Different spectra of recurrent gene mutations in subsets of chronic lymphocytic leukemia harboring stereotyped B-cell receptors

Lesley-Ann Sutton,[1] Emma Young,[1] Panagiotis Baliakas,[1] Anastasia Hadzidimitriou,[2] Theodoros Moysiadis,[2] Karla Plevova,[3] Davide Rossi,[4] Jana Kminkova,[3] Evangelia Stalika,[2] Lone Bredo Pedersen,[5] Jitka Malcikova,[3] Andreas Agathangelidis,[6,7] Zadie Davis,[8] Larry Mansouri,[1] Lydia Scarfò,[6,7] Myriam Boudjoghra,[9] Alba Navarro,[10] Alice F. Muggen,[11] Xiao-Jie Yan,[12] Florence Nguyen-Khac,[9] Marta Larrayoz,[13] Panagiotis Panagiotidis,[14] Nicholas Chiorazzi,[12] Carsten Utoft Niemann,[5] Chrysoula Belessi,[15] Elias Campo,[10] Jonathan C. Strefford,[13] Anton W. Langerak,[11] David Oscier,[8] Gianluca Gaidano,[4] Sarka Pospisilova,[3] Frederic Davi,[9] Paolo Ghia,[6,7] Kostas Stamatopoulos,[1,2,16*] Richard Rosenquist,[1*] and on behalf of ERIC, the European Research Initiative on CLL

[1]Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Uppsala University, Uppsala, Sweden; [2]Institute of Applied Biosciences, CERTH, Thessaloniki, Greece; [3]Central European Institute of Technology, Masaryk University and University Hospital Brno, Czech Republic; [4]Division of Haematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy; [5]Department of Hematology, Rigshospitalet, Copenhagen, Denmark; [6]Università Vita-Salute San Raffaele, Milan, Italy; [7]Division of Experimental Oncology and Department of Onco-Hematology, IRCCS, San Raffaele Scientific Institute, Milan, Italy; [8]Department of Haematology, Royal Bournemouth Hospital, Bournemouth, UK; [9]Hematology Department and University Pierre et Marie Curie, Hopital Pitie-Salpetriere, Paris, France; [10]Hematopathology Unit and Department of Hematology, Hospital Clinic, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi iSunyer (IDIBAPS), Barcelona, Spain; [11]Department of Immunology, Erasmus MC, University Medical Center Rotterdam, The Netherlands; [12]The Feinstein Institute for Medical Research, North Shore-Long Island Jewish Health System, Manhasset, New York, NY, USA; [13]Cancer Sciences, Faculty of Medicine, University of Southampton, UK; [14]First Department of Propaedeutic Medicine, University of Athens, Greece; [15]Hematology Department, Nikea General Hospital, Piraeus, Greece; and [16]Hematology Department and HCT Unit, G. Papanicolaou Hospital, Thessaloniki, Greece

**KS and RR contributed equally to this work.*

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Correspondence: richard.rosenquist@igp.uu.se

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The supplemental material consists of the following tables and figures:

Supplemental Tables 1-9

Supplemental Figure 1

Supplemental Table 1. The two 'sub-subsets' of subset #8 were considered as a single entity within this study.

IMMUNOGENETICS	#8 (n=14) 18 AA VH CDR3	UM IGHV4-39 #8 (n=29) 19 AA VH CDR3	p-value
MUTATIONS			
***NOTCH1*^{mut}**	3/14 (21%)	10/29 (34%)	ns
***TP53*^{mut}**	1/14 (7%)	0/29 (0%)	ns
***SF3B1*^{mut}**	0/14 (0%)	0/29 (0%)	ns
***BIRC3*^{mut}**	0/14 (0%)	3/28 (11%)	ns
***MYD88*^{mut}**	0/14 (0%)	0/29 (0%)	ns
CONCURRENT MUTATIONS			
***Notch1*^{mut} only**	3/3 (100%)	8/10 (80%)	ns
Concurrent *Notch1*^{mut}	0/3 (0%)	2/10 (20%)	ns
***TP53*^{mut} only**	1/1 (100%)	NA	ns
Concurrent *TP53*^{mut}	0/1 (0%)	NA	ns
***SF3B1*^{mut} only**	NA	NA	ns
Concurrent *SF3B1*^{mut}	NA	NA	ns
***BIRC3*^{mut} only**	NA	1/3 (33%)	ns
Concurrent *BIRC3*^{mut}	NA	2/3 (67%)	ns
GENETIC ABERRATIONS			
del(17p)	2/6 (33%)	1/17 (5.9%)	0.09
del(11q)	0/6 (0%)	3/16 (19%)	ns
trisomy 12	2/6 (33%)	11/14 (79%)	0.05
del(13q)*	0/6 (0%)	1/14 (7%)	ns
no RCAs	2/6 (33%)	1/14 (7%)	0.13

