THE LANCET Oncology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Burger JA, Keating MJ, Wierda WG, et al. Safety and activity of ibrutinib plus rituximab for patients with high-risk chronic lymphocytic leukaemia: a single-arm, phase 2 study. *Lancet Oncol* 2014; published online Aug 21. http://dx.doi.org/10.1016/S1470-2045(14)70335-3.

Supplementary Index

Burger, Keating, Wierda et al:

"The combination of ibrutinib and rituximab (iR) is well tolerated and induces a high rate of durable remissions in patients with high-risk Chronic Lymphocytic Leukemia (CLL)"

A. Extended Experimental Procedures

Patients

The EORTC QLQ-C30 (version 3.0), a 30-item core questionnaire developed by the EORTC, was used to assess health-related quality of life (QOL) at baseline, after 2 weeks, and after months 1, 3, 6, and 12. EORTC-QOL raw scores on global health status subscale were summarized using standard descriptive statistics and measures of central tendency, including frequencies, means, medians, range, and standard deviations. The answers to questionnaires were scored according to instructions described in the EORTC QLQ-C30 Manual (ISBN 2-9300 64-22-6) and missing values were scored following the method proposed by Aaronson[1].

BTK occupancy test (probe assay)

Occupancy test was performed as previously described.[2] Briefly, $1x10^7$ B-ALL cells were incubated in regular growth medium in presence of 0.1% DMSO or increasing concentrations of ibrutinib (0.0001-1.0 μM) for 1 hour. Then cells were collected by centrifugation and lysed by 4 freeze/thaw cycles. Protein concentration was determined using Bio-Rad DC Protein Assay Kit (Bio-Rad). Equal amounts of total protein were labelled with 2.5 μM PCI-33380 for 1 hour. The reaction mixtures were resolved by SDS/PAGE electrophoresis, gels were scanned using Typhoon FLA7000 Imager (Ex. 532/ Em. 555). Next gels were blotted and membranes stained for BTK and GAPDH.

Chemotaxis assay

The chemotaxis assay across polycarbonate transwell inserts was performed as described[3]. Briefly, 15 CLL samples ($1x10^7$ cells/ml) were incubated in complete RPMI medium (control) or in complete medium supplemented with 10 μg/ml of anti-IgM at 37°C in 5% CO_2. After 48 hours, CLL cells were suspended to a concentration of $1x10^7$ cells/ml in RPMI1640 with 0.5% BSA and a total of 100 μl, containing $1x10^6$ cells, was added to the top chamber of a 6.5-mm diameter transwell culture inserts (Costar, Cambridge, MA, USA) with a pore size of 5 μm. Filters then were transferred to wells containing medium with or without 200ng/mL of CXCL12 (Upstate, Charlottesville, VA) or 1 μg/mL of CXCL13 (R&D Systems, Minneapolis, MN). The chambers were incubated for 3 hours at 37°C in 5% CO_2. After this incubation, the cells in the lower chamber were suspended and divided into aliquots for counting with a FACSCalibur for 20 seconds at 60 μL/min in duplicates. A 1:20 dilution of input cells was counted under the same conditions.

Gene expression analysis

In order to purify the CLL B cells prior to RNA isolation, CLL PBMC were passed through a 30 μm nylon mesh to obtain a single-cell suspension. Then CLL B cells were purified with CD19 MicroBeads. Using TRIzol from Invitrogen, B cells were lysed according to the manufacturer's instructions (Invitrogen, Carlsbad, CA).

Total RNA extraction then was performed with the PureLink Micro-to-Midi Total RNA Purification System as described by the manufacturer (Invitrogen). The RNA was quantified using a NanoDrop 1000 spectrophotometer (Fisher Scientific, Pittsburgh, PA). Gene expression studies were performed using HG U133 plus 2.0 oligonucleotide arrays from Affymetrix (Affymetrix, Santa Clara, CA). The samples were processed following the protocol for eukaryotic samples in the expression analysis technical manual from Affymetrix (available at www.affymetrix.com). In detail, cDNA synthesis was performed with a starting amount of 1-2 µg total RNA using the One-cycle cDNA synthesis kit (Affymetrix) following the Affymetrix standard protocol. Double stranded cDNA and cRNA was purified with the GeneChip sample clean-up module. Synthesis of biotin-labelled cRNA was performed using the IVT labelling kit from Affymetrix, followed by clean-up and fragmentation. After 16 h of hybridization at 45°C the arrays were washed, stained (Fluidics Station 450) and laser scanned (Affymetrix GC scanner 3000) following the Affymetrix manual. The array images were visually checked for hybridization irregularities. The average probe array signals were scaled to a target signal of 500 by using the GeneChip operating software (GCOS).

B. Supplemental Tables

True median PFS	Pr(stop)	Mean number of patients (25%, 75%)
3 months	0.975	23.3 (14, 33)
4 months	0.632	31.8 (24, 40)
5 months	0.240	36.6 (40, 40)
6 months	0.078	38.6 (40, 40)
7 months	0.038	39.1 (40, 40)
8 months	0.018	39.6 (40, 40)

TableS1: Simulation study with maximum 40 patients

	Questionnaires N=39		Questionnaires N=25		
EORTC – QOL- C30 v.3 Measure	Mean score baseline	SD	Mean score 12 months	SD	p-value
Global health status	70.9	18.8	79.3	10.2	.04
Functioning scale					
Physical	88.0	17.8	95.5	20.0	.12
Role	90.2	19.0	96.0	12.0	.18
Social	81.6	22.9	94.7	20.8	.02
Emotional	83.8	14.5	94.7	20.8	.02
Cognitive	92.3	12.6	97.3	10.4	.10
Symptom scale					
Nausea/vomiting	20.5	14.0	0		≤.001
Pain	13.2	25.1	2.7	13.3	.06
Fatigue	24.8	23.7	4.4	14.0	≤.001
Single item					
Insomnia	24.8	26.2	1.3	6.7	≤.001
Appetite loss	10.2	17.4	0		.004
Diarrhoea	2.6	9.0	6.7	13.6	.15
Constipation	6.0	15.0	4.0	20.0	.65
Dyspnoea	19.6	27.3	2.7	9.2	.003
Financial impact	12.0	20.9	2.7	13.3	.05

Table S2: Quality of life in CLL patients before (baseline) and after 12 months of treatment with iR. There were significant improvements in global health, functional and symptom scales, and other items.

	Age, gender (M/F)	FISH CG, hierarchical	On study (# of cycles)	Reason for dis-continuation	Best response	Post-progression treatments	Cause of death
1	69, M	11q	15	Death in remission	PR	NA	Unknown (passed away in his sleep)
2	36, F	11q	6	Progressive disease	PR	None	Pneumonia, sepsis
3	58, F	17p	5	Mucositis	SD	NA	N/A
4	64, M	17p	16	Ear and pulmonary infections	PR	Poly-chemotherapy for Richter's transformation	Pneumonia, Richter's transformation
5	77, M	17p, 11q	2	Pneumonia, brain abscess	NR	NA	Pneumonia, brain abscess
6	66, F	11q	13	Richter's transformation	PR	PI3 kinase inhibitor, high-dose corticosteroids plus rituximab	Richter's transformation
7	83, M	17p	8	Progressive COPD and CHF	PR	NA	Progressive COPD and CHF
8	74, F	17p	11	Progressive disease	PR	None	Progressive disease
9	62, M	17p, 11q	5	Resistant pneumonia	PR	NA	Resistant pneumonia

TableS3: Patients who discontinued iR therapy: reasons for study discontinuation and outcome.

