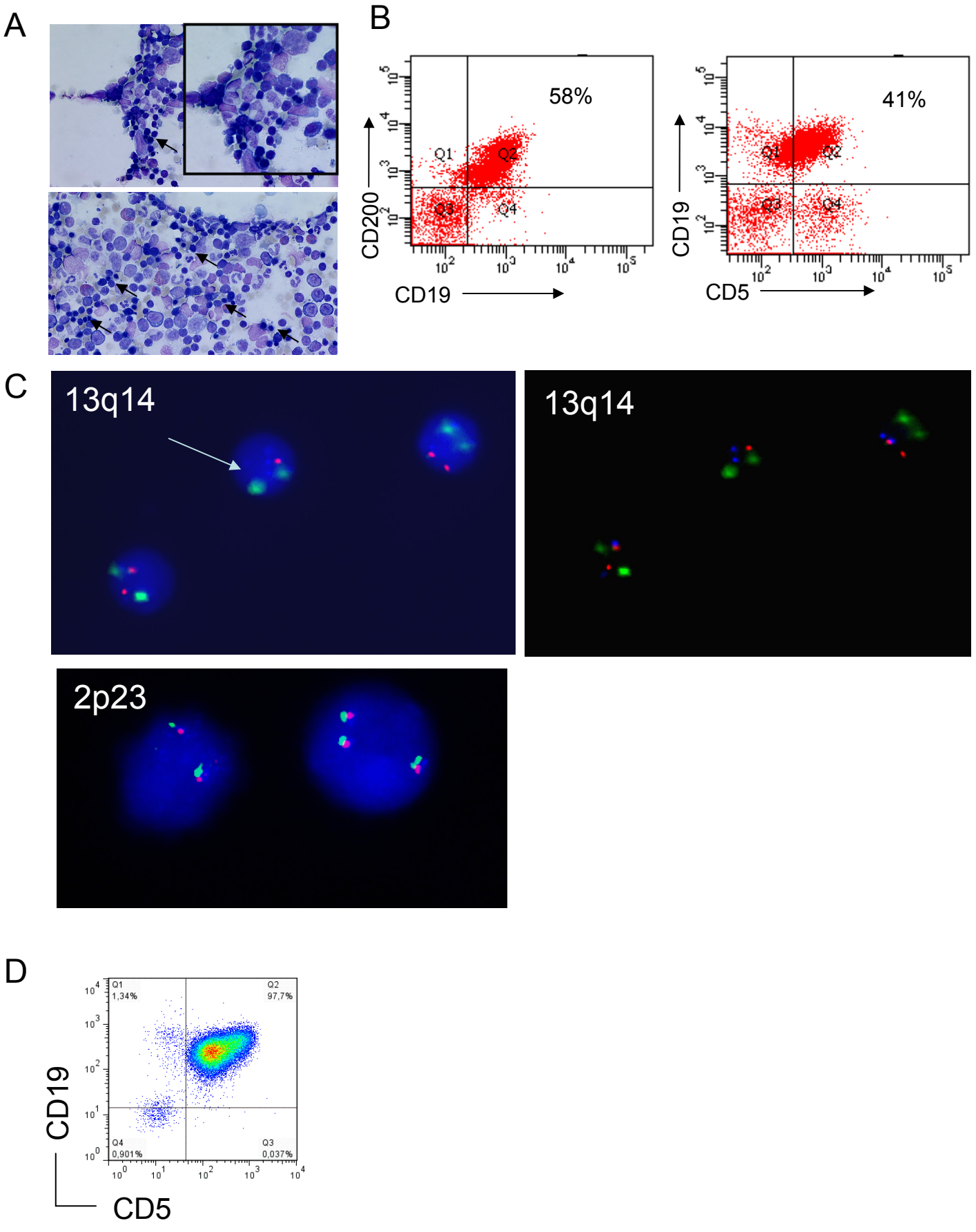
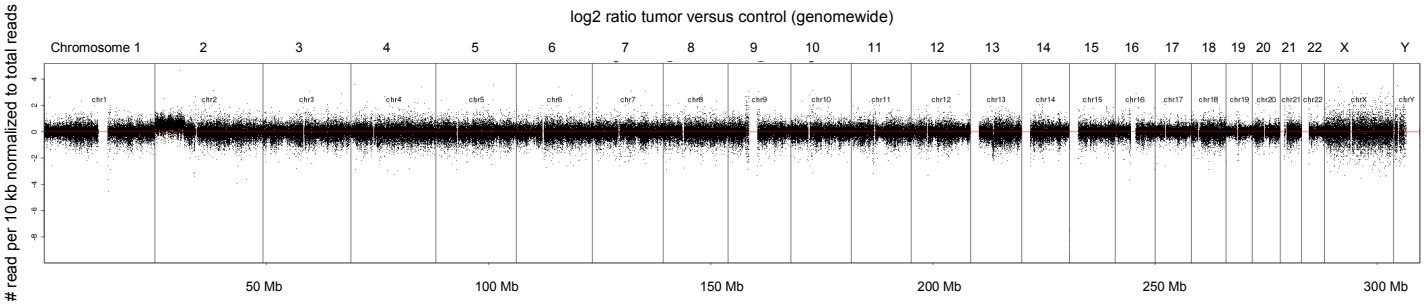
Suppl. Figure 1