**refers to del(13q) as the sole aberration. RCAs: recurrent cytogenetic aberrations; NOTCH1^{mut}: mutation in NOTCH1; TP53^{mut}: mutation in TP53; SF3B1^{mut}: mutation in SF3B1; BIRC3^{mut}: mutation in BIRC3; MYD88^{mut}: mutation in MYD88; NA: not applicable. Concurrent mutations indicate that the mutation specified coincides with a mutation in at least one of the other four genes analyzed. UM: cases with unmutated IGHV genes; ns: not significant.*

Supplemental Table 2. The percent of cases within each subset tested prior to or after the administration of treatment.

Subset	Tested prior to treatment %	Tested after treatment %
#1	81,48	19,61
#2	80,60	19,40
#3	85,00	15,00
#4	93,85	6,15
#5	70,00	30,00
#6	75,68	16,22
#7	100,00	0,00
#8	89,66	10,34
#59	64,29	35,71
#99	92,86	7,14

Supplemental Table 3. Overview of methodologies utilized by each collaborating institution.

	BIRC3	*MYD88*	*NOTCH1*	*SF3B1*	*TP53*
Czech Republic: Brno (n=63)	Sanger sequencing, exons 6-9	Sanger sequencing, exon 5	Sanger sequencing, exon 34, del7544_7545 hotspot	Sanger sequencing, exons 14-16	FASAY & Sanger sequencing, exons 4-10
Denmark: Copenhagen (n=44)	Sanger sequencing, exons 6-9	Sanger sequencing, exon 5	GeneScan & Sanger sequencing, exon 34, del7544_7545 hotspot	Sanger sequencing, exons 14-16	Sanger sequencing, exons 4-8
France: Paris (n=74)	Sanger sequencing, exons 6-9	Sanger sequencing & HRM analysis, exon 5	Sanger sequencing & HRM analysis, exon 34, del7544_7545 hotspot	Sanger sequencing & HRM analysis, exons 14-16	Sanger sequencing & HRM analysis, exons 4-9
Greece: Athens (n=37)	Sanger sequencing, exons 6-9	Sanger sequencing, exon 5	GeneScan & Sanger sequencing, exon 34, del7544_7545 hotspot	Sanger sequencing, exons 14-16	Sanger sequencing, exons 4-8
Greece: Piraeus (n=19)	Sanger sequencing, exons 6-9	Sanger sequencing, exon 5	Allele specific PCR for del7544_7545 & Sanger sequencing	Sanger sequencing, exons 14-16	FASAY & Sanger sequencing, exons 4-10
Greece: Thessaloniki (n=47)	Sanger sequencing, exons 6-9	Sanger sequencing, exon 5	Allele specific PCR for del7544_7545 & Sanger sequencing	Sanger sequencing, exons 14-16	FASAY & Sanger sequencing, exons 4-10
Italy: Milan (n=11)	Sanger sequencing, exons 6-9	Sanger sequencing, exon 5	GeneScan & Sanger sequencing, exon 34, del7544_7545 hotspot	Sanger sequencing, exons 14-16	Sanger sequencing, exons 4-8
Italy: Novara (n=32)	Sanger sequencing, exons 6-9	Sanger sequencing, exons 3 & 5	Sanger sequencing, exon 34	Sanger sequencing, exons 14-16	Sanger sequencing, exons 4-9
Netherlands: Rotterdam (n=63)	Sanger sequencing, exons 6-9	Sanger sequencing, exon 5	GeneScan & Sanger sequencing, exon 34, del7544_7545 hotspot	Sanger sequencing, exons 14-16	Sanger sequencing, exons 4-9
Spain: Barcelona (n=10)	Sanger sequencing, exons 6-9	Sanger sequencing, exon 5	Sanger sequencing, exon 34, del7544_7545 hotspot	Sanger sequencing & NGS, exons 14-16	Sanger sequencing & NGS, exons 4-9
Sweden: Uppsala (n=58)	Sanger sequencing, exons 6-9	Sanger sequencing, exon 5	GeneScan & Sanger sequencing, exon 34, del7544_7545 hotspot	Sanger sequencing, exons 14-16	Sanger sequencing, exons 4-9
UK: Southampton/ Bournemouth (n=63)	Sanger sequencing & HRM analysis, exons 6-9	Sanger sequencing & HRM analysis, exons 3 & 5	Sanger sequencing & HRM analysis, exon 34, del7544_7545 hotspot	Sanger sequencing & HRM analysis, exons 14-16	SSCP & Sanger sequencing, exons 5-8
US: New York (n=44)	Sanger sequencing, exons 6-9	Sanger sequencing, exon 5	GeneScan & Sanger sequencing, exon 34, del7544_7545 hotspot	Sanger sequencing, exons 14-16	Sanger sequencing, exons 4-8

