Supplemental data

EGR2 mutations define a new clinically aggressive subgroup of chronic lymphocytic leukemia

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Supplemental Tables

Table S1: Clinical and biological characteristics of 366 CLL patients treated within the LRF UK CLL4 trial patient cohort.

Age	
Median (years)	65
<55 years - no. (%)	52 (14%)
>71 years - no. (%)	80 (22%)
Sex	
Female- no. (%)	100 (27%)
Male - no. (%)	266 (63%)
Binet stage	
A (%) - no. (%)	81 (22%)
B/C (%) - no. (%)	285 (78%)
CD38^{+}	
High (>30%) - no. (%)	135 (44%)
Low (≤30%) - no. (%)	172 (56%)
No information	59
IGHV	
Mutated (<98% identity) - no. (%)	121 (38%)
Unmutated (≥98% identity) - no. (%)	197 (62%)
No information	51
ZAP-70	
Positiv (≥20%) - no. (%)	98 (34%)
Negativ - no. (%)	193 (66%)
No information	75
del(13)(q14)	
Absent - no. (%)	191 (58%)
Present - no. (%)	138 (42%)
No information	37
del(11)(q22)	
Absent - no. (%)	264 (80%)
Present - no. (%)	65 (20%)
No information	37
+12	
Absent - no. (%)	285 (87%)
Present - no. (%)	44 (13%)
No information	37
del(17)(p13)	
Absent - no. (%)	311 (95%)
Present - no. (%)	18 (5%)
No information	37

Recurrent genomic aberrations were classified according to the Döhner classification.

Table S2: Clinical and biological characteristics of 490 CLL patients collected within the CLL Research Consortium (CRC).

Age	
Median (years)	57
<55 years - no. (%)	215 (44%)
>71 years - no. (%)	49 (10%)
no information	4
Sex	
Female - no. (%)	159 (32%)
Male - no. (%)	331 (68%)
Rai stage	
0 - no. (%)	145 (54%)
I-II - no. (%)	112 (42%)
III-IV - no. (%)	10 (4%)
no information	223
CD38^{+}	
High (>30%) - no. (%)	168 (38%)
Low (≤30%) - no. (%)	272 (62%)
No information	50
IGHV	
Mutated (<98% identity) - no. (%)	207 (42%)
Unmutated (≥98% identity) - no. (%)	283 (58%)
ZAP-70	
Positiv (≥20%) - no. (%)	241 (49%)
Negativ - no. (%)	249 (51%)
del(13)(q14)	
Absent - no. (%)	118 (66%)
Present - no. (%)	62 (34%)
No information	310
del(11)(q22)	
Absent - no. (%)	160 (89%)
Present - no. (%)	20 (11%)
No information	310
+12	
Absent - no. (%)	158 (88%)
Present - no. (%)	22 (12%)
No information	310
del(17)(p13)	
Absent - no. (%)	160 (89%)
Present - no. (%)	20 (11%)
no information	310

Recurrent genomic aberrations were classified according to the Döhner classification.

Table S3: Clinical and biological characteristics of 233 Chinese CLL patients.

Age	
Median (years)	59
<55 years - no. (%)	73 (31%)
>71 years - no. (%)	42 (18%)
Sex	
Female - no. (%)	76 (33%)
Male - no. (%)	157 (67%)
Binet stage	
A - no. (%)	82 (35%)
B/C - no. (%)	150 (65%)
no information	1
CD38^{+}	
High (>30%) - no. (%)	56 (29%)
Low (≤30%) - no. (%)	124 (71%)
No information	43
IGHV	
Mutated (<98% identity) - no. (%)	127 (56%)
Unmutated (≥98% identity) - no. (%)	98 (44%)
No information	8
ZAP-70	
Positiv (≥20%) - no. (%)	98 (49%)
Negativ - no. (%)	102 (51%)
No information	33
del(13)(q14.3)	
Absent - no. (%)	136 (84%)
Present - no. (%)	25 (16%)
No information	72
del(11)(q22.3)	
Absent - no. (%)	180 (87%)
Present - no. (%)	19 (13%)
No information	26
+12	
Absent - no. (%)	164 (86%)
Present - no. (%)	26 (14%)
No information	43
del(17)(p13)	
Absent - no. (%)	180 (79%)
Present - no. (%)	48 (21%)
No information	5

Recurrent genomic aberrations were classified according to the Döhner classification.

Table S4: Overview of genes and target regions included in the HaloPlex Panel used for NGS analysis.