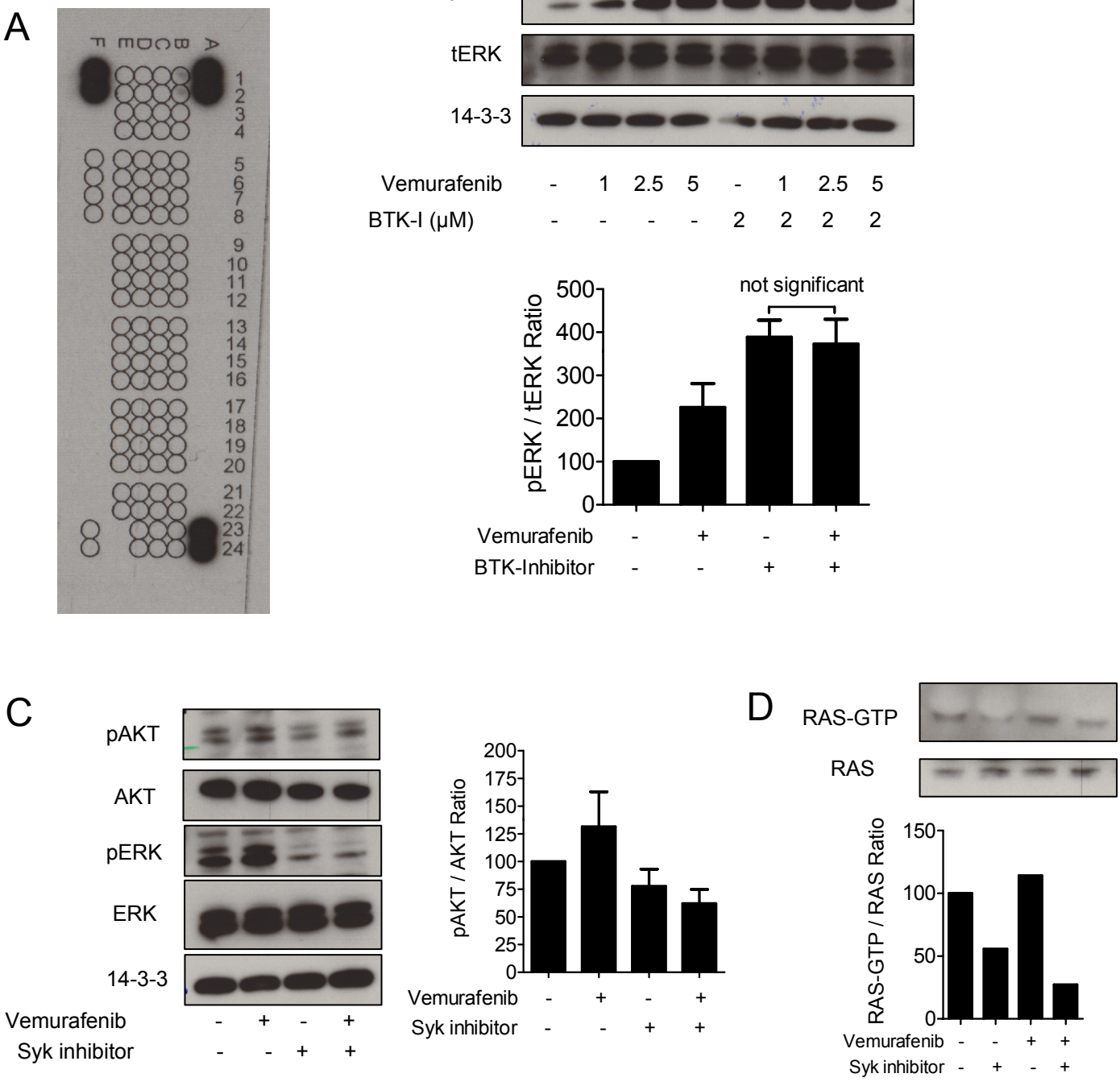
Suppl. Figure 2



start	stop	event_type	Chromosome arm	genes
49580147	49796568	deletion	13q	MLNR;FNDC3A
49839873	51969726	deletion	13q	ARL11;CTAGE10P;MIR16-1;MIR15A;ST13P4;CDADC1;SETDB2;PHF11;RCBTB1;EBPL;C13orf1;TRIM13;DLEU1;GUCY1B2;FAM124A;SERPINE3;INTS6;CAB39L;DLEU2;KCNRG;RNASEH2B;DLEU7;KPNA3
106322296	106539572	deletion	14q	ADAM6;KIAA0125
5245315	5865099	amplification	2p	SOX11
22786727	23177123	deletion	22q	PRAME;GGTLC2;MIR650;ZNF280B;ZNF280A;LOC648691;POM121L1P

Chromosome	Position	Gene	Exonic classification	Annovar transcripts	Cytoband
1	162344365	C1orf111	nonsynonymous SNV	C1orf111:NM_182581:exon3:c.C259T:p.R87W,	1q23.3
1	175365689	TNR	nonsynonymous SNV	TNR:NM_003285:exon5:c.G1231T:p.V411L,	1q25.1
1	226426724	LIN9	nonsynonymous SNV	LIN9:NM_173083:exon12:c.T1241C:p.L414P,	1q42.12
4	187172721	KLKB1	nonsynonymous SNV	KLKB1:NM_000892:exon9:c.G949A:p.V317I,	4q35.2
5	146435290	PPP2R2B	nonsynonymous SNV	PPP2R2B:NM_181676:exon1:c.G17A:p.R6H,	5q32
6	47647958	GPR111	nonsynonymous SNV	GPR111:NM_153839:exon6:c.C419G:p.P140R,	6p12.3
12	45784240	ANO6	nonsynonymous SNV	ANO6:NM_001142678:exon12:c.T1291C:p.C431R,ANO6:NM_001142680:exon13	12q12