FASAY: functional analysis of separated allele in yeast; HRM: high resolution melting; NGS: next generation sequencing; SSCP: single strand conformational polymorphism.

Supplemental Table 4. P-values obtained from the pairwise comparison of gene mutations within stereotyped subsets using Fisher's exact test.

4A.

Rank		2	3	4	5	6	7	8	9	10
	Subset	#99	#59	#3	#5	#6	#7	#8	#2	#4
1	#1	0,7824	0,5821	0,0099	0,0683	0,5632	0,2974	0,6990	0,0000	0,0000
2	#99		0,7112	0,1417	0,3752	1,0000	0,6221	0,7552	0,0150	0,0041
3	#59			0,0134	0,0565	0,3599	0,1931	1,0000	0,0005	0,0001
4	#3				0,6020	0,0463	0,5377	0,0116	1,0000	0,4393
5	#5					0,1935	1,0000	0,0646	0,3273	0,1372
6	#6						0,4260	0,4700	0,0006	0,0002
7	#7							0,1562	0,4423	0,2502
8	#8								0,0000	0,0000
9	#2									0,4432

Pairwise comparison to evaluate the null hypothesis that the two percentages (NOTCH1=yes/total # of cases) are equal for all possible combinations among the 10 subsets included in the study (45 comparisons in total). Due to multiple testing, Bonferroni correction was performed and every pairwise correction was checked at a level of significance, p=0.001. Color scale is based on the level of significance.

4B.

Rank		2	3	4	5	6	7	8	9	10
	Subset	#99	#59	#3	#5	#6	#7	#8	#2	#4
1	#1	0,5995	0,6182	0,0000	0,6790	0,2119	0,0583	0,1171	0,0000	0,0280
2	#99		0,4857	0,0005	0,5017	0,1727	0,0542	1,0000	0,0001	1,0000
3	#59			0,0210	1,0000	1,0000	0,3644	0,0836	0,0054	0,0336
4	#3				0,0039	0,0037	0,2943	0,0000	1,0000	0,0000
5	#5					0,7037	0,3035	0,1317	0,0003	0,0571
6	#6						0,3742	0,0266	0,0001	0,0021
7	#7							0,0084	0,2352	0,0019
8	#8								0,0000	1,0000
9	#2									0,0000

Pairwise comparison to evaluate the null hypothesis that the two percentages (SF3B1=yes/total # of cases) are equal for all possible combinations among the 10 subsets included in the study (45 comparisons in total). Due to multiple testing, Bonferroni correction was performed and every pairwise correction was checked at a level of significance, p=0.001. Color scale is based on the level of significance.

4C.