Related adverse events	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Lung Infection	5 (13%)	9 (23%)	2 (5%)	
Diarrhoea	9 (23%)	1 (3%)		
Neutropenia			1 (3%)	1 (3%)
Fatigue	4 (10%)	3 (8%)		
Upper respiratory infection	3 (8%)	10 (25%)	1 (3%)	
Nausea/Acid reflux	10 (25%)	3 (8%)		
Arthralgia	8 (20%)	3 (8%)		
Transaminase increase			1 (3%)	
Bleeding events (Bruising/Rash/ Epistaxis)	8 (20%)	5 (13%)		
Peripheral neuropathy	1 (3%)	1 (3%)	1 (3%)	
Weight gain		4 (10%)		
Eye disorders (itching/watery eyes)	1 (3%)	2 (5%)		
Mucositis	1 (3%)	1 (3%)	1 (3%)	
Constipation	1 (3%)			
Alopecia	1 (3%)			
Atrial Fibrillation	1 (3%)	1 (3%)		
Unrelated adverse events	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
UTI (Urinary tract infection)		3 (8%)		
Insomnia		4 (10%)		
Headache	3 (8%)			
Anaemia	1 (3%)	2 (5%)		
Osteoporosis		1 (3%)		
Hot flashes		2 (5%)		
Constipation	1 (3%)	2 (5%)		
Nausea/vomiting		2 (5%)		
Anxiety		2 (5%)		
Dry mouth	1 (3%)	1 (3%)		
Dyspnoea		1 (3%)		
Subdural haematoma			1 (3%)	
Sepsis			1 (3%)	

Table S4: ***Related and unrelated adverse events***

log2 fold GE change	Gene	Description	Well ID	Feature ID
-1.9894625		Transcribed locus	1461881	215565_at
-1.7917125	PIGR	polymeric immunoglobulin receptor (PIGR), mRNA.	1503168	226147_s_at
-1.7607625	CCL3	chemokine (C-C motif) ligand 3 (CCL3), mRNA.	1493951	205114_s_at
-1.72925	CCL5	chemokine (C-C motif) ligand 5 (CCL5), transcript variant 1, mRNA.	1506815	1555759_a_at
-1.7281125	CD1C	CD1c molecule (CD1C), mRNA.	1457096	205987_at
-1.5580625	EGR3	early growth response 3 (EGR3), transcript variant 1, mRNA.	1457170	206115_at
-1.5479	SFTPB	surfactant protein B (SFTPB), transcript variant 1, mRNA.	1454143	37004_at
-1.525875	SLCO4A1	solute carrier organic anion transporter family, member 4A1 (SLCO4A1), mRNA.	1500721	219911_s_at
-1.4978375	FCRL5	Fc receptor-like 5	1502795	224404_s_at
-1.4345875	PIGR	Polymeric immunoglobulin receptor	1503691	229659_s_at
-1.4227625	TP53I3	tumor protein p53 inducible protein 3 (TP53I3), transcript variant 1, mRNA.	1496618	210609_s_at
-1.405025	CCL5	chemokine (C-C motif) ligand 5 (CCL5), transcript variant 1, mRNA.	1454449	1405_i_at
-1.404175	OAS3	2'-5'-oligoadenylate synthetase 3, 100kDa (OAS3), mRNA.	1463481	218400_at
-1.3926875	PHACTR1	phosphatase and actin regulator 1 (PHACTR1), transcript variant 1, mRNA.	1460764	213638_at
-1.3912125	YME1L1	YME1-like 1 (S. cerevisiae)	1499571	217143_s_at
-1.3855625		CDNA FLJ41339 fis, clone BRASW1000053	1476553	236099_at
-1.366725	MT1HL1	metallothionein 1H-like 1 (MT1HL1), mRNA.	1497197	211456_x_at
-1.2947875	FCRL3	Fc receptor-like 3 (FCRL3), mRNA.	1506001	1553196_a_at
-1.26805	EGR1	early growth response 1 (EGR1), mRNA.	1492182	201694_s_at
-1.25985	IFI30	interferon, gamma-inducible protein 30 (IFI30), mRNA.	1454801	201422_at
-1.2576375	TLR10	toll-like receptor 10 (TLR10), transcript variant 1, mRNA.	1502493	223750_s_at
-1.2473625	DNPH1	2'-deoxynucleoside 5'-phosphate N-hydrolase 1 (DNPH1), transcript variant 1, mRNA.	1493545	204238_s_at
-1.23035	BIK	BCL2-interacting killer (apoptosis-inducing) (BIK), mRNA.	1456963	205780_at
-1.2161875	ADA	adenosine deaminase (ADA), mRNA.	1499388	216705_s_at
-1.2124625	LILRA4	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 4 (LILRA4), mRNA.	1459212	210313_at
-1.1734375	CTNS	cystinosin, lysosomal cystine transporter (CTNS), transcript variant 2, mRNA.	1456453	204925_at
-1.1712	GRN	granulin (GRN), mRNA.	1497082	211284_s_at
-1.1684375	MS4A1	membrane-spanning 4-domains, subfamily A, member 1 (MS4A1), transcript variant 3, mRNA.	1499700	217418_x_at
-1.16455	MS4A1	membrane-spanning 4-domains, subfamily A, member 1 (MS4A1), transcript variant 3, mRNA.	1496472	210356_x_at
-1.1638125	YME1L1	YME1-like 1 (S. cerevisiae)	1499159	216191_s_at
-1.15785	ZBTB32	zinc finger and BTB domain containing 32 (ZBTB32), mRNA.	1464555	220118_at
-1.150275	MS4A1	membrane-spanning 4-domains, subfamily A, member 1 (MS4A1), transcript variant 3, mRNA.	1470291	228599_at
-1.148625	PHACTR1	PREDICTED: phosphatase and actin regulator 1 (PHACTR1), transcript variant X1, mRNA.	1503200	226397_s_at
-1.1316875	PLEK	pleckstrin (PLEK), mRNA.	1493174	203471_s_at
-1.1233875	HIST1H1E	histone cluster 1, H1e (HIST1H1E), mRNA.	1458459	208553_at
-1.115775	CAV1	caveolin 1, caveolae protein, 22kDa (CAV1), transcript variant 1, mRNA.	1459698	212097_at
-1.111675	GM2A	GM2 ganglioside activator (GM2A), transcript variant 1, mRNA.	1460163	212737_at
-1.111125	PPAPDC1B	PREDICTED: phosphatidic acid phosphatase type 2 domain containing 1B (PPAPDC1B), transcript variant X3, mRNA.	1468189	226150_at
-1.11085	EGR2	early growth response 2 (EGR2), transcript variant 1, mRNA.	1456644	205249_at

-1.1095125	LOC101927402	PREDICTED: uncharacterized LOC101927402 (LOC101927402), mRNA.	1478773	238559_at
-1.0992375	SFTPB	surfactant protein B (SFTPB), transcript variant 1, mRNA.	1458978	209810_at
-1.0929875		Transcribed locus	1507595	1559067_a_at
-1.0928875	PTPLA	protein tyrosine phosphatase-like (proline instead of catalytic arginine), member A (PTPLA), mRNA.	1464238	219654_at
-1.087375	BZRAP1-AS1	BZRAP1 antisense RNA 1 (BZRAP1-AS1), transcript variant 1, long non-coding RNA.	1470484	228828_at
-1.0866375	FCRL5	Fc receptor-like 5	1466824	224405_at
-1.0863375		Transcribed locus	1479440	239287_at
-1.0808625	KMO	kynurenine 3-monooxygenase (kynurenine 3-hydroxylase) (KMO), mRNA.	1494029	205306_x_at
-1.0804375	CHI3L2	chitinase 3-like 2 (CHI3L2), transcript variant 1, mRNA.	1497928	213060_s_at
-1.079025	APOBEC3G	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G (APOBEC3G), mRNA.	1498728	214995_s_at
-1.0762875	YME1L1	YME1-like 1 (S. cerevisiae)	1460869	213830_at
-1.07065	TYMS	thymidylate synthetase (TYMS), mRNA.	1455278	202589_at
-1.069375	TRAF4	TNF receptor-associated factor 4 (TRAF4), mRNA.	1497551	211899_s_at
-1.066125	STAP2	signal transducing adaptor family member 2 (STAP2), transcript variant 1, mRNA.	1501456	221610_s_at
-1.0544625	APOBEC3G	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G (APOBEC3G), mRNA.	1456075	204205_at
-1.0533375	TRAF4	TNF receptor-associated factor 4 (TRAF4), mRNA.	1482245	242473_at
-1.046575	LILRB4	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 4 (LILRB4), transcript variant 1, mRNA.	1459124	210152_at
-1.0461625	DCAF12	DDB1 and CUL4 associated factor 12 (DCAF12), mRNA.	1467039	224789_at
-1.03775	IL2RB	interleukin 2 receptor, beta (IL2RB), mRNA.	1456669	205291_at
-1.0367	APOBEC3B	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B (APOBEC3B), transcript variant 1, mRNA.	1494531	206632_s_at
-1.0234875	RHOF	ras homolog family member F (in filopodia) (RHOF), mRNA.	1506408	1554539_a_at
-1.0232125	NME1	NME/NM23 nucleoside diphosphate kinase 1 (NME1), transcript variant 2, mRNA.	1454867	201577_at
-1.02245	TOP2A	topoisomerase (DNA) II alpha 170kDa (TOP2A), mRNA.	1454746	201292_at
-1.02075	FMO1	flavin containing monooxygenase 1 (FMO1), transcript variant 2, mRNA.	1456894	205666_at
-1.020075	FOS	FBJ murine osteosarcoma viral oncogene homolog (FOS), mRNA.	1458683	209189_at
-1.0185625	E2F1	E2F transcription factor 1 (E2F1), mRNA.	1456464	204947_at
-1.01835	HILPDA	hypoxia inducible lipid droplet-associated (HILPDA), transcript variant 1, mRNA.	1463537	218507_at
-1.015775	GEM	GTP binding protein overexpressed in skeletal muscle (GEM), transcript variant 1, mRNA.	1456209	204472_at
-1.0144875		Transcribed locus	1487064	1559066_at
-1.011575	CCL5	chemokine (C-C motif) ligand 5 (CCL5), transcript variant 1, mRNA.	1456315	204655_at