Gene	Transcript ID	Targeted exons
ATM	ATM-201 ENST00000278616	2-63
BCOR	BCOR-201 ENST00000342274	2-15
BDKRB2	BDKRB2-001 ENST00000554311	2-3
BIRC3	BIRC3-002 ENST00000263464	2-9
BRAF	BRAF-001 ENST00000288602	11,12,15
CREBBP	CREBBP-001 ENST00000262367	1-31
DDX3X	DDX3X-001 ENST00000399959	1-17
EGR2	EGR2-001 ENST00000242480	2
FBXW7	FBXW7-001 ENST00000281708	2-12
HIST1H1E	HIST1H1E-001 ENST00000304218	1
IRF4	IRF4-001 ENST00000380956	2-9
KLHL6	KLHL6-001 ENST00000341319	1
KRAS	KRAS-001 ENST00000311936	2,3
MED12	MED12-002 ENST00000374080	1-2
MYD88	MYD88-201 ENST00000417037	3-5
NFKBIE	NFKBIE-001 ENST00000275015	1-6
NOTCH1	NOTCH1-001 ENST00000277541	34
NRAS	NRAS-001 ENST00000369535	2,3
POT1	POT1-001 ENST00000357628	5-10, 18
PREX2	PREX2-001 ENST00000288368	1-40
SAMHD1	SAMHD1-001 ENST00000262878	1-16
SF3B1	SF3B1-001 ENST00000335508	14-16
SPEN	SPEN-001 ENST00000375759	1-15
TET2	TET2-202 ENST00000540549	3-11
TP53	TP53-202 ENST00000617185	2-10
UBP1	UBP1-001 ENST00000283629	1-16
XPO1	XPO1-001 ENST00000401558	15-16
ZMYM3	ZMYM3-001 ENST00000373998	2-25

Table S5: Treatment status for cases screened for *EGR2* mutations in individual cohorts

	No. *EGR2* mutated	No. *EGR2* mutated tested prior to treatment	No. *EGR2* mutated tested after treatment	No. *EGR2* mutated missing treatment data
Screening	50	35	9	6
UK CLL4	12	12	0	0
CRC	18	13	5	0
Chinese	9	8	1	0

Table S6: Low-burden *EGR2*-mutated CLL patients (n=14) verified in an independent experiment.

Sample Name	First VAF (%)	Second VAF (%)	AA change
H012	3.3	4.9	p.H384N
U018	4.3	4.9	p.D411H
H003	2.2	3.2	p.H384N
B009	0.7	2.9	p.H384N
H008	0.9	2.5	p.H384N
U013	3.5	2.0	p.E412G
B002	3.6	1.9	p.E412Q
B010	2.1	1.5	p.E356K
H004	1.1	1.3	p.E356K
R002	0.6	1.1	p.D411H
B001	3.1	1	p.D411H
B004	1.1	0.9	p.H384N
U019	1.0	0.8	p.H384N
H006	0.6	0.7	p.E356G

AA, amino acid; VAF, variant allele frequency.

Table S7: Mean coverage obtained per targeted region of the HaloPlex panel.

Sample	Mean Coverage	Fraction Cov 10X	Fraction Cov 50X	Fraction Cov 100X	Fraction Cov 500X	Fraction Cov 1000X
B011	4565	99	99	98	95	90
I014	3318	99	98	98	94	85
U010	2993	99	99	98	95	88
B002	4279	99	99	99	97	93
B006	3488	99	98	97	91	83
B006	6819	99	99	99	97	95
H013	3088	99	98	98	93	84
U009	5935	99	99	99	97	95
U014	4192	99	99	99	95	91
R001	3383	99	99	98	96	89
I001	2279	99	98	97	87	74
T004	5885	99	99	98	97	93
U008	2478	99	98	97	91	80
H004	4442	99	99	99	96	92
B005	2229	97	95	94	76	64
I004	2128	99	99	98	90	76
I003	2229	99	98	98	92	80
U007	7220	99	99	99	97	96
B003	3162	99	99	99	96	90
H010	5305	99	99	98	98	95
B007	4300	99	98	97	92	85
I005	2933	99	98	97	93	83
U006	4842	99	99	99	97	94
U016	4983	99	99	99	97	94
I011	3619	99	98	98	95	90
U005	6583	99	99	99	97	95
U013	3556	99	99	99	96	90
U015	4315	99	99	99	96	91
B008	5236	99	98	98	96	92
B012	2813	99	99	98	94	86
I013	2546	99	99	98	92	81
U004	3815	99	99	99	96	93
U012	5154	99	99	99	96	94
I006	3400	99	99	99	95	89
B014	3308	99	98	97	92	82
I009	3339	99	99	98	94	84
U003	7871	99	99	99	98	96
U011	3764	99	99	98	94	88
Mean	4100	99	99	98	94	88

Table S8: Co-existing mutations in 38 *EGR2*-mutated CLL identified by targeted enrichment (HaloPlex).