Rank		2	3	4	5	6	7	8	9	10
	Subset	#99	#59	#3	#5	#6	#7	#8	#2	#4
1	#1	0,0934	0,1356	0,5343	0,0468	0,0696	1,0000	0,0298	0,0000	0,0119
2	#99		0,0191	0,0517	0,0031	0,0051	0,3642	0,0019	0,0000	0,0012
3	#59			0,5017	1,0000	1,0000	0,3571	1,0000	1,0000	1,0000
4	#3				0,4898	0,6131	1,0000	0,5496	0,1495	0,5926
5	#5					0,5342	0,2857	1,0000	1,0000	1,0000
6	#6						0,4591	1,0000	0,3262	1,0000
7	#7							0,3447	0,2295	0,3883
8	#8								1,0000	1,0000
9	#2									0,4141

Pairwise comparison to evaluate the null hypothesis that the two percentages (TP53=yes/total # of cases) are equal for all possible combinations among the 10 subsets included in the study (45 comparisons in total). Due to multiple testing, Bonferroni correction was performed and every pairwise correction was checked at a level of significance, p=0.001. Color scale is based on the level of significance.

Supplemental Table 5. Overview of mutational analysis per subset.

Subset	No. of cases	*MYD88*	*NOTCH1*	*TP53*	*SF3B1*	*BIRC3*
1	137	135 (99%)	137 (100%)	135 (99%)	137 (100%)	131 (96%)
2	162	159 (98%)	162 (100%)	150 (93%)	161 (99%)	153 (94%)
3	26	25 (96%)	26 (100%)	25 (96%)	26 (100%)	25 (96%)
4	78	78 (100%)	78 (100%)	78 (100%)	78 (100%)	77 (99%)
5	25	24 (96%)	24 (96%)	25 (100%)	25 (100%)	21 (84%)
6	46	45 (98%)	45 (98%)	45 (98%)	46 (100%)	45 (98%)
7	12	12 (100%)	12 (100%)	10 (83%)	12 (100%)	12 (100%)
8	43	43 (100%)	43 (100%)	43 (100%)	43 (100%)	42 (98%)
59	18	18 (100%)	18 (100%)	18 (100%)	18 (100%)	18 (100%)
99	18	18 (100%)	18 (100%)	18 (100%)	18 (100%)	17 (94%)
	565	**557 (99%)**	**563 (99%)**	**547 (97%)**	**564 (99%)**	**541 (96%)**

Supplemental Table 6. Co-occurrence of gene mutations within stereotyped CLL subsets.

	#1 (n=137)	#99 (n=18)	#59 (n=18)	#3 (n=26)	#5 (n=25)	#6 (n=46)	#7 (n=12)	#8 (n=43)	#2 (n=162)	#4 (n=78)	n=289
IMMUNOGENETICS	**UM Clan I genes**			**UM IGHV1-69**				**UM IGHV4-39**	**M & UM IGHV3-21**	**M IGHV4-34**	**Heterogeneous CLL**
MUTATIONS											
***NOTCH1*^{mut}**	37/137 (27%)	4/18 (22%)	6/18 (33%)	1/26 (4%)	2/24 (8%)	10/45 (22%)	1/12 (8%)	13/43 (30%)	7/162 (4%)	1/78 (1%)	10/280 (3.6%)
***TP53*^{mut}**	21/135 (16%)	6/18 (33%)	0/18 (0%)	2/25 (8%)	0/25 (0%)	2/45 (4%)	1/10 (10%)	1/43 (2%)	3/150 (2%)	3/78 (4%)	11/237 (4.6%)
***SF3B1*^{mut}**	9/137 (7%)	0/18 (0%)	2/18 (11%)	12/26 (46%)	2/25 (8%)	6/46 (13%)	3/12 (25%)	0/43 (0%)	72/161 (45%)	0/78 (0%)	10/280 (3.6%)
***BIRC3*^{mut}**	2/131 (2%)	0/17 (0%)	0/18 (0%)	0/25 (0%)	1/21 (5%)	0/45 (0%)	1/12 (8%)	3/42 (7%)	0/153 (0%)	0/77 (0%)	0/189 (0%)
***MYD88*^{mut}**	0/135 (0%)	0/18 (0%)	0/18 (0%)	0/25 (0%)	0/24 (0%)	0/45 (0%)	0/12 (0%)	0/42 (0%)	0/159 (0%)	0/78 (0%)	5/206 (2.4%)[†]
CONCURRENT MUTATIONS											
***Notch1*^{mut} only**	31/37 (84%)	2/4 (50%)	5/6 (83%)	0/1 (0%)	2/2 (100%)	8/10 (80%)	0/1 (0%)	11/13 (85%)	5/7 (71%)	1/1 (100%)	10/10 (100%)
Concurrent *Notch1*^{mut}	6/37 (16%)	2/4 (50%)	1/6 (17%)	1/1 (100%)	0/2 (0%)	2/10 (20%)	1/1 (100%)	2/13 (15%)	2/7 (29%)	0/1 (0%)	0/10 (0%)
***TP53*^{mut} only**	11/21 (52%)	4/6 (67%)	NA	0/2 (0%)	NA	1/2 (50%)	0/1 (0%)	1/1 (100%)	1/3 (33%)	3/3 (100%)	9/11 (82%)
Concurrent *TP53*^{mut}	10/21 (48%)	2/6 (33%)	NA	2/2 (100%)	NA	1/2 (50%)	1/1 (100%)	0/1 (0%)	2/3 (67%)	0/3 (0%)	2/11 (18%)
***SF3B1*^{mut} only**	4/9 (44%)	NA	1/2 (50%)	9/12 (75%)	2/2 (100%)	5/6 (83%)	2/3 (67%)	NA	68/72 (94%)	NA	9/10 (90%)
Concurrent *SF3B1*^{mut}	5/9 (56%)	NA	1/2 (50%)	3/12 (25%)	0/2 (0%)	1/6 (17%)	1/3 (18%)	NA	4/72 (6%)	NA	1/10 (10%)
***BIRC3*^{mut} only**	0/2 (0%)	NA	NA	NA	1/1 (100%)	NA	0/1 (0%)	1/3 (33%)	NA	NA	NA
Concurrent *BIRC3*^{mut}	2/2 (100%)	NA	NA	NA	0/1 (0%)	NA	1/1 (100%)	2/3 (67%)	NA	NA	NA

