Interestingly, both GS- 1101 (CAL-101 (now GS-1101) a reversible small molecule inhibitor of PI3Kdelta) and Ibrutinib (irreversible BTK inhibitor) appear to mobilize CLL cells from the lymphatic niches to the circulation, resulting in significant and sustained leukocytosis that probably reflects disruption of signaling that mediates adhesion of CLL cells to the microenvironment, including the **CXCL12-CXCR4 axis**.

				Abnormalities types						
HGNC-ID	Approved name	Synonyms	Chromosomal location	Chromosome - Gene alteration	Gene / miR expression	Protein level / modification	Role in apoptosis / proliferation of the anomalies	Basic signaling mechanism	Notes	PubMed / data-bases source
CXCR4	chemokine (C-X-C motif) receptor 4	FB22; HM89; LAP3; LCR1; NPYR; WHIM; CD184; LESTR; NPY3R; NPYRL; HSY3RR; NPYY3R; D2S201E	2q21		Over expressed	Over expressed			This gene encodes a CXC chemokine receptor specific for stromal cell-derived factor-1. The protein has 7 transmembrane regions and is located on the cell surface. It acts with the CD4 protein to support HIV entry into cells and is also highly expressed in breast cancer cells. Mutations in this gene have been associated with WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome. Alternate transcriptional splice variants, encoding different isoforms, have been characterized	
CXCL12	chemokine (C-X-C motif) ligand 12	IRH; PBSF; SDF1; TLSF; TPAR1; SCYB12	10q11.1						This gene encodes a stromal cell-derived alpha chemokine member of the intercrine family. The encoded protein functions as the ligand for the G-protein coupled receptor, chemokine (C-X-C motif) receptor 4, and plays a role in many diverse cellular functions, including embryogenesis, immune surveillance, inflammation response, tissue homeostasis, and tumor growth and metastasis. Mutations in this gene are associated with resistance to human immunodeficiency virus type 1 infections. Multiple transcript variants encoding different isoforms have been found for this gene	
PIM1	pim-1 oncogene		6p21.2		Over expressed	Over expressed	increase of survival and anti-apoptotic. CXCR4 339 ser phosphorylation by PIM1 reduces ligand-dependent CXCR4 internalization favouring CXCR4 overexpression maintainance	Ser/Thr protein kinase	The protein encoded by this gene belongs to the Ser/Thr protein kinase family, and PIM subfamily. This gene is expressed primarily in B-lymphoid and myeloid cell lines, and is overexpressed in hematopoietic malignancies and in prostate cancer. It plays a role in signal transduction in blood cells, contributing to both cell proliferation and survival, and thus provides a selective advantage in tumorigenesis.	PIM kinases are essential for chronic lymphocytic leukemia cell survival (PIM2/3) and CXCR4 mediated microenvironmental interactions (PIM1).
PIM2	pim-2 oncogene		Xp11.23		Over expressed	Over expressed	increase of survival and anti-apoptotic.	Ser/Thr protein kinase		
PIM3	pim-3 oncogene		22q13		Over expressed	Over expressed	increase of survival and anti-apoptotic.	Ser/Thr protein kinase		
BCR	B-cell receptor								This gene is overexpressed in hematological and epithelial tumors and is associated with MYC conexpression The B cell receptor (BCR) signaling pathway plays a crucial role in the pathogenesis of CLL. In a normal B cell, the engagement of the BCR by antigen triggers a signaling pathway controlling proliferation, differentiation and antibody production. Activated BCR recruits kinases such as spleen tyrosine kinase (SYK) and the SRC kinase LYN that phosphorylate ITAM motifs on the cytoplasmic domains of the Ig co-receptors CD79a and CD79b. Such phosphorylation recruits and activates Bruton's tyrosine kinase (BTK) and phosphoinositide 3-kinase (PI3K), subsequently activating many downstream targets including AKT/mTOR, NF-B, and ERK. Interestingly, BCR activation can occur in a ligand-independent manner, The latter mechanism is especially important, as it is thought to be involved in B cell malignancies including CLL.	
LYN	v-yes-1 Yamaguchi sarcoma viral related oncogene homolog	JTK8; p53Lyn; p56Lyn	8q13							
SYK	spleen tyrosine kinase	p72-Syk	9q22						SYK kinase contributes to the initiation and amplification of BCR signaling upon BCR activation by antigen binding and also during ligand-independent activa- tion	
BTK	Bruton agammaglobulinemia tyrosine kinase	AT; ATK; BPK; XLA; IMD1; AGMX1; PSCTK1	Xq21.33-q22						The BTK is activated downstream of SYK/LYN following BCR stimulation, and in turn leads to activation of the PI3K/AKT and NF- B pathways.	
PIK3C2A	phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 alpha	PI3K-C2alpha	11p15.5-p14	Not studied	Not studied	Phsophorylated	increase of survival	AKT1 activation		Curr Hematol Malig Rep. 2013 Mar;8(1):71-80. doi: 10.1007/s11899-012-0150-1. Signal transduction in the chronic leukemias: implications for targeted therapies. Ahmed W1, Van Etten RA.