Sample ID	Chr	Start	End	Reference base	Variant base	Gene	Type	Exonic type	Variant allele ratio %	#reference alleles	#variant alleles	Read depth	Cosmic ID	Transcripts
B011	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**44.74**	3589	2906	6495	COSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K
I014	11	108121753	108121754	AG	-	***ATM***	exonic	frameshift deletion	**32.05**	475	224	696	-	ATM:NM_000051:exon10:c.1561_1562del:p.R521fs
I014	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**40.74**	2797	1923	4720	ICOSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K
U010	10	64573248	64573248	G	T	***EGR2***	exonic	nonsynonymous SNV	**29.86**	2548	1085	3634	COSM145363	EGR2:NM_000399:exon2:c.C1150A:p.H384N
U010	17	7577535	7577535	C	A	***TP53***	exonic	nonsynonymous SNV	**32.56**	932	450	1382	COSM1649403 COSM326724	TP53:NM_001126115:exon3:c.G350T:p.R117M
B002	10	64573164	64573164	C	G	***EGR2***	exonic	nonsynonymous SNV	**1.89**	5092	98	5628	-	EGR2:NM_000399:exon2:c.G1234C:p.E412Q
B006	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**39.62**	2170	1424	3594	COSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K
B006	17	7577538	7577538	C	T	***TP53***	exonic	nonsynonymous SNV	**52.64**	997	1108	2105	COSM99021 COSM99020	TP53:NM_001126115:exon3:c.G347A:p.R116Q
B006	X	41205629	41205629	G	A	***DDX3X***	exonic	nonsynonymous SNV	**76.61**	174	570	744	-	DDX3X:NM_001193417:exon12:c.G1415A:p.R472H
I010	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**37.35**	4976	2967	7943	COSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K
H013	11	108143485	108143504	ATGGG AAAAG ACTTT CCTGT	-	***ATM***	exonic	frameshift deletion	**13.48**	841	131	972	-	ATM:NM_000051:exon22:c.3190_3209del:p.M1064fs
H013	11	108143268	108143268	A	-	***ATM***	exonic	frameshift deletion	**41.96**	848	613	1458	-	ATM:NM_000051:exon21:c.3087delA:p.T1029fs
H013	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**46.59**	1834	1600	3434	COSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K
U009	7	124511044	124511044	C	T	***POT1***	exonic	nonsynonymous SNV	**12.96**	1639	244	1883	-	POT1:NM_015450:exon7:c.G176A:p.C59Y
U009	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**21.24**	4913	1325	6238	COSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K
U014	10	64573165	64573165	A	T	***EGR2***	exonic	nonsynonymous SNV	**5.31**	3904	219	4127	-	EGR2:NM_000399:exon2:c.T1233A:p.D411E
U014	12	25398281	25398281	C	T	***KRAS***	exonic	nonsynonymous SNV	**5.57**	1526	90	1616	COSM1140132 COSM532	KRAS:NM_004985:exon2:c.G38A:p.G13D
U014	7	140453134	140453134	T	C	***BRAF***	exonic	nonsynonymous SNV	**8.64**	2315	219	2534	COSM478	BRAF:NM_004333:exon15:c.A1801G:p.K601E
U014	2	198267373	198267373	G	A	***SF3B1***	exonic	nonsynonymous SNV	**47.15**	1037	925	1962	-	SF3B1:NM_012433:exon14:c.C1984T:p.H662Y
R001	3	38182749	38182753	GCCTT	-	***MYD88***	exonic	frameshift deletion	**37.17**	1374	813	2186	-	MYD88:NM_001172568:exon4:c.767_771del:p.R256fs