14	23415771	HAUS4	nonsynonymous SNV	HAUS4:NM_017815:exon10:c.G1055A:p.R352Q,HAUS4:NM_001166269:exon10	14q11.2
17	18145834	LLGL1	nonsynonymous SNV	LLGL1:NM_004140:exon21:c.C3008T:p.P1003L,	17p11.2
X	3239036	MXRA5	nonsynonymous SNV	MXRA5:NM_015419:exon5:c.G4690A:p.D1564N,	Xp22.33

Suppl. Figure 3



(A) Primary CLL cells from the melanoma patient were highly purified (>97% $CD19^{+}CD5^{+}$) and phosphorylation of different RTKs (n=49, some RTKs are in duplicate) was analyzed. No RTK phosphorylation was identified. (B) Western blot analysis for pERK and tERK of the protein lysate of at the indicated concentrations of Vemurafenib (2.5 µM), SYK inhibitor (R406, 1 µM) or BTK inhibitor (Ibrutinib, 2 µM) and quantification of the protein amounts of the described groups are displayed. The experiment was performed three times with similar results. (C) Primary CLL cells were exposed to vemurafenib, SYK inhibitor (R406, 1 µM) or DMSO as control at the indicated concentrations and the resulting western blot and the pAKT/tAKT ratios pooled from 4 independent western blot analyses are shown. (D) Primary CLL cells were exposed to vemurafenib, Syk inhibitor (R406, 1 µM) or DMSO as control at the indicated concentrations and the resulting western blot and the RAS-GTP/tRAS ratios are shown.