PIK3C2B	phosphatidylinositol-4-phosphate 3-kinase, catalytic subunit type 2 beta	C2-PI3K, PI3K-C2beta	1q32	Not studied	Not studied	Phsophorylated	increase of survival	AKT1 activation		
PIK3CD	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta	APDS; PI3K; IMD14; p110D; P110DELTA	1p36.2				increase of survival	Phosphoinositide 3-kinases (PI3Ks) phosphorylate inositol lipids and are involved in the immune response. The protein encoded by this gene is a class I PI3K found primarily in leukocytes. Like other class I PI3Ks (p110-alpha p110-beta, and p110-gamma), the encoded protein binds p85 adapter proteins and GTP-bound RAS. However, unlike the other class I PI3Ks, this protein phosphorylates itself, not p85 protein	The predominant PI3K catalytic p110 subunit isoform in hematopoietic cells and lymphocytes is the delta isoform. Mice lacking p110delta have normal hematopoiesis except for the B-lymphoid lineage, where there is a reduction both in mature B cells and in BCR signaling	
AKT1	v-akt murine thymoma viral oncogene homolog 1	RAC, PKB, PRKBA, AKT	14q32.32-q32.33	Not studied	Not studied	Phsophorylated	anti-apoptosis	BAD phosphorylation and inhibition; NFkB1 activation		
MTOR	mechanistic target of rapamycin (serine/threonine kinase)	FRAP; FRAP1; FRAP2; RAFT1; RAPT1	1p36.2						The protein encoded by this gene belongs to a family of phosphatidylinositol kinase-related kinases. These kinases mediate cellular responses to stresses such as DNA damage and nutrient deprivation. This protein acts as the target for the cell-cycle arrest and immunosuppressive effects of the FKBP12-rapamycin complex. The ANGPTL7 gene is located in an intron of this gene.	
PRKCB	protein kinase C, beta	PKCB; PRKCB1; PRKCB2; PKC-beta	16p11.2		Over expressed at mRNA level		increase of survival	Mediates intracellular signals following B-cell receptor (BCR) engagement leading to the survival and clonal expansion of CLL cells.	CLL-cell induced, PKC-β- dependent, NF-κB activity in stromal cells was shown to be critical for the anti- apoptotic effects of the stroma on the leukemic cells, suggesting that cross-talk between CLL cells and the tumor microenvironment and the survival of the proliferating disease compartment may also be dependent on PKC signaling.	Leukemia & Lymphoma, October 2013; 54(10): 2098–2099 © 2013 Informa UK, Ltd. Protein kinase C isoform expression in chronic lymphocytic leukemia: a potential target for therapy? O. Giles Best1 & Constantine Tam
PRKCG	protein kinase C, gamma	PKCC; PKCG; SCA14; PKC-gamma	19q13.4							
PRKCD	protein kinase C, delta	MAY1; PKCD; CVID9; nPKC-delta	3p21.31			constitutively active in CLL by BCR-induced phosphoinositide 3-kinase (PI3-kinase)		Mediates intracellular signals following B-cell receptor (BCR) engagement leading to the survival and clonal expansion of CLL cells.		
PRKCE	protein kinase C, epsilon	PKCE; nPKC-epsilon	2p21					Mediates intracellular signals following B-cell receptor (BCR) engagement leading to the survival and clonal expansion of CLL cells.		
PRKCZ	protein kinase C, zeta	PKC2; PKC-ZETA	1p36.33-p36.2		Over expressed at mRNA level		increase of survival	Mediates intracellular signals following B-cell receptor (BCR) engagement leading to the survival and clonal expansion of CLL cells.		
MAP3K14	mitogen-activated protein kinase kinase kinase 14	HS; NIK; HSNIK; FTDCR1B	17q21			Increased expression due to lacking of BIRC3-mediated degradation	anti-apoptosis		This gene encodes mitogen-activated protein kinase kinase kinase 14, which is a serine/threonine protein-kinase. This kinase binds to TRAF2 and stimulates NF-kappaB activity. It shares sequence similarity with several other MAPKK kinases. It participates in an NF-kappaB-inducing signalling cascade common to receptors of the tumour-necrosis/nerve-growth factor (TNF/NGF) family and to the interleukin-1 type-I receptor	
PTK2	protein tyrosine kinase 2	FADK, FAK, FAK1, PPP1R71, "protein phosphatase 1, regulatory subunit 71"	8q24.3				pro-apoptosis		PTK2 inhibition blunted rituximab-dependent cell death in vitro. Retrospective analysis from 2 independent trials revealed that increased PTK2 expression is associated with improved outcomes for CLL patients treated with R-FC vs FC. PTK2 expression may be a useful biomarker for patient selection in future trial	PTK2 expression and immunochemotherapy outcome in chronic lymphocytic leukemia. Blood. 2014 Jun 10. pii: blood-2013-12-538975. [Epub ahead of print]