R001	2	61719472	61719472	C	T	***XPO1***	exonic	nonsynonymous SNV	**42**	1146	830	1976	COSM96797	XPO1:NM_003400:exon15:c.G1711A:p.E571K
R001	11	108202712	108202712	G	C	***ATM***	exonic	nonsynonymous SNV	**49.67**	2145	2117	4262	-	ATM:NM_000051:exon52:c.G7736C:p.R2579T
R001	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**50.38**	1745	1772	3517	COSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K
R001	1	16260708	16260708	T	-	***SPEN***	exonic	frameshift deletion	**50.39**	880	894	1758	-	SPEN:NM_015001:exon11:c.7973delT:p.V2658fs
R001	11	108100002	108100002	C	T	***ATM***	exonic	stopgain	**96.77**	17	510	527	-	ATM:NM_000051:exon4:c.C283T:p.Q95X
I001	3	183273173	183273173	A	G	***KLHL6***	exonic	nonsynonymous SNV	**36**	2107	1185	3292	-	KLHL6:NM_130446:exon1:c.T269C:p.L90P
I001	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**3.73**	2347 0	909	2490 8	COSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K
T004	4	153249385	153249385	G	A	***FBXW7***	exonic	nonsynonymous SNV	**16.35**	3174	621	3798	COSM1154293 COSM170727	FBXW7:NM_001013415:exon8:c.C1039T:p.R347C
T004	10	64573248	64573248	G	T	***EGR2***	exonic	nonsynonymous SNV	**41.84**	5328	3843	9192	COSM145363	EGR2:NM_000399:exon2:c.C1150A:p.H384N
T004	17	7576897	7576897	G	A	***TP53***	exonic	stopgain	**63.3**	1330	2296	3627	COSM1709728 COSM10786	TP53:NM_001126115:exon5:c.C553T:p.Q185X
T004	X	70460923	70460923	T	C	***ZMYM3***	exonic	nonsynonymous SNV	**89.87**	222	1969	2191	-	ZMYM3:NM_001171162:exon25:c.A3920G:p.Y1307C
U008	17	7578265	7578265	A	G	***TP53***	exonic	nonsynonymous SNV	**8.78**	3116	300	3417	COSM116924 COSM11089	TP53:NM_001126115:exon2:c.T188C:p.I63T
U008	10	64573335	64573335	C	T	***EGR2***	exonic	nonsynonymous SNV	**42.29**	1419	1040	2459	-	EGR2:NM_000399:exon2:c.G1063A:p.D355N
U008	3	183273210	183273210	C	G	***KLHL6***	exonic	nonsynonymous SNV	**43.87**	1429	1117	2546	-	KLHL6:NM_130446:exon1:c.G232C:p.V78L
U008	11	108164196	108164196	C	T	***ATM***	exonic	nonsynonymous SNV	**45.58**	406	340	746	-	ATM:NM_000051:exon31:c.C4768T:p.L1590F
H004	10	64573248	64573248	G	T	***EGR2***	exonic	nonsynonymous SNV	**1.13**	5677	65	5987	COSM145363	EGR2:NM_000399:exon2:c.C1150A:p.H384N
B005	11	108200961	108200961	G	A	***ATM***	exonic	nonsynonymous SNV	**6.42**	1006	69	1075	COSM20404 COSM1474994	ATM:NM_000051:exon50:c.G7328A:p.R2443Q
B005	2	61719472	61719472	C	T	***XPO1***	exonic	nonsynonymous SNV	**32.74**	682	332	1014	COSM96797	XPO1:NM_003400:exon15:c.G1711A:p.E571K
B005	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**50.34**	2868	2907	5775	COSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K
I004	11	108186605	108186605	G	A	***ATM***	exonic	nonsynonymous SNV	**20.12**	1501	378	1879	-	ATM:NM_000051:exon41:c.G6062A:p.C2021Y
I004	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**40.95**	1906	1322	3228	COSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K
I004	8	69017544	69017544	C	T	***PREX2***	exonic	nonsynonymous SNV	**56.04**	462	589	1051	-	PREX2:NM_025170:exon24:c.C2887T:p.P963S
I003	10	64573248	64573248	G	T	***EGR2***	exonic	nonsynonymous SNV	**45.14**	1473	1212	2685	COSM145363	EGR2:NM_000399:exon2:c.C1150A:p.H384N
U007	10	64573248	64573248	G	T	***EGR2***	exonic	nonsynonymous SNV	**36.01**	5342	3007	8350	COSM145363	EGR2:NM_000399:exon2:c.C1150A:p.H384N
U007	6	26156632	26156632	C	T	***HIST1H1E***	exonic	nonsynonymous SNV	**49.01**	3754	3608	7362	-	HIST1H1E:NM_005321:exon1:c.C14T:p.A5V
B003	7	140453136	140453136	A	T	***BRAF***	exonic	nonsynonymous SNV	**47.65**	993	904	1897	COSM476	BRAF:NM_004333:exon15:c.T1799A:p.V600E