Tables S4: Most down-regulated genes after 7 days of treatment with ibrutinib plus rituximab.

log2 fold GE change	Gene	Description	Well ID	Feature ID
-2.41485	PIGR	polymeric immunoglobulin receptor (PIGR), mRNA.	1503 168	226147_s_at
-2.2884	FCRL3	Fc receptor-like 3 (FCRL3), mRNA.	1506 001	1553196_a_at
-2.2717125		Transcribed locus	1461 881	215565_at
-2.2492	MS4A1	membrane-spanning 4-domains, subfamily A, member 1 (MS4A1), transcript variant 3, mRNA.	1496 472	210356_x_at
-2.222225	MS4A1	membrane-spanning 4-domains, subfamily A, member 1 (MS4A1), transcript variant 3, mRNA.	1470 291	228599_at
-2.2221625	MS4A1	membrane-spanning 4-domains, subfamily A, member 1 (MS4A1), transcript variant 3, mRNA.	1499 700	217418_x_at
-1.9623	TLR10	toll-like receptor 10 (TLR10), transcript variant 1, mRNA.	1502 494	223751_x_at
-1.9414125	MS4A1	membrane-spanning 4-domains, subfamily A, member 1 (MS4A1), transcript variant 3, mRNA.	1470 284	228592_at
-1.9125875	MS4A1	Membrane-spanning 4-domains, subfamily A, member 1	1472 668	231418_at
-1.9073	CHI3L2	chitinase 3-like 2 (CHI3L2), transcript variant 1, mRNA.	1497 928	213060_s_at
-1.834325		Transcribed locus	1479 440	239287_at
-1.8176875	CPNE5	copine V (CPNE5), mRNA.	1469 102	227189_at
-1.813975	CCL5	chemokine (C-C motif) ligand 5 (CCL5), transcript variant 1, mRNA.	1456 315	204655_at
-1.80495	CD1C	CD1c molecule (CD1C), mRNA.	1457 096	205987_at
-1.7973625	TLR10	toll-like receptor 10 (TLR10), transcript variant 1, mRNA.	1502 493	223750_s_at
-1.790875	TP53I3	tumor protein p53 inducible protein 3 (TP53I3), transcript variant 1, mRNA.	1496 618	210609_s_at
-1.775	ITGAX	integrin, alpha X (complement component 3 receptor 4 subunit) (ITGAX), transcript variant 2, mRNA.	1459 146	210184_at
-1.758525	CCL3	chemokine (C-C motif) ligand 3 (CCL3), mRNA.	1493 951	205114_s_at
-1.738475	CCL5	chemokine (C-C motif) ligand 5 (CCL5), transcript variant 1, mRNA.	1506 815	1555759_a_at
-1.7302875	AGMAT	agmatine ureohydrolase (agmatinase) (AGMAT), mRNA.	1501 480	221648_s_at
-1.7217125	GM2A	GM2 ganglioside activator (GM2A), transcript variant 1, mRNA.	1454 117	35820_at
-1.7123375	PIGR	Polymeric immunoglobulin receptor	1503 691	229659_s_at
-1.7069625	LOC339260	Uncharacterized LOC339260	1488 832	1562754_at
-1.687625	KIAA0101	KIAA0101 (KIAA0101), transcript variant 1, mRNA.	1492 658	202503_s_at
-1.6726875	CST7	cystatin F (leukocystatin) (CST7), mRNA.	1459 118	210140_at
-1.663475		Transcribed locus	1507 595	1559067_a_at
-1.6618875	PLEK	pleckstrin (PLEK), mRNA.	1493 174	203471_s_at
-1.6579375	HLA-DPB2	Major histocompatibility complex, class II, DP beta 2 (pseudogene)	1480 066	239975_at
-1.6364625	LILRA4	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 4 (LILRA4), mRNA.	1459 212	210313_at
-1.63095	GRN	granulin (GRN), mRNA.	1497 082	211284_s_at
-1.587025	HIST1H2AC	Histone cluster 1, H2ac	1498 757	215071_s_at
-1.5857625	FMO1	flavin containing monooxygenase 1 (FMO1), transcript variant 2, mRNA.	1456 894	205666_at
-1.5826125	P2RX5	purinergic receptor P2X, ligand-gated ion channel, 5 (P2RX5), transcript variant 1, mRNA.	1496 525	210448_s_at

-1.57235	RHOF	ras homolog family member F (in filopodia) (RHOF), mRNA.	1506408	1554539_a_at
-1.5503125	DNPH1	2'-deoxynucleoside 5'-phosphate N-hydrolase 1 (DNPH1), transcript variant 1, mRNA.	1493545	204238_s_at
-1.529575	GSTZ1	glutathione S-transferase zeta 1 (GSTZ1), transcript variant 3, mRNA.	1458845	209531_at
-1.522175	MPEG1	macrophage expressed 1 (MPEG1), mRNA.	1468793	226841_at
-1.5205375	CCL5	chemokine (C-C motif) ligand 5 (CCL5), transcript variant 1, mRNA.	1454449	1405_i_at
-1.518125	GM2A	GM2 ganglioside activator (GM2A), transcript variant 1, mRNA.	1460163	212737_at
-1.50075	YME1L1	YME1-like 1 (S. cerevisiae)	1499571	217143_s_at
-1.4987625	IL17RB	interleukin 17 receptor B (IL17RB), mRNA.	1502648	224156_x_at
-1.498325	PTPLA	protein tyrosine phosphatase-like (proline instead of catalytic arginine), member A (PTPLA), mRNA.	1464238	219654_at
-1.484725	LOC101927402	PREDICTED: uncharacterized LOC101927402 (LOC101927402), mRNA.	1478773	238559_at
-1.473275	CLECL1	C-type lectin-like 1 (CLECL1), transcript variant 1, mRNA.	1483950	244413_at
-1.4668	HN1	hematological and neurological expressed 1 (HN1), transcript variant 1, mRNA.	1463167	217755_at
-1.4499125		Full length insert cDNA clone YI54A07	1485995	1556281_at
-1.4469375	FMOD	fibromodulin (FMOD), transcript variant 1, mRNA.	1455332	202709_at
-1.4443875	PLEK	pleckstrin (PLEK), mRNA.	1493173	203470_s_at
-1.4366	PNOC	prepronociceptin (PNOC), transcript variant 1, mRNA.	1457039	205901_at
-1.4311375	PPAPDC1B	PREDICTED: phosphatidic acid phosphatase type 2 domain containing 1B (PPAPDC1B), transcript variant X3, mRNA.	1468189	226150_at
-1.4291375	TNFRSF17	tumor necrosis factor receptor superfamily, member 17 (TNFRSF17), mRNA.	1457505	206641_at
-1.4127875	HIST1H2BH	histone cluster 1, H2bh (HIST1H2BH), mRNA.	1495461	208546_x_at
-1.4097375	HILPDA	hypoxia inducible lipid droplet-associated (HILPDA), transcript variant 1, mRNA.	1463537	218507_at
-1.404175	IFI30	interferon, gamma-inducible protein 30 (IFI30), mRNA.	1454801	201422_at
-1.400775	RNASE6	ribonuclease, RNase A family, k6 (RNASE6), mRNA.	1460725	213566_at
-1.398425	MPEG1	macrophage expressed 1 (MPEG1), mRNA.	1468774	226818_at
-1.3869	FCRL3	PREDICTED: Fc receptor-like 3 (FCRL3), transcript variant X3, mRNA.	1472381	231093_at
-1.381825	ACP5	acid phosphatase 5, tartrate resistant (ACP5), transcript variant 4, mRNA.	1456303	204638_at
-1.3778	PHACTR1	phosphatase and actin regulator 1 (PHACTR1), transcript variant 1, mRNA.	1460764	213638_at
-1.374975	HIST1H2BD	histone cluster 1, H2bd (HIST1H2BD), transcript variant 2, mRNA.	1496249	209911_x_at
-1.367625	LOC102724334	PREDICTED: histone H2B type F-S-like (LOC102724334), mRNA.	1495470	208579_x_at
-1.3675875	ITGB2-AS1	ITGB2 antisense RNA 1 (ITGB2-AS1), transcript variant 1, long non-coding RNA.	1503581	229041_s_at
-1.3450875	RP11-960L18.1	PREDICTED: uncharacterized LOC101928342 (RP11-960L18.1), ncRNA.	1489134	1563263_at
-1.3371625	RAC2	ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2) (RAC2), mRNA.	1494831	207419_s_at
-1.3349875	LOC64563	WDNM1-like pseudogene (LOC645638), non-coding RNA.	1471097	229566_at