[†]one MYD88-mutant case also carried a mutation within TP53. NOTCH1^{mut}: mutation in NOTCH1; TP53^{mut}: mutation in TP53; SF3B1^{mut}: mutation in SF3B1; BIRC3^{mut}: mutation in BIRC3; MYD88^{mut}: mutation in MYD88; NA: not applicable. Concurrent mutations indicate that the mutation specified coincides with a mutation in at least one of the other genes analyzed. UM: cases with unmutated IGHV genes; M: cases with mutated IGHV genes. 'The 'Heterogeneous CLL' cases described in the last column of this table refers to newly diagnosed CLL patients from a population-based cohort called SCALE (Scandinavian Lymphoma Etiology). Within this study, 330 CLL cases had immunogenetic and mutation data available, resulting in 41 cases (12%) carrying stereotyped BcR IGs and therefore being assigned to a major subset. For comparison purposes, the frequency of recurrent mutations and cytogenetic aberrations in the remaining cases carrying heterogeneous BcR IGs (n=289) are provided.

Supplemental Table 7. Cases carrying genetic aberrations within *BIRC3*.

Case	Subset	Genetic lesions within *BIRC3*	Genetic aberration*	Concurrent mutations
1	#1	c. 1299_1302delAAGA; p. R434fs	del(11q), del(13q)	*TP53*: c.T479C:p.M160T
2	#1	c.1282_1286 del AGGGA; p.R428fs	trisomy 12	*NOTCH1:* c.7544_7545 delCT
3	#5	c. 1708_1710delATT; p.I570del	del(11q), trisomy 12, del(13q)	No
4	#7	c.1536_1537delCT; p.N512_513fs	ND	*NOTCH1:* c.7544_7545 delCT
5	#8†	c.1285dupG; p.E429fs	trisomy 12	*NOTCH1:* c.7544_7545 delCT
6	#8†	c.1663_1666; p.R555fs	trisomy 12	*NOTCH1:* c.7544_7545 delCT
7	#8†	c.1648A>G; p.R550G	del(11q), trisomy 12	No

*ND: not determined; *cytogenetic aberrations detected by FISH; †Subset #8 cases with 19 amino acid VH CDR3.*

Supplemental Table 8. *SF3B1* mutations detected in the present study.