B003	10	64573248	64573248	G	T	***EGR2***	exonic	nonsynonymous SNV	**49.2**	2074	2009	4083	COSM145363	EGR2:NM_000399:exon2:c.C1150A:p.H384N
B003	2	198266831	198266831	C	A	***SF3B1***	exonic	nonsynonymous SNV	**50.61**	1953	2002	3956	COSM130408	SF3B1:NM_012433:exon15:c.G2101T:p.V701F
H010	4	153249385	153249385	G	A	***FBXW7***	exonic	nonsynonymous SNV	**19.54**	3130	761	3894	COSM1154293 COSM170727	FBXW7:NM_001013415:exon8:c.C1039T:p.R347C
H010	10	64573389	64573389	C	T	***EGR2***	exonic	nonsynonymous SNV	**35.85**	2319	1296	3615	-	EGR2:NM_000399:exon2:c.G1009A:p.E337K
H010	16	3820885	3820885	T	C	***CREBBP***	exonic	nonsynonymous SNV	**45.77**	2169	1831	4000	-	CREBBP:NM_001079846:exon13:c.A2452G:p.T818A
B007	3	33450823	33450823	T	A	***UBP1***	exonic	nonsynonymous SNV	**5.61**	4338	258	4596	-	UBP1:NM_001128160:exon7:c.A724T:p.R242W
B007	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**32.82**	4050	1979	6029	COSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K
B007	11	102207502	102207506	ATAAA	-	***BIRC3***	exonic	frameshift deletion	**37.6**	239	144	383	-	BIRC3:NM_001165:exon8:c.1591_1595del:p.I531fs
B007	4	106197606	106197606	C	T	***TET2***	exonic	nonsynonymous SNV	**44.64**	2133	1720	3853	-	TET2:NM_001127208:exon11:c.C5939T:p.T1980I
I005	10	64573248	64573248	G	T	***EGR2***	exonic	nonsynonymous SNV	**37.86**	2478	1510	3989	COSM145363	EGR2:NM_000399:exon2:c.C1150A:p.H384N
I005	11	108181014	108181014	A	G	***ATM***	exonic	nonsynonymous SNV	**45.72**	1282	1080	2362	-	ATM:NM_000051:exon39:c.A5890G:p.K1964E
U006	10	64573335	64573335	C	T	***EGR2***	exonic	nonsynonymous SNV	**25.75**	4060	1408	5468	-	EGR2:NM_000399:exon2:c.G1063A:p.D355N
U016	11	108141793	108141793	T	G	***ATM***	exonic	stopgain	**27.69**	969	371	1340	-	ATM:NM_000051:exon19:c.T2841G:p.Y947X
U016	4	153249384	153249384	C	T	***FBXW7***	exonic	nonsynonymous SNV	**35.1**	3117	1686	4803	COSM117310 COSM117309	FBXW7:NM_001013415:exon8:c.G1040A:p.R347H
U016	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**38.22**	3187	1972	5159	COSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K
U016	17	7576911	7576911	G	C	***TP53***	exonic	nonsynonymous SNV	**45.04**	1733	1420	3154	COSM44967	TP53:NM_001126115:exon5:c.C539G:p.T180S
I011	10	64573248	64573248	G	T	***EGR2***	exonic	nonsynonymous SNV	**25.1**	4030	1351	5383	COSM145363	EGR2:NM_000399:exon2:c.C1150A:p.H384N
U005	10	64573248	64573248	G	T	***EGR2***	exonic	nonsynonymous SNV	**25.74**	5435	1884	7320	COSM145363	EGR2:NM_000399:exon2:c.C1150A:p.H384N
U005	9	139390649	139390650	AG	-	***NOTCH1***	exonic	frameshift deletion	**35.36**	1684	921	2588	COSM12774 COSM1292819	NOTCH1:NM_017617:exon34:c.7541_7542del:p.P2514fs
U013	4	106193872	106193872	A	G	***TET2***	exonic	nonsynonymous SNV	**48.2**	1092	1016	2108	-	TET2:NM_001127208:exon10:c.A4334G:p.Q1445R
U013	10	64573163	64573163	T	C	***EGR2***	exonic	nonsynonymous SNV	**1.96**	4657	93	5041	-	EGR2:NM_000399:exon2:c.A1235G:p.E412G
U015	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**37.22**	2728	1617	4345	COSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K
U015	11	108168061	108168061	C	T	***ATM***	exonic	stopgain	**63.55**	199	347	546	-	ATM:NM_000051:exon33:c.C4957T:p.Q1653X
B008	17	7578550	7578550	G	A	***TP53***	exonic	nonsynonymous SNV	**83.24**	748	3716	4464	COSM216414 COSM3378368	TP53:NM_001126118:exon4:c.C263T:p.S88F
B008	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**4.09**	6541	279	7135	COSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K

B012	9	139390649	139390650	AG	-	***NOTCH1***	exonic	frameshift deletion	**35.49**	809	445	1246	COSM12774 COSM1292819	NOTCH1:NM_017617:exon34:c.7541_7542del:p.P2514fs
B012	10	64573248	64573248	G	T	***EGR2***	exonic	nonsynonymous SNV	**36.14**	2093	1185	3279	COSM145363	EGR2:NM_000399:exon2:c.C1150A:p.H384N
I013	11	108201102	108201102	T	G	***ATM***	exonic	nonsynonymous SNV	**12.67**	1068	155	1223	-	ATM:NM_000051:exon50:c.T7469G:p.L2490R
I013	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**34.08**	2009	1039	3049	COSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K
I013	11	108153521	108153521	T	A	***ATM***	exonic	nonsynonymous SNV	**38.95**	279	178	457	-	ATM:NM_000051:exon25:c.T3661A:p.W1221R
U004	9	139390649	139390650	AG	-	***NOTCH1***	exonic	frameshift deletion	**19.62**	1610	393	1997	COSM12774 COSM1292819	NOTCH1:NM_017617:exon34:c.7541_7542del:p.P2514fs
U004	11	64573248	64573248	G	T	***EGR2***	exonic	nonsynonymous SNV	**33.94**	2703	1389	4092	COSM145363	EGR2:NM_000399:exon2:c.C1150A:p.H384N
U012	17	7577599	7577599	-	A	***TP53***	exonic	stopgain	**37.86**	1537	937	2475	COSM69213	TP53:NM_001126115:exon3:c.285dupT:p.D96_C97delinsX
U012	10	64573248	64573248	G	T	***EGR2***	exonic	nonsynonymous SNV	**41.18**	3601	2522	6124	COSM145363	EGR2:NM_000399:exon2:c.C1150A:p.H384N
U012	14	96706744	96706744	G	A	***BDKRB2***	exonic	nonsynonymous SNV	**51.96**	2414	2611	5025	COSM959336	BDKRB2:NM_000623:exon3:c.G79A:p.D27N
I006	2	198267484	198267484	G	A	***SF3B1***	exonic	nonsynonymous SNV	**24.11**	768	244	1012	COSM110696	SF3B1:NM_012433:exon14:c.C1873T:p.R625C
I006	10	64573121	64573121	C	T	***EGR2***	exonic	nonsynonymous SNV	**45.66**	2881	2422	5304	-	EGR2:NM_000399:exon2:c.G1277A:p.R426Q
B014	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**52.74**	2707	3021	5728	COSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K
I009	6	394951	394951	T	A	***IRF4***	exonic	nonsynonymous SNV	**35.3**	2277	1243	3521	-	IRF4:NM_001195286:exon3:c.T347A:p.L116Q
I009	11	108192065	108192065	G	A	***ATM***	exonic	nonsynonymous SNV	**35.97**	1111	624	1735	COSM1474991 COSM22475	ATM:NM_000051:exon45:c.G6490A:p.E2164K
I009	10	64573332	64573332	C	T	***EGR2***	exonic	nonsynonymous SNV	**39.53**	3118	2038	5156	COSM145364	EGR2:NM_000399:exon2:c.G1066A:p.E356K
U003	2	198267385	198267385	A	G	***SF3B1***	exonic	nonsynonymous SNV	**9.63**	4122	439	4561	-	SF3B1:NM_012433:exon14:c.T1972C:p.W658R
U003	11	108117756	108117757	AT	-	***ATM***	exonic	frameshift deletion	**10.53**	2455	289	2741	-	ATM:NM_000051:exon8:c.967_968del:p.I323fs
U003	11	108201023	108201023	T	C	***ATM***	exonic	nonsynonymous SNV	**11.16**	2491	313	2804	COSM758329	ATM:NM_000051:exon50:c.T7390C:p.C2464R
U003	10	64573248	64573248	G	T	***EGR2***	exonic	nonsynonymous SNV	**43.88**	4941	3863	8804	COSM145363	EGR2:NM_000399:exon2:c.C1150A:p.H384N
U011	10	64573248	64573248	G	T	***EGR2***	exonic	nonsynonymous SNV	**44.06**	2562	2020	4586	COSM145363	EGR2:NM_000399:exon2:c.C1150A:p.H384N