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-1.3317875	SLCO4A1	solute carrier organic anion transporter family, member 4A1 (SLCO4A1), mRNA.	1500 721	219911_ s_at
-1.32665	YME1L1	YME1-like 1 (S. cerevisiae)	1497 554	211902_ x_at
-1.31925		Transcribed locus	1478 188	237880_ at
-1.3145125	MIR22HG	MIR22 host gene (non-protein coding) (MIR22HG), transcript variant 1, long non-coding RNA.	1461 324	214696_ at
-1.3131625	IL17RB	interleukin 17 receptor B (IL17RB), mRNA.	1500 520	219255_ x_at
-1.3099875	KCNG1	potassium voltage-gated channel, subfamily G, member 1 (KCNG1), mRNA.	1461 259	214595_ at
-1.300125	FABP5	fatty acid binding protein 5 (psoriasis-associated) (FABP5), mRNA.	1492 561	202345_ s_at
-1.297675	RASGRP1	RAS guanyl releasing protein 1 (calcium and DAG-regulated) (RASGRP1), transcript variant 1, mRNA.	1456 845	205590_ at
-1.2881625	HIST1H2BD	histone cluster 1, H2bd (HIST1H2BD), transcript variant 1, mRNA.	1501 676	222067_ x_at
-1.2838125	RAC2	ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2) (RAC2), mRNA.	1498 109	213603_ s_at
-1.27555	YME1L1	YME1-like 1 (S. cerevisiae)	1499 159	216191_ s_at
-1.27465	GCHFR	GTP cyclohydrolase I feedback regulator (GCHFR), mRNA.	1456 428	204867_ at
-1.2728375	EGR3	early growth response 3 (EGR3), transcript variant 1, mRNA.	1457 170	206115_ at
-1.271325	ADAM8	ADAM metallopeptidase domain 8 (ADAM8), transcript variant 1, mRNA.	1493 986	205180_ s_at
-1.2617375	ZBTB32	zinc finger and BTB domain containing 32 (ZBTB32), mRNA.	1464 555	220118_ at
-1.2563625	BIK	BCL2-interacting killer (apoptosis-inducing) (BIK), mRNA.	1456 963	205780_ at
-1.25525	OAS3	2'-5'-oligoadenylate synthetase 3, 100kDa (OAS3), mRNA.	1463 481	218400_ at
-1.25125	GPR137B	G protein-coupled receptor 137B (GPR137B), mRNA.	1456 039	204137_ at
-1.2459125	GRN	granulin (GRN), mRNA.	1499 116	216041_ x_at
-1.2318875		CDNA FLJ41339 fis, clone BRASW1000053	1476 553	236099_ at
-1.224075	BAIAP2-AS1	BAIAP2 antisense RNA 1 (head to head) (BAIAP2-AS1), long non-coding RNA.	1507 422	1558147 _a_at
-1.2225375	YME1L1	YME1-like 1 (S. cerevisiae)	1460 869	213830_ at
-1.2214125	CCND2	cyclin D2 (CCND2), mRNA.	1491 737	200951_ s_at
-1.21685	LIME1	Lck interacting transmembrane adaptor 1 (LIME1), mRNA.	1464 161	219541_ at
-1.210875	ANKRD44	ankyrin repeat domain 44 (ANKRD44), transcript variant B, mRNA.	1476 258	235777_ at
-1.2103125		CDNA FLJ36989 fis, clone BRACE2006753	1487 354	1559776 _at
-1.21025	HIST1H2BK	histone cluster 1, H2bk (HIST1H2BK), mRNA.	1458 977	209806_ at
-1.207325	LOC100131043	Uncharacterized LOC100131043	1483 604	244029_ at
-1.2053125	WARS	tryptophanyl-tRNA synthetase (WARS), transcript variant 1, mRNA.	1454 507	200629_ at
-1.205025	GRN	granulin (GRN), mRNA.	1491 550	200678_ x_at
-1.2034375		Transcribed locus	1489 884	1565894 _at
-1.2014875	APOBEC3	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G (APOBEC3G), mRNA.	1456 075	204205_ at

	G			
-1.2012	TRAF4	TNF receptor-associated factor 4 (TRAF4), mRNA.	1497 551	211899_ s_at
-1.196925	PHEX	phosphate regulating endopeptidase homolog, X-linked (PHEX), transcript variant 1, mRNA.	1479 384	239229_ at
-1.19305	IL27RA	Interleukin 27 receptor, alpha	1465 621	222062_ at
-1.1917125	LINC00173	long intergenic non-protein coding RNA 173 (LINC00173), transcript variant 1, long non-coding RNA.	1477 929	237591_ at
-1.1883375	SUSD1	sushi domain containing 1 (SUSD1), transcript variant 2, mRNA.	1468 285	226264_ at
-1.1879	POM121L9P	POM121 transmembrane nucleoporin-like 9, pseudogene (POM121L9P), non-coding RNA.	1504 171	232736_ s_at
-1.184175	GNG8	guanine nucleotide binding protein (G protein), gamma 8 (GNG8), mRNA.	1475 019	234284_ at
-1.1820125	FCRL5	Fc receptor-like 5	1502 795	224404_ s_at
-1.1815875	LY96	lymphocyte antigen 96 (LY96), transcript variant 1, mRNA.	1457 467	206584_ at
-1.1788375	CHDH	choline dehydrogenase (CHDH), mRNA.	1487 269	1559590 _at
-1.17425	KIF15	kinesin family member 15 (KIF15), mRNA.	1464 004	219306_ at
-1.17025	SASH3	SAM and SH3 domain containing 3 (SASH3), mRNA.	1456 451	204923_ at
-1.1694	LILRB4	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 4 (LILRB4), transcript variant 1, mRNA.	1459 124	210152_ at
-1.1682875	HN1	hematological and neurological expressed 1 (HN1), transcript variant 1, mRNA.	1465 805	222396_ at
-1.16585	OGT	O-linked N-acetylglucosamine (GlcNAc) transferase (OGT), transcript variant 1, mRNA.	1497 716	212307_ s_at
-1.1649	TNNI2	troponin I type 2 (skeletal, fast) (TNNI2), transcript variant 1, mRNA.	1457 359	206393_ at
-1.16265	ABRACL	ABRA C-terminal like (ABRACL), mRNA.	1466 247	223361_ at
-1.1624375		Full length insert cDNA clone YI46G04	1469 754	227952_ at
-1.1616	GSN	gelsolin (GSN), transcript variant 1, mRNA.	1491 562	200696_ s_at
-1.1609875	ZBP1	Z-DNA binding protein 1 (ZBP1), transcript variant 1, mRNA.	1505 355	242020_ s_at
-1.1584125	PLEKHA7	pleckstrin homology domain containing, family A member 7 (PLEKHA7), mRNA.	1470 163	228450_ at
-1.1558625	SFTPB	surfactant protein B (SFTPB), transcript variant 1, mRNA.	1458 978	209810_ at
-1.1491	IL17RB	interleukin 17 receptor B (IL17RB), mRNA.	1502 768	224361_ s_at
-1.1451625	RASGRF1	Ras protein-specific guanine nucleotide-releasing factor 1 (RASGRF1), transcript variant 1, mRNA.	1496 583	210550_ s_at
-1.1441375	GLIPR2	GLI pathogenesis-related 2 (GLIPR2), transcript variant 1, mRNA.	1503 091	225604_ s_at
-1.14315	UBE2E2	ubiquitin-conjugating enzyme E2E 2 (UBE2E2), mRNA.	1467 760	225651_ at
-1.1412375	IGFLR1	IGF-like family receptor 1 (IGFLR1), mRNA.	1464 263	219690_ at
-1.1331875		Transcribed locus	1503 977	231597_ x_at
-1.1282875	OGT	O-linked N-acetylglucosamine (GlcNAc) transferase (OGT), transcript variant 1, mRNA.	1494 897	207563_ s_at
-1.1252375	TRAF4	TNF receptor-associated factor 4 (TRAF4), mRNA.	1482 245	242473_ at
-1.1244	LILRA2	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 2 (LILRA2), transcript variant 1, mRNA.	1496 958	211100_ x_at
-1.1237125	EFCAB4A	PREDICTED: EF-hand calcium binding domain 4A (EFCAB4A), transcript variant X1, mRNA.	1469 303	227429_ at
-1.12335		Transcribed locus, strongly similar to NP_078795.2 FAM65A gene product [Homo sapiens]	1503 896	230980_ x_at

