CN Loss	21068.484	p13.3 - p11.2	SNP 6.0
1339	1339-01-03TD	chr17:69,849,471-71,800,560	CN Loss	1951.09	q25.1	SNP 6.0
1339	1339-01-03TD	chr17:4,380,954-5,460,392	CN Loss	1079.439	p13.2	SNP 6.0
1339	1339-01-03TD	chr13:52,395,148-112,164,722	CN Gain	59769.575	q21.1 - q34	SNP 6.0

1339	1339-01-03TD	chr14:70,945,059-88,295,050	CN Loss	17349.992	q24.2 - q31.3	SNP 6.0
1339	1339-01-03TD	chr17:16,168,502-16,406,159	CN Loss	237.658	p11.2	SNP 6.0
1345	1345-01-03TD	chr1:35,339-36,403,849	CN Gain	36368.511	p36.33 - p34.3	SNP 6.0
1345	1345-01-03TD	chr1:76,242,281-85,141,280	CN Loss	8899	p31.1 - p22.3	SNP 6.0
1345	1345-01-03TD	chr13:43,479,728-43,749,804	CN Loss	270.077	q14.11	SNP 6.0
1345	1345-01-03TD	chr13:46,176,741-50,701,058	CN Loss	4524.318	q14.13 - q14.3	SNP 6.0
1345	1345-01-03TD	chr13:64,678,782-65,578,368	CN Loss	899.587	q21.32	SNP 6.0
1345	1345-01-03TD	chr13:73,501,081-78,021,746	CN Loss	4520.666	q22.1 - q31.1	SNP 6.0
1345	1345-01-03TD	chr13:78,858,109-79,014,249	CN Loss	156.141	q31.1	SNP 6.0
1345	1345-01-03TD	chr13:79,234,086-81,758,481	CN Loss	2524.396	q31.1	SNP 6.0
1345	1345-01-03TD	chr13:82,685,561-83,152,847	CN Loss	467.287	q31.1	SNP 6.0
1345	1345-01-03TD	chr17:0-21,641,068	CN Loss	21641.069	p13.3 - p11.2	SNP 6.0
1345	1345-01-03TD	chr20:0-22,386,451	CN Loss	22386.452	p13 - p11.21	SNP 6.0

Chr, chromosome, CN, copy number; CNN-LOH, copy number neutral-loss of heterozygosity.

Supplemental Table 4: Treatment received by patients with *de novo* TP53 aberrations who required therapy (N = 20)

Treatment	N (%)
Chlorambucil	5 (25)
Fludarabine monotherapy	1 (5)
Cladribine monotherapy	3 (15)
Fludarabine, cyclophosphamide and mitoxantrone	2 (10)
Rituximab, fludarabine, cyclophosphamide and mitoxantrone	3 (15)
Cyclophosphamide, doxorubicin, vincristine and prednisone	3 (15)
Alemtuzumab monotherapy	3 (15)

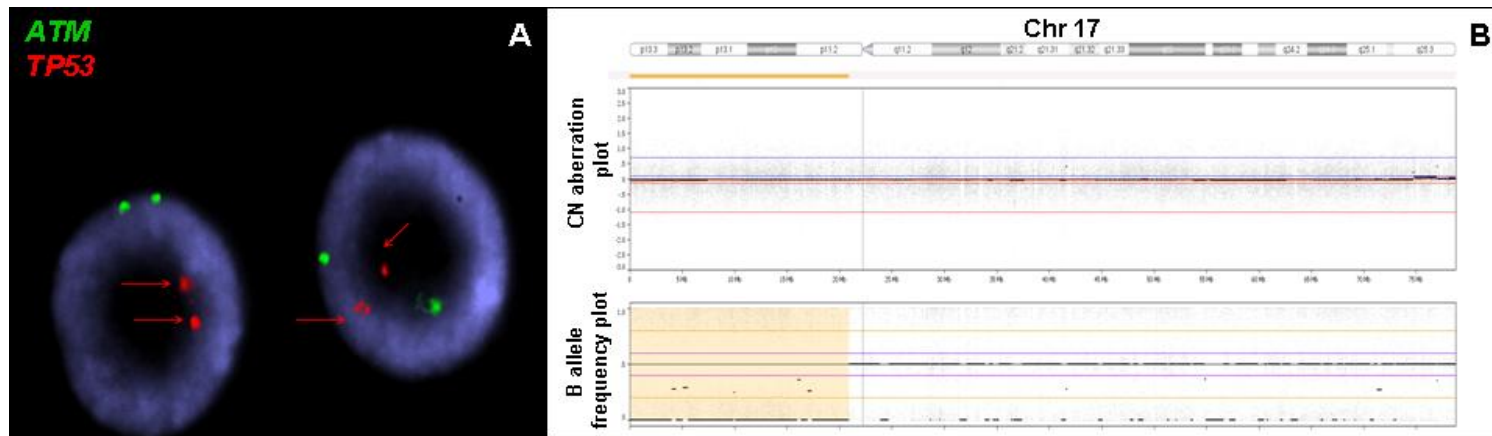
Supplemental Table 5: Univariate and multivariate analysis of time to first treatment and overall survival. P values were adjusted for multiple testing using Bonferroni's correction