Table S9: Multivariate Cox proportional hazard analysis of time-to-first-treatment (TTFT, cases, n=735; events, n=478) and overall survival (OS, cases, n=688; events, n=285) in the screening cohort.

	TTFT			OS		
Variable	**Hazard ratio**	**95% Confidence interval**	**P-value**	**Hazard ratio**	**95% Confidence interval**	**P-value**
EGR2 mutation status	1.52	1.06 – 2.20	.024	1.92	1.23 – 2.97	.003
Age	1.07	0.88 – 1.28	.490	2.48	1.93 – 3.18	< .001
Gender	1.11	0.92 – 1.34	.264	1.18	0.92 – 1.52	.193
Binet stage	NA	NA	NA	1.90	1.47 – 2.46	< .001
IGHV mutation status	3.77	3.03 – 4.65	< .001	3.14	2.36 – 4.17	< .001
NOTCH1 mutation status	1.12	0.85 – 1.49	.429	1.30	0.90 – 1.86	.159
SF3B1 mutation status	1.60	1.22 – 2.06	< .001	1.47	1.03 – 2.10	.035
*TP53*abn	1.35	1.05 – 1.60	.019	1.80	1.30 – 2.48	< .001

Table S10: Multivariate Cox proportional hazard analysis of time-to-first-treatment (TTFT, cases, n=428; events, n=294) and overall survival (OS, cases, n=486; events, n=128) in the CRC cohort.

	TTFT			OS		
Variable	**Hazard ratio**	**95% Confidence interval**	**P-value**	**Hazard ratio**	**95% Confidence interval**	**P-value**
EGR2 mutation status	1.92	1.11 – 3.32	.020	1.90	0.88 – 4.12	.10
Age	1.05	0.84 – 1.33	.66	1.70	1.19 – 2.43	.004
Gender	1.06	0.82 – 1.36	.65	1.46	0.97 – 2.18	.07
IGHV mutation status	2.06	1.60 – 2.64	< .001	2.55	1.68 – 3.86	< .001

Table S11: Cytogenetics and mutation allele frequencies of 38 *EGR2*-mutated CLL samples investigated by Haloplex gene panel.

Sample ID	*EGR2* VAF (%)	Cytogenetic aberration	del(11q) (%)	*TP53* VAF (%)	*NOTCH1* VAF (%)	*SF3B1* VAF (%)	*ATM* VAF (%)
H013	46.6	del(13q)					13.5/41.9
I014	40.7	del(11q)	91				32.1
U016	38.2	del(13q)		45.0			27.7
U015	37.2	del(11q)	75				63.6
U008	42.3	no RCA		8.8			45.6
U003	43.9	del(11q)	NA			9.6	10.5/11.2
R001	50.4	NA					96.8/49.7
B005	50.3	del(11q)	87				6.4/5.8
I009	39.5	del(11q)	77				36.0
I013	34.1	del(11q)	97				12.7/38.9
I005	37.9	+12					45.7
I004	40.9	del(11q)	80				20.1
T004	41.8	del(17p)		63.3			
U012	41.2	no RCA		37.7			
U010	29.9	del(17p)		32.6			
B006	39.6	del(11q)	NA	52.6			
U014	5.3	no RCA				47.2	
B003	49.2	no RCA				50.6	
I006	45.7	del(13q)				24.1	
B012	36.1	del(13q)			35.5		
U004	33.9	del(13q)			19.6		
U005	25.7	+12			35.4		
H010	35.9	del(13q)					
B007	32.8	del(11q)	99				
U007	36.0	+12					
U006	25.8	NA					
B011	44.7	del(11q)	89				
U009	21.2	no RCA					
B014	52.7	del(11q)	98				
U011	44.1	no RCA					
I010	37.4	+12					
I011	25.1	no RCA					
I003	45.1	del(13q)					
I001	3.7	no RCA					
U013	2.0	no RCA					
B008	4.1	del(13q)		83.2			
B002	1.9	no RCA					
H004	1.1	del(13q)					

NA, not applicable; RCA, recurrent cytogenetic aberration, VAF, variant allele frequency.