Exon	Codon	AA change	#2 n=75	%*	#3 n=12	%*	#1 n=9	%*	#5 n=2	%*	#6 n=7	%*	#7 n=3	%*	#59 n=2	%*	
14	622	p.E622D	2	2.7	1	8.3	0	-	0	-	0	-	0	-	0	-	**3**
14	622	p.E622V	1	1.3	0	-	0	-	0	-	0	-	0	-	0	-	**1**
14	623	p.Y623C	3	4	2	16.7	0	-	0	-	1	14	0	-	0	-	**6**
14	625	p.R625H	1	1.3	1	8.3	0	-	0	-	0	-	1	33	0	-	**3**
14	625	p.R625C	1	1.3	1	8.3	0	-	0	-	0	-	0	-	0	-	**2**
14	626	p.N626I	1	1.3	0	-	0	-	0	-	0	-	0	-	0	-	**1**
14	626	p.N626S	0	-	0	-	1	11	0	-	0	-	0	-	0	-	**1**
14	630	p.R630S	0	-	0	-	1	11	0	-	0	-	0	-	0	-	**1**
14	658	p.W658C	1	1.3	0	-	0	-	0	-	0	-	0	-	0	-	**1**
14	662	p.H662D	2	2.7	0	-	0	-	1	50	0	-	0	-	0	-	**3**
14	662	p.H662Q	1	1.3	1	8.3	0	-	0	-	1	14	0	-	0	-	**3**
14	662	p.H662Y	0	-	1	8.3	0	-	0	-	0	-	0	-	0	-	**1**
14	663	p.T663I	0	-	1	8.3	1	11	0	-	2	29	0	-	0	-	**4**
14	666	p.K666E	0	-	0	-	0	-	1	50	1	14	0	-	1	50	**3**
15	700	p.K700E	43	57	4	33	2	22	0	-	0	-	1	33	0	-	**50**
15	704	p.I704F	1	1.3	0	-	1	11	0	-	1	14	1	33	0	-	**4**
15	704	p.I704N	0	-	0	-	1	11	0	-	0	-	0	-	1	50	**2**
15	740	p.G740E	1	1.3	0	-	0	-	0	-	0	-	0	-	0	-	**1**
16	742	p.G742D	15	20	0	-	2	22	0	-	1	14	0	-	0	-	**18**
16	745	p.A745P	1	1.3	0	-	0	-	0	-	0	-	0	-	0	-	**1**
16	784	p.M784_K785delins	1	1.3	0	-	0	-	0	-	0	-	0	-	0	-	**1**
			75	**100**	**12**	**100**	**9**	**100**	**2**	**100**	**7**	**100**	**3**	**100**	**2**	**100**	**110**

**refers to the frequency of a particular SF3B1 mutation within each major subset. AA: amino acid.*

Supplemental Table 9. *TP53* abnormalities detected in the present study.

Subset	*TP53^{mut} only*	*del(17p) only*	*Both TP53^{mut} and del(17p)*	*Cases analyzed for only one type of aberration and positive*	*Cases with aberrant TP53*
#1	8	2	10	2	22/100 (22%)
#59	0	0	0	0	0/12 (0%)
#99	2	0	2	2	6/15 (40%)
#3	1	2	0	1	4/19 (21%)
#5	0	0	0	0	0/20 (0%)
#6	1	1	1	0	3/33 (9%)
#7	0	1	1	1	3/8 (37.5%)
#8	0	2	1	0	3/23 (13%)
#2	3	0	0	0	3/128 (2%)
#4	3	0	0	0	3/59 (5%)

Cases which were analyzed for only one type of *TP53* lesion i.e. mutation or deletion, could be included in the counts provided in the table above if they demonstrated positivity (since a single *TP53* defect is sufficient to render the case as aberrant with respect to *TP53*). In the same vein, cases analyzed for only one type of *TP53* lesion and negative (wild-type) for that specific analysis were excluded from the counts since the case could still prove to have aberrant TP53.

Supplemental Figure 1. Prognostic implications of *SF3B1* mutations within subset #2. del(11q) is associated with shorter TTFT within subset #2 (A). Impact of *SF3B1* mutations on TTFT for all subset #2 cases (all stages) included in the study (B). Effect of *SF3B1* mutations on OS (C) and (TTFT) in subset #2 patients harboring del(11q) (D). Impact of the p.K700E mutation versus all other *SF3B1* mutations on OS (A) and TTFT (B) in cases assigned to subset #2.