-1.1215375	S100A4	S100 calcium binding protein A4 (S100A4), transcript variant 1, mRNA.	1493020	203186_s_at
-1.118425	ZDHHC12	zinc finger, DHHC-type containing 12 (ZDHHC12), mRNA.	1468139	226088_at
-1.1181125	CBR1	carbonyl reductase 1 (CBR1), transcript variant 1, mRNA.	1458694	209213_at
-1.1146	MT1HL1	metallothionein 1H-like 1 (MT1HL1), mRNA.	1497197	211456_x_at
-1.113625	TREX1	three prime repair exonuclease 1 (TREX1), transcript variant 5, mRNA.	1494250	205875_s_at
-1.1133625	FAM129C	PREDICTED: family with sequence similarity 129, member C (FAM129C), transcript variant X4, misc_RNA.	1472292	230983_at
-1.1105375	DUS2	dihydrouridine synthase 2 (DUS2), transcript variant 1, mRNA.	1464124	219486_at
-1.110425	GEM	GTP binding protein overexpressed in skeletal muscle (GEM), transcript variant 1, mRNA.	1456209	204472_at
-1.10985	BACE2	beta-site APP-cleaving enzyme 2 (BACE2), transcript variant a, mRNA.	1499888	217867_x_at
-1.1082	ADA	adenosine deaminase (ADA), mRNA.	1499388	216705_s_at
-1.1077625	CD82	CD82 molecule (CD82), transcript variant 1, mRNA.	1493392	203904_x_at
-1.1056125	ISG15	ISG15 ubiquitin-like modifier (ISG15), mRNA.	1494101	205483_s_at
-1.1032	SULF2	sulfatase 2 (SULF2), transcript variant 1, mRNA.	1466989	224724_at
-1.103025	UTS2	urotensin 2 (UTS2), transcript variant 2, mRNA.	1501012	220784_s_at
-1.10025		Transcribed locus, strongly similar to XP_003953345.1 PREDICTED: uncharacterized protein LOC101058300 [Pan troglodytes]	1472612	231356_at
-1.0970375	ADAP2	ArfGAP with dual PH domains 2 (ADAP2), mRNA.	1500560	219358_s_at
-1.0963375	SRD5A1	steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1) (SRD5A1), mRNA.	1496844	210959_s_at
-1.0947875		Transcribed locus	1482643	242947_at
-1.0939625	C1orf85	chromosome 1 open reading frame 85 (C1orf85), transcript variant 1, mRNA.	1507518	1558693_s_at
-1.091425	WARS	tryptophanyl-tRNA synthetase (WARS), transcript variant 1, mRNA.	1491521	200628_s_at
-1.091075	CYB561A3	cytochrome b561 family, member A3 (CYB561A3), transcript variant 2, mRNA.	1466999	224735_at
-1.0904375	TP63	tumor protein p63 (TP63), transcript variant 1, mRNA.	1496222	209863_s_at
-1.0863625	LDHA	lactate dehydrogenase A (LDHA), transcript variant 1, mRNA.	1491534	200650_s_at
-1.0860125		CDNA FLJ12909 fis, clone NT2RP2004400	1472006	230650_at
-1.0818375		Transcribed locus	1478460	238183_at
-1.0784	AGMAT	agmatine ureohydrolase (agmatinase) (AGMAT), mRNA.	1502125	222930_s_at
-1.0773375	ITGB7	integrin, beta 7 (ITGB7), transcript variant 1, mRNA.	1456925	205718_at
-1.0771125	EVI2A	ecotropic viral integration site 2A (EVI2A), transcript variant 2, mRNA.	1456378	204774_at
-1.0758375	EHD3	EH-domain containing 3 (EHD3), mRNA.	1463780	218935_at
-1.075625	HMOX1	heme oxygenase (decycling) 1 (HMOX1), mRNA.	1455791	203665_at
-1.0737625	DUSP2	dual specificity phosphatase 2 (DUSP2), mRNA.	1456388	204794_at
-1.072575		Transcribed locus	1483125	243489_at
-1.07155	TLR6	toll-like receptor 6 (TLR6), mRNA.	1457996	207446_at
-1.0712875	BATF	basic leucine zipper transcription factor, ATF-like (BATF), mRNA.	1457081	205965_at