Supplemental Figures

Figure S1: Multiple alignment of the amino acid sequences of the three *EGR2* zinc-finger domains (highlighted in pink) with 7 orthologous *EGR2* proteins. Mutations affecting E356, H384, and D411 are marked with a red star .

Figure S2: Overall survival according to *ATM* aberration status (i.e. mutations and/or deletions) in 45 *EGR2*-mutated CLL patients.

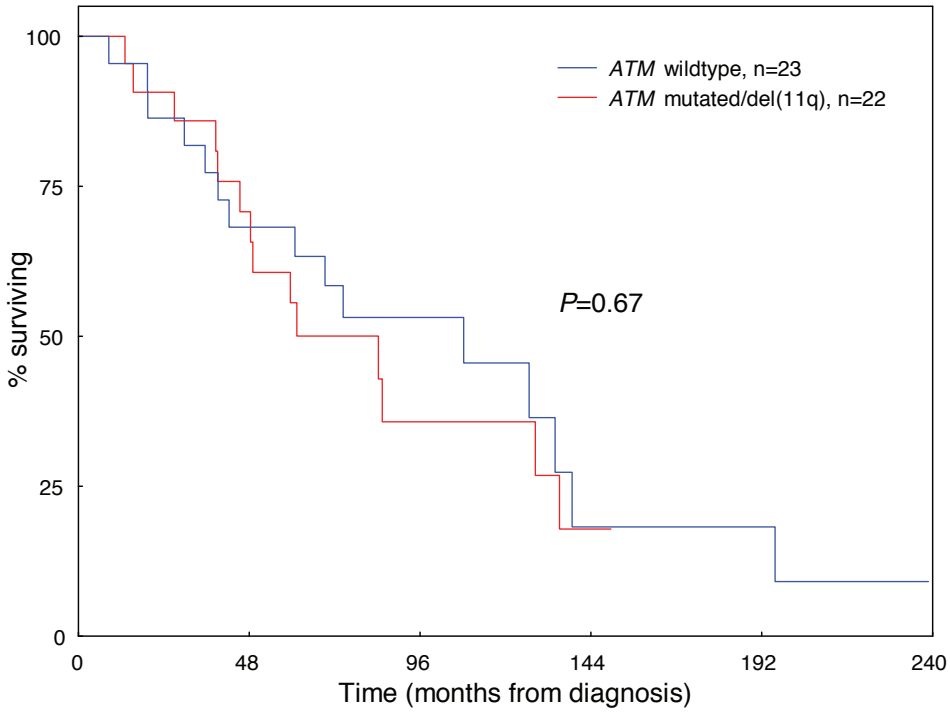

Figure S3: Overall survival according to *EGR2* mutation status in 691 IGHV-unmutated CLL patients.

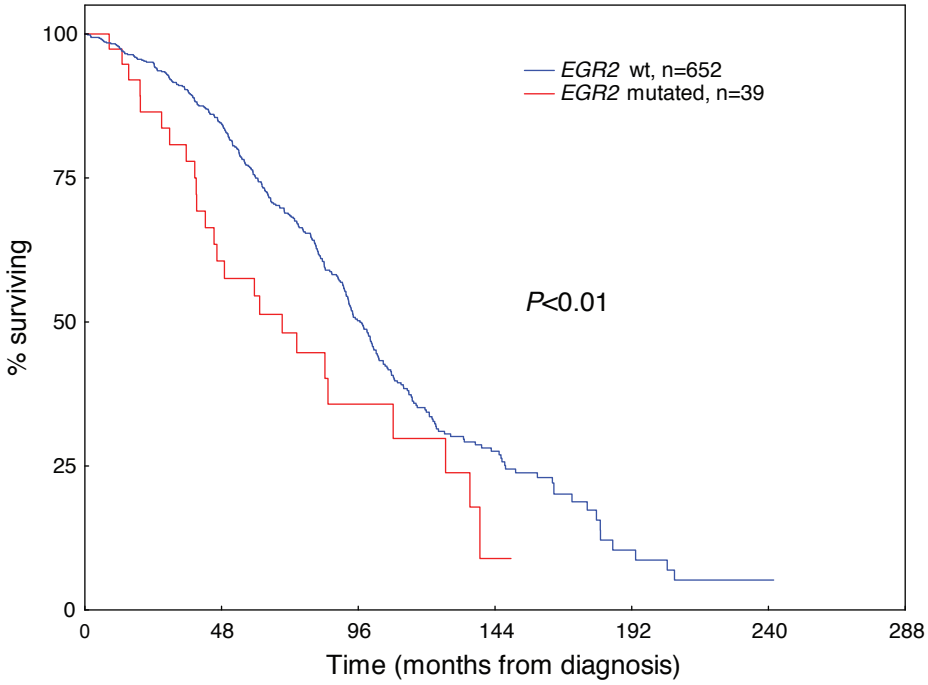

Figure S4: Overall survival according to *EGR2* mutation status in 164 patients with *TP53* abnormalities.