Supplementary Figure 1: Hematopathological findings

A: Bone marrow aspirate of the patient while being under vemurafenib treatment is shown at a magnification of x400. The insets show the aspirate at higher magnification (x600). Arrows indicate areas with lymphocytic infiltration.

B: Immunophenotyping of the white blood cells during vemurafenib treatment revealed a $CD19^{+}CD200^{+}$ population that could also be seen as $CD19^{+}CD5^{+}$ cells

C: FISH analysis of the PBMCs of the patient while being under vemurafenib treatment. Left image: three interphase nuclei with DAPI as DNA counterstain. Two of them have two red signals for 13q14.3 and two green signals for centromere of chromosome 12. One nucleus with deletion 13q14 had only one red signal for 13q14.3 and two green signals for 12 centromers (white arrow). Right image: the same picture without filter for DAPI counterstain. Two blue signals for 13q34 LAMP1 are present in all three interphase nuclei indicating a deletion of 13q14.3 and not monosomy 13. 13q14.3 DLEU-SpectrumOrange, 13q34LAMP1: Aqua (blue), 12cen: SpectrumGreen. For detection of 2p23 Vysis LSI ALK (2p23) (Abbott, Wiesbaden) was used.

D. $CD19^{+}CD5^{+}$ cells obtained from the patient were highly purified (>97%) by MACS enrichment with CD5 and CD19 beads.

Supplementary Figure 2: Whole-exome sequencing results

CLL developing under BRAF inhibition showed somatically acquired copy number variations and single nucleotide variants as summarized. Copy number aberrations included a focal deletion on 13q14 including the mir15/16 and DLEU1/2 locus and a small amplification on chromosome 2p, validated by FISH.

Supplementary Table 1: CLL is not commonly found in patients under Vemurafenib treatment

ID	Age	Gender	Treatment with Vemurafenib (months)	Detection of $CD5^{+}$ $CD19^{+}$ cells in peripheral blood	Increased leukocyte count under Vemurafenib
01	41	female	2.5	no	no
02	70	male	5	no	no
03	63	male	4	no	no
04	40	female	5	no	no
05	73	female	4	no	no
06	64	male	1	no	no
07	51	male	2	no	no

Supplementary Table 2: Sequencing for mutations in CLL cells

BRAF exons 11 and 15	KRAS exon 2 and 3	NRAS exon 2 and 3	EZH2 exon 16	MYD88_exons 3 and 5
SF3B1 exons 14 and 15	TP53 exons 4-10	NOTCH1 exon 34	PIK3CA exons 9 and 20	

No mutations were found in the sequencing analysis of these genes with $CD19^{+}CD5^{+}$ CLL cells.

Suppl. Table 3 Characteristics of the patients and the CLL cells

#ID	Sex	Age	Rai stage	IgVH	Genetic abberations in CLL cells
1	male	71	0	um	del 13q14
2	male	70	III	m	del 17p13, trisomy12
3	female	81	IV	m	trisomy12, del 13q14
4	female	73	II	um	del 17p13, del 13q14
5	male	51	II	um	del 11q22, del 13q14
6	male	50	I	m	trisomy12
7	male	57	II	m	trisomy12, del 13q14
8	male	81	I	um	del 17p13
9	female	77	II	m	trisomy12, del 13q14
10	male	80	III	um	del 11q22, del 13q14

Abbreviations: um = unmutated Immunoglobulin Variable (IgVH) region, m = mutated IgVH, del = deletion, CLL = chronic lymphocytic leukemia