-1.0696125	CACNA1D	calcium channel, voltage-dependent, L type, alpha 1D subunit (CACNA1D), transcript variant 1, mRNA.	1459102	210108_at
-1.0683375	CDK2AP1	cyclin-dependent kinase 2 associated protein 1 (CDK2AP1), transcript variant 1, mRNA.	1455008	201938_at
-1.066	MRPS25	mitochondrial ribosomal protein S25 (MRPS25), mRNA.	1502975	224869_s_at
-1.0648	KEAP1	kelch-like ECH-associated protein 1 (KEAP1), transcript variant 2, mRNA.	1455214	202417_at
-1.0627	LOC400958	uncharacterized LOC400958 (LOC400958), long non-coding RNA.	1491072	1570006_at
-1.0595375	ARPC1B	actin related protein 2/3 complex, subunit 1B, 41kDa (ARPC1B), mRNA.	1455018	201954_at
-1.05795	FAM46C	family with sequence similarity 46, member C (FAM46C), mRNA.	1464683	220306_at
-1.0566375	FGD2	FYVE, RhoGEF and PH domain containing 2 (FGD2), mRNA.	1506190	1553906_s_at
-1.054025	LILRA6	PREDICTED: leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 6 (LILRA6), transcript variant X1, mRNA.	1495481	208594_x_at
-1.053525	GPSM1	G-protein signaling modulator 1 (GPSM1), transcript variant 1, mRNA.	1468099	226043_at
-1.049025	GGCX	Gamma-glutamyl carboxylase	1460957	214005_at
-1.0477625	SYTL1	synaptotagmin-like 1 (SYTL1), transcript variant 2, mRNA.	1469055	227134_at
-1.0454625	BCAR3	breast cancer anti-estrogen resistance 3 (BCAR3), transcript variant 2, mRNA.	1455975	204032_at
-1.043625	SFTPB	surfactant protein B (SFTPB), transcript variant 1, mRNA.	1454143	37004_at
-1.0436125	FCRL5	Fc receptor-like 5	1466824	224405_at
-1.043175	IRF5	interferon regulatory factor 5 (IRF5), transcript variant 2, mRNA.	1479560	239412_at
-1.040825	ANXA4	annexin A4 (ANXA4), mRNA.	1491954	201301_s_at
-1.04065	ZNF836	zinc finger protein 836 (ZNF836), mRNA.	1508447	1569076_a_at
-1.040025	MST1	macrophage stimulating 1 (hepatocyte growth factor-like) (MST1), mRNA.	1494152	205614_x_at
-1.0397625	DLEU1	deleted in lymphocytic leukemia 1 (non-protein coding) (DLEU1), transcript variant 2, long non-coding RNA.	1494174	205677_s_at
-1.0379625	C17orf49	chromosome 17 open reading frame 49 (C17orf49), transcript variant 2, mRNA.	1466871	224574_at
-1.0372375	NAPRT1	nicotinate phosphoribosyltransferase domain containing 1 (NAPRT1), transcript variant 1, mRNA.	1468675	226707_at
-1.036825	APOBEC3G	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G (APOBEC3G), mRNA.	1498728	214995_s_at
-1.0356625	OAS1	2'-5'-oligoadenylate synthetase 1, 40/46kDa (OAS1), transcript variant 2, mRNA.	1494130	205552_s_at
-1.035175	DUS2	dihydrouridine synthase 2 (DUS2), transcript variant 1, mRNA.	1454289	47105_at
-1.033625	C3orf14	chromosome 3 open reading frame 14 (C3orf14), transcript variant 1, mRNA.	1463994	219288_at
-1.0331875	UGT2B17	UDP glucuronosyltransferase 2 family, polypeptide B17 (UGT2B17), mRNA.	1457880	207245_at
-1.0322	DSCR3	Down syndrome critical region gene 3 (DSCR3), mRNA.	1499653	217309_s_at
-1.029775	HES6	hes family bHLH transcription factor 6 (HES6), transcript variant 1, mRNA.	1468446	226446_at
-1.0257875	KDM4B	lysine (K)-specific demethylase 4B (KDM4B), mRNA.	1497758	212492_s_at
-1.0253625	TYMS	thymidylate synthetase (TYMS), mRNA.	1455278	202589_at
-1.0252625	PHACTR1	PREDICTED: phosphatase and actin regulator 1 (PHACTR1), transcript variant X1, mRNA.	1503200	226397_s_at
-1.0242125	BLMH	bleomycin hydrolase (BLMH), mRNA.	1455108	202179_at

-1.0231875	NLRP4	NLR family, pyrin domain containing 4 (NLRP4), mRNA.	1482131	242334_at
-1.02315	ZC3HAV1L	Zinc finger CCCH-type, antiviral 1-like	1470018	228280_at
-1.0227625	NPM3	nucleophosmin/nucleoplasmin 3 (NPM3), mRNA.	1456571	205129_at
-1.0223625	POM121L8P	POM121 transmembrane nucleoporin-like 8 pseudogene (POM121L8P), non-coding RNA.	1486534	1557633_at
-1.0198625	COCH	cochlin (COCH), transcript variant 2, mRNA.	1493997	205229_s_at
-1.0193125	IL27RA	interleukin 27 receptor, alpha (IL27RA), mRNA.	1457055	205926_at
-1.018725	LOC102724614	PREDICTED: uncharacterized LOC102724614 (LOC102724614), mRNA.	1504846	237367_x_at
-1.0186875	GPX1	glutathione peroxidase 1 (GPX1), transcript variant 1, mRNA.	1491588	200736_s_at
-1.014225	GM2A	GM2 ganglioside activator (GM2A), transcript variant 1, mRNA.	1458937	209727_at
-1.0105875	SRGN	serglycin (SRGN), transcript variant 1, mRNA.	1492283	201858_s_at
-1.0101	BZRAP1-AS1	BZRAP1 antisense RNA 1 (BZRAP1-AS1), transcript variant 1, long non-coding RNA.	1470484	228828_at
-1.007575	RHOF	ras homolog family member F (in filopodia) (RHOF), mRNA.	1502060	222812_s_at
-1.0067125	SNHG20	small nucleolar RNA host gene 20 (non-protein coding) (SNHG20), long non-coding RNA.	1465391	221621_at
-1.006625	NCR3	natural cytotoxicity triggering receptor 3 (NCR3), transcript variant 1, mRNA.	1496887	211010_s_at
-1.0060625	GUCY2C	guanylate cyclase 2C (heat stable enterotoxin receptor) (GUCY2C), mRNA.	1457306	206312_at
-1.0057375	SLC25A19	solute carrier family 25 (mitochondrial thiamine pyrophosphate carrier), member 19 (SLC25A19), transcript variant 2, mRNA.	1466171	223222_at
-1.0022625	ATP6V1D	ATPase, H+ transporting, lysosomal 34kDa, V1 subunit D (ATP6V1D), mRNA.	1458581	208898_at
-1.0021375	TOP2A	topoisomerase (DNA) II alpha 170kDa (TOP2A), mRNA.	1454746	201292_at
-1.0018375	LINC00152	long intergenic non-protein coding RNA 152 (LINC00152), transcript variant 1, long non-coding RNA.	1467888	225799_at
-1.0015125	IL13RA1	interleukin 13 receptor, alpha 1 (IL13RA1), mRNA.	1454986	201887_at

Tables S5: Most down-regulated genes after 28 days of treatment with ibrutinib plus rituximab.

log2 fold GE change	Gene	Description	Well ID	Feature ID
1.2921125	TCAP	titin-cap (TCAP), mRNA.	1456952	205766_at
1.2387375		Transcribed locus	1483125	243489_at
1.1882375	IDH3G	isocitrate dehydrogenase 3 (NAD+) gamma (IDH3G), transcript variant 2, mRNA.	1498469	214333_x_at
1.181425		Transcribed locus	1503977	231597_x_at
1.12865	TLN1	Talin 1	1473792	232763_at
1.0952	SLC16A6	solute carrier family 16, member 6 (SLC16A6), transcript variant 2, mRNA.	1457761	207038_at
1.09375	TCL1B	T-cell leukemia/lymphoma 1B (TCL1B), mRNA.	1494440	206413_s_at

1.06955	DOCK9-AS2	DOCK9 antisense RNA 2 (head to head) (DOCK9-AS2), long non-coding RNA.	147235 8	231062_at
1.06605		CDNA FLJ36012 fis, clone TESTI2015987	148989 4	1565909_at
1.06185	AVIL	Advillin	150838 9	1568706_s_ at
1.0504875		CDNA FLJ13776 fis, clone PLACE4000387	146163 8	215197_at
1.04545	BRWD1	bromodomain and WD repeat domain containing 1 (BRWD1), transcript variant 2, mRNA.	147302 4	231860_at
1.0314625		Transcribed locus	148318 2	243554_at
1.01985		Transcribed locus	147775 3	237400_at
1.0167875	MTURN	maturin, neural progenitor differentiation regulator homolog (Xenopus) (MTURN), mRNA.	146807 7	226018_at
1.0123	ENDOU	endonuclease, polyU-specific (ENDOU), transcript variant 2, mRNA.	145748 1	206605_at
1.0086125	POU6F1	POU class 6 homeobox 1 (POU6F1), transcript variant 1, mRNA.	147129 4	229809_at
1.0034		Transcribed locus	148375 9	244202_at
1.0013625		Transcribed locus	148178 7	241928_at
1.0000875			150289 8	224549_x_ at