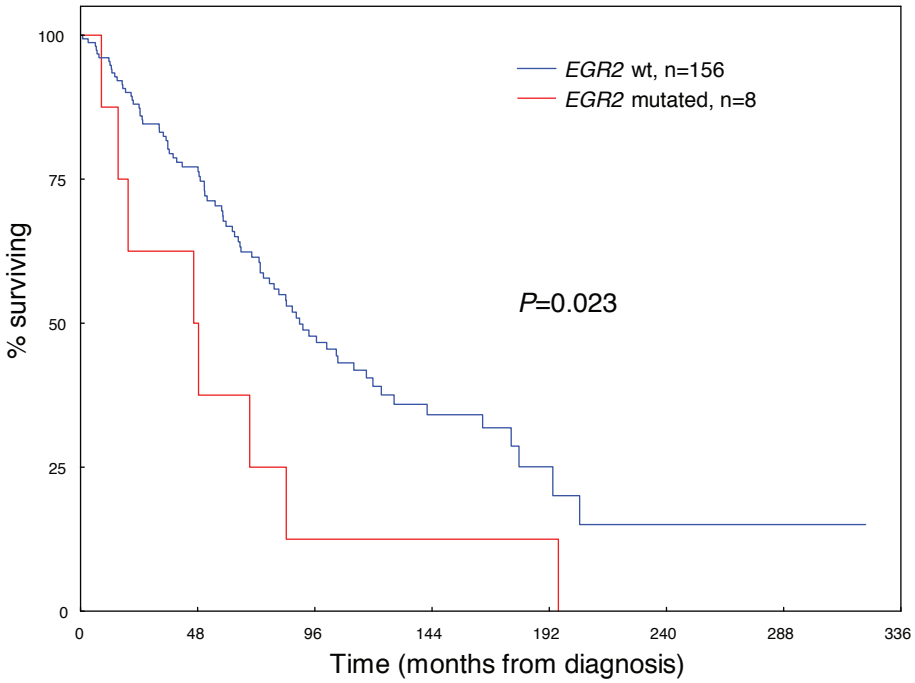

Figure S5: Overall survival according to subclonal *EGR2* mutation status (<5% VAF) in the screening cohort.

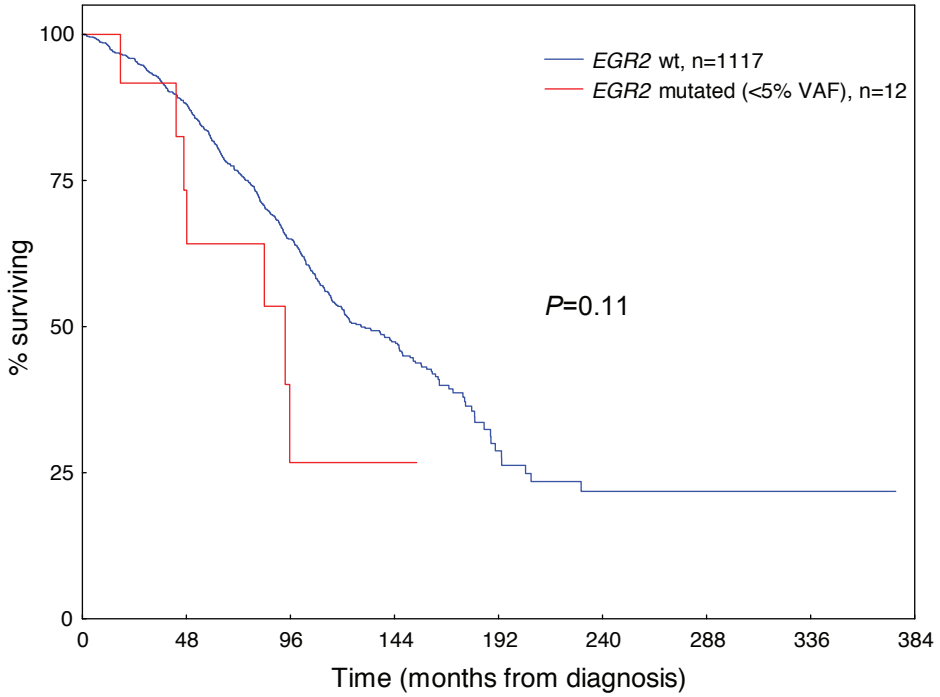

Figure S6: Clonal dynamics of somatic mutations identified by WES prior to FCR treatment and after relapse. Selected CLL driver mutations are highlighted in addition to *EGR2* (for full list of gene mutations see Ljungström et al, Blood 2016).