Variable	Time to first treatment						Overall survival					
	Univariate analysis (Kaplan-Meier and log-rank test)			Multivariate analysis (Cox regression)			Univariate analysis (Kaplan-Meier and log-rank test)			Multivariate analysis (Cox regression)		
	Median (months)	95% CI	P value	HR	95% CI	P value	Median (months)	95% CI	P value	HR	95% CI	P value
CNAs												
0-3							53	14-92	0.024			
4-9							37	24-51		7.6	1.6-37	0.011*
>9							24	19-29		7.4	1.6-33	0.010**
IGHV gene												
Unmutated	1.1	0.6-1.7	.011	13.8	1.7-113	0.014						
Mutated	NR	-										
ZAP70												
Low	NR	-	.011									
High	1.1	0.6-1.6										

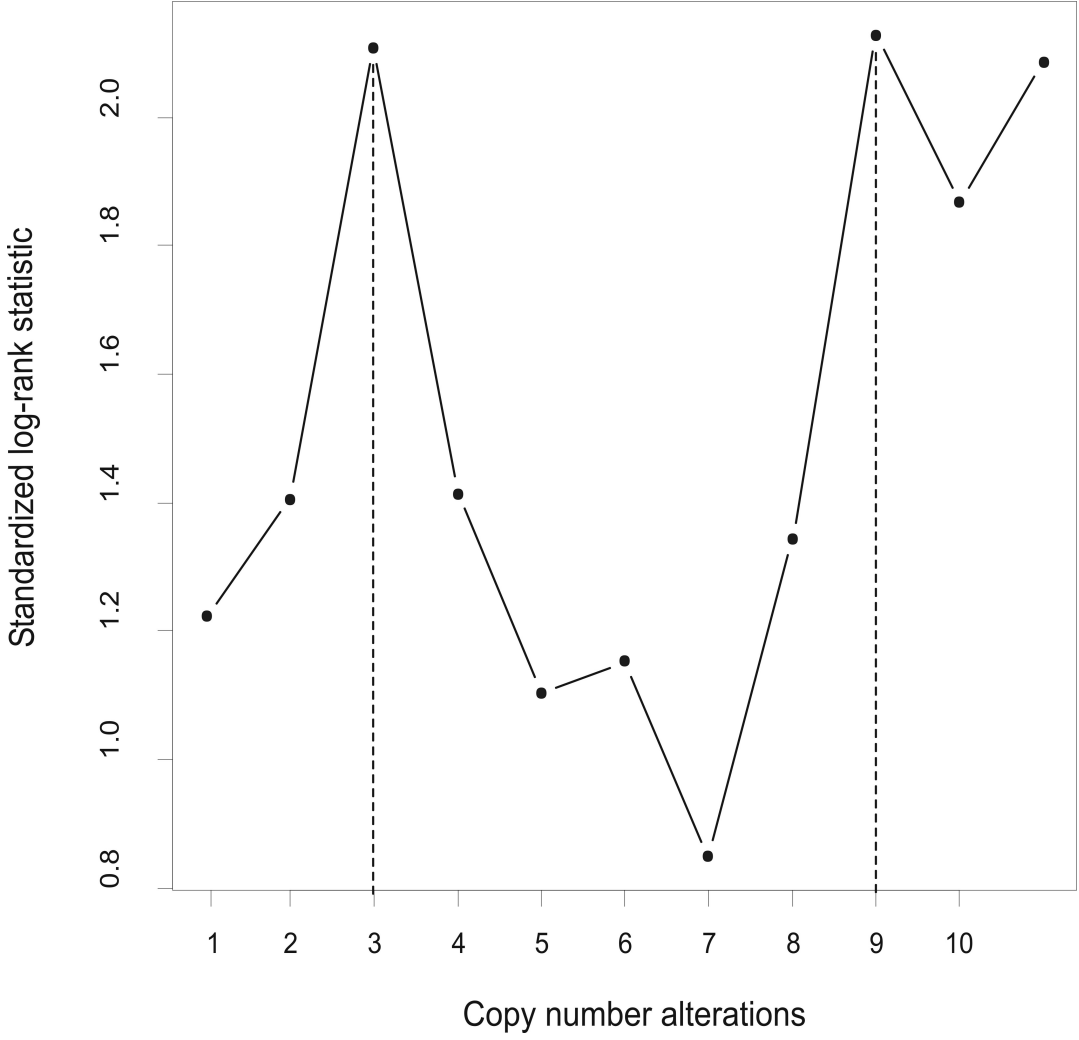
*This P value corresponds to the 0-3 vs. 4-9 comparison.

**This P value corresponds to the 4-9 vs. >9 comparison.

Supplemental Figure 1. Status of *TP53* locus in case 816. (A) FISH analysis of *TP53* (Spectrum orange) and *ATM* (Spectrum green). The picture shows two normal representative nuclei carrying 2 copies of *TP53*. (B) Chromosome 17 in horizontal represented from pter to qter showing a copy number neutral-loss of heterozygosity region (yellow) covering the whole 17p arm. CN, copy number.



Supplemental Figure 2: Maximally selected rank statistics for number of copy number alterations related to overall survival. The plot shows two possible cut-off points with a similar discrimination of the survival curves at 3 and 9 alterations.



Supplemental Figure 3: Integrated Brier scores of the prediction error curves for different values of the cut-off points for copy number alterations. For the cut-off validation, the time-integrated Brier score from time 0 to time 54 was used, which measures the difference between the predicted and the observed curves across time. Cut-off points observed using this method were not exactly 3/9 alterations, but 3/10 or 3/11.