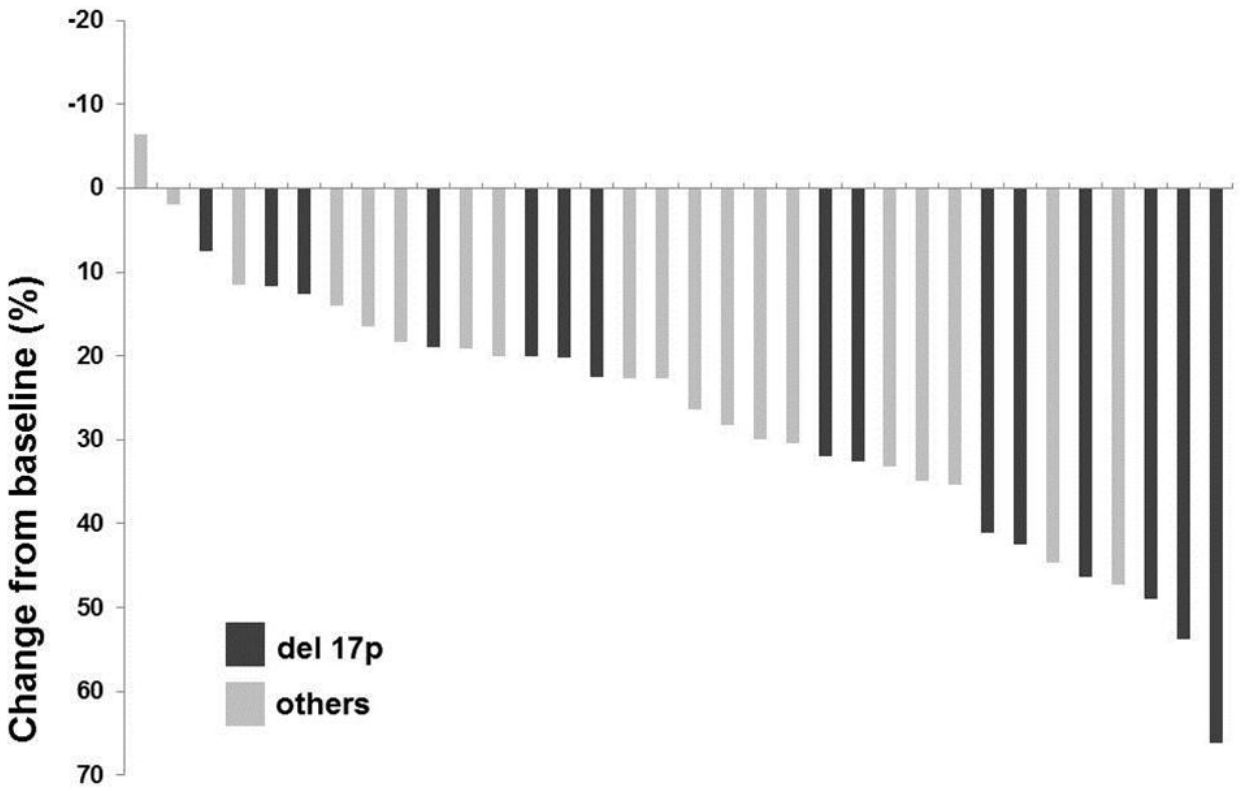
Tables S6: Most up-regulated genes after 7 days of treatment with ibrutinib plus rituximab.

log2 fold GE change	Gene	Description	Well ID	Feature ID
2.3756625	C10orf10	chromosome 10 open reading frame 10 (C10orf10), mRNA.	14958 68	209183_s_at
1.4567125	SNX2	sorting nexin 2 (SNX2), transcript variant 1, mRNA.	14731 89	232049_at
1.4441625	NPTX1	neuronal pentraxin I (NPTX1), mRNA.	14563 34	204684_at
1.4032375		Transcribed locus	14817 87	241928_at
1.37395	LOC100128751	INM04	14736 75	232623_at
1.3727625	SGSM1	small G protein signaling modulator 1 (SGSM1), transcript variant 2, mRNA.	14717 00	230287_at
1.33075	LOC100287598	Uncharacterized LOC100287598	14767 01	236260_at
1.3270875	ZC3H12B	zinc finger CCCH-type containing 12B (ZC3H12B), mRNA.	14708 19	229234_at
1.31485	LOC550643	Uncharacterized LOC550643	14672 32	225028_at
1.310775		CDNA: FLJ22606 fis, clone HSI04766	14752 97	234649_at
1.2982875	FAM111B	family with sequence similarity 111, member B (FAM111B), transcript variant 1, mRNA.	15072 19	1557129_a_at
1.2931125	TLN1	Talin 1	14737 92	232763_at
1.24635		Transcribed locus	14777 53	237400_at
1.2388875	ZNF324	zinc finger protein 324 (ZNF324), mRNA.	14939 87	205182_s_at
1.228925	DOCK9-AS2	DOCK9 antisense RNA 2 (head to head) (DOCK9-AS2), long non-coding RNA.	14723 58	231062_at
1.2167875	LOC101928403	PREDICTED: uncharacterized LOC101928403 (LOC101928403), ncRNA.	14773 76	236990_at
1.2131		Transcribed locus	15054 86	242818_x_at
1.2003375	TAPT1	transmembrane anterior posterior transformation 1 (TAPT1), mRNA.	14789 84	238798_at
1.1887125		MRNA; cDNA DKFZp434C1427 (from clone DKFZp434C1427)	14895 01	1564334_at
1.1755375	TAPT1	transmembrane anterior posterior transformation 1 (TAPT1), mRNA.	14692 85	227407_at
1.174125	SMEK2	SMEK homolog 2, suppressor of mek1 (Dictyostelium)	14657 11	222270_at
1.16555		Transcribed locus	14761 52	235662_at
1.15615		Transcribed locus	14839 13	244373_at
1.155325	SPRY2	sprouty homolog 2 (Drosophila) (SPRY2), mRNA.	14559 66	204011_at
1.1422875		CDNA FLJ12367 fis, clone MAMMA1002413	14743 54	233440_at
1.1418875	MATN1-AS1	MATN1 antisense RNA 1 (MATN1-AS1), long non-coding RNA.	14864 95	1557557_at
1.1404	RIMKLB	PREDICTED: ribosomal modification protein rimK-like family member B (RIMKLB), transcript variant X1, mRNA.	15031 71	226164_x_at
1.1357375	ID3	inhibitor of DNA binding 3, dominant negative helix-loop-helix protein (ID3), mRNA.	14950 31	207826_s_at
1.1319375		Transcribed locus	14799 17	239809_at
1.117475	AVIL	Advillin	15083 89	1568706_s_at
1.1163125	DERL3	derlin 3 (DERL3), transcript variant 1, mRNA.	14705 43	228897_at
1.1163125		CDNA clone IMAGE:5267748	14885 66	1562280_at

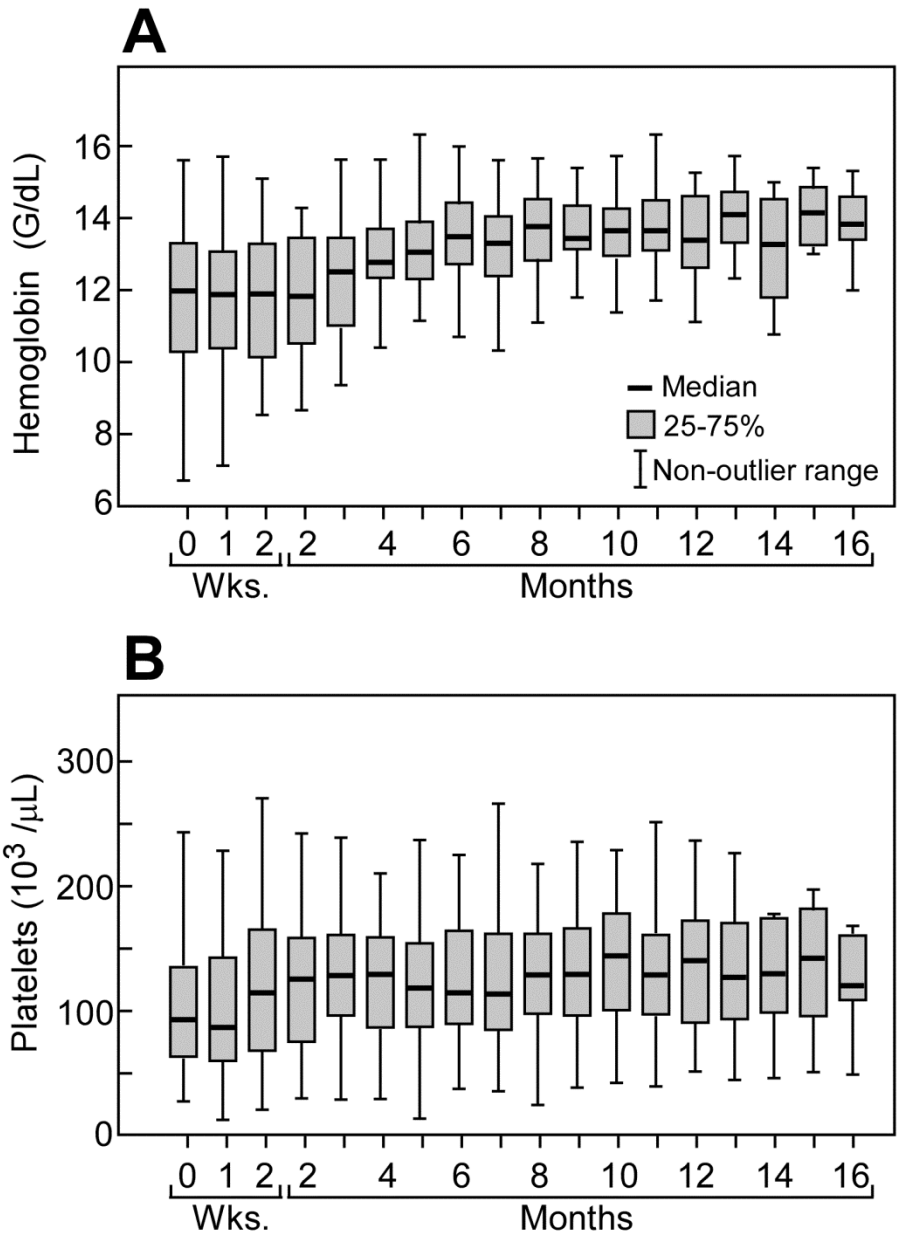
1.1045375	ZBTB42	zinc finger and BTB domain containing 42 (ZBTB42), mRNA.	14711 98	229691_at
1.0928		Transcribed locus	14831 82	243554_at
1.0869125	CSNK1E	casein kinase 1, epsilon (CSNK1E), transcript variant 2, mRNA.	14551 79	202332_at
1.0816375		Transcribed locus	14787 29	238512_at
1.0715625	PRCD	Progressive rod-cone degeneration	14714 64	230015_at
1.0621625	FAM111B	family with sequence similarity 111, member B (FAM111B), transcript variant 1, mRNA.	14863 13	1557128_at
1.05755	DERL3	derlin 3 (DERL3), transcript variant 2, mRNA.	15037 01	229721_x_at
1.0534375	KLF7	Kruppel-like factor 7 (ubiquitous) (KLF7), transcript variant 1, mRNA.	15051 49	240432_x_at
1.0529125	SLC27A2	solute carrier family 27 (fatty acid transporter), member 2 (SLC27A2), transcript variant 1, mRNA.	14569 54	205769_at
1.049325	ZNF629	zinc finger protein 629 (ZNF629), mRNA.	14604 77	213196_at
1.0418	ZNF37BP	zinc finger protein 37B, pseudogene (ZNF37BP), non-coding RNA.	14988 49	215358_x_at
1.040075	MATN1-AS1	MATN1 antisense RNA 1 (MATN1-AS1), long non-coding RNA.	15073 07	1557558_s_at
1.040025	KLF3	Kruppel-like factor 3 (basic) (KLF3), mRNA.	14673 26	225133_at
1.03835	MAFF	v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog F (MAFF), transcript variant 1, mRNA.	14541 33	36711_at
1.0326625	FLJ38717	PREDICTED: FLJ38717 protein (FLJ38717), misc_RNA.	14874 21	1559964_at
1.03055	SMAD4	SMAD family member 4	14897 81	1565703_at
1.0278625	ZNF441	zinc finger protein 441 (ZNF441), mRNA.	14847 49	1553192_at
1.024475		Transcribed locus	14713 77	229914_at
1.0244625	CSNK1E	Casein kinase 1, epsilon	14688 08	226858_at
1.023175	CD24	CD24 molecule (CD24), transcript variant 1, mRNA.	14955 23	208651_x_at
1.0224875		Transcribed locus	14768 56	236428_at
1.020775	GABRB2	gamma-aminobutyric acid (GABA) A receptor, beta 2 (GABRB2), transcript variant 2, mRNA.	15072 16	1557122_s_at
1.0192625	RNF38	Ring finger protein 38	14862 00	1556849_at
1.017975	MLXIP	MLX interacting protein (MLXIP), mRNA.	14673 49	225157_at
1.0150625	DCAF8	DDB1 and CUL4 associated factor 8	14745 06	233637_at
1.011325	THAP7-AS1	THAP7 antisense RNA 1 (THAP7-AS1), transcript variant 2, long non-coding RNA.	14791 85	239015_at
1.0076125	TMED4	Transmembrane emp24 protein transport domain containing 4	15074 07	1558053_s_at
1.0072125		CDNA clone IMAGE:6342029	14787 45	238529_at
1.002825		Transcribed locus	14784 69	238192_at
1.0004125		CDNA clone IMAGE:3639730	14864 84	1557539_at
1.000025	KANK2	KN motif and ankyrin repeat domains 2 (KANK2), transcript variant 1, mRNA.	15001 68	218418_s_at

Tables S7: Most up-regulated genes after 28 days of treatment with ibrutinib plus rituximab.

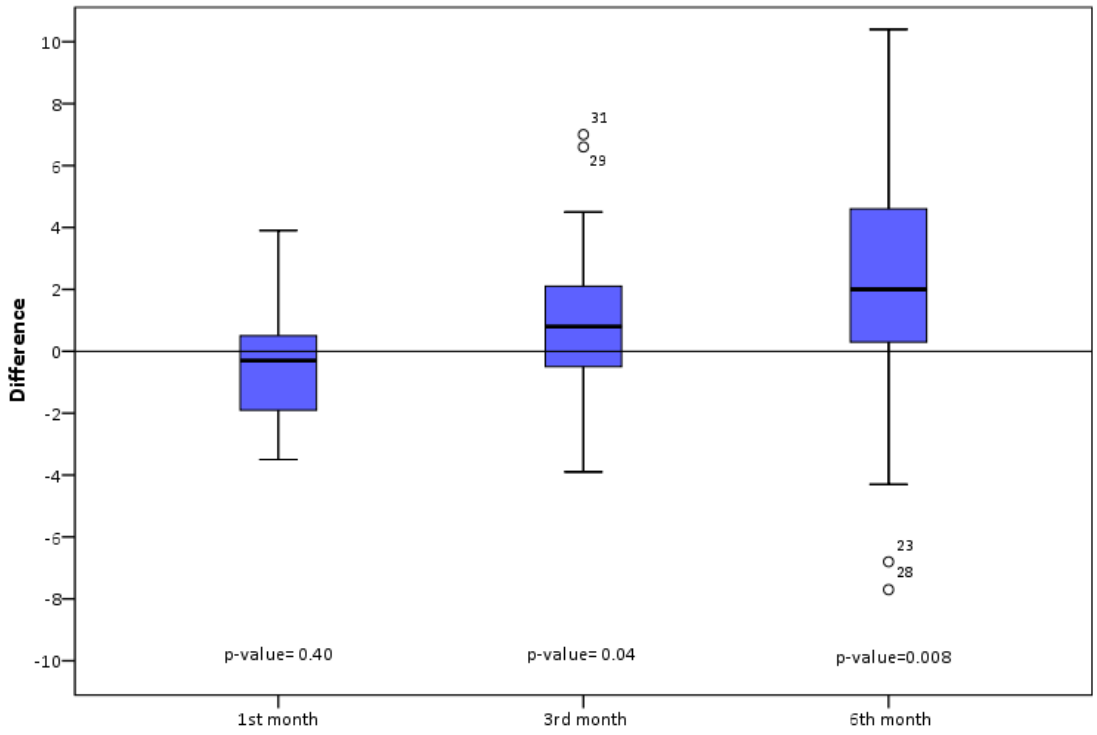
D. Supplemental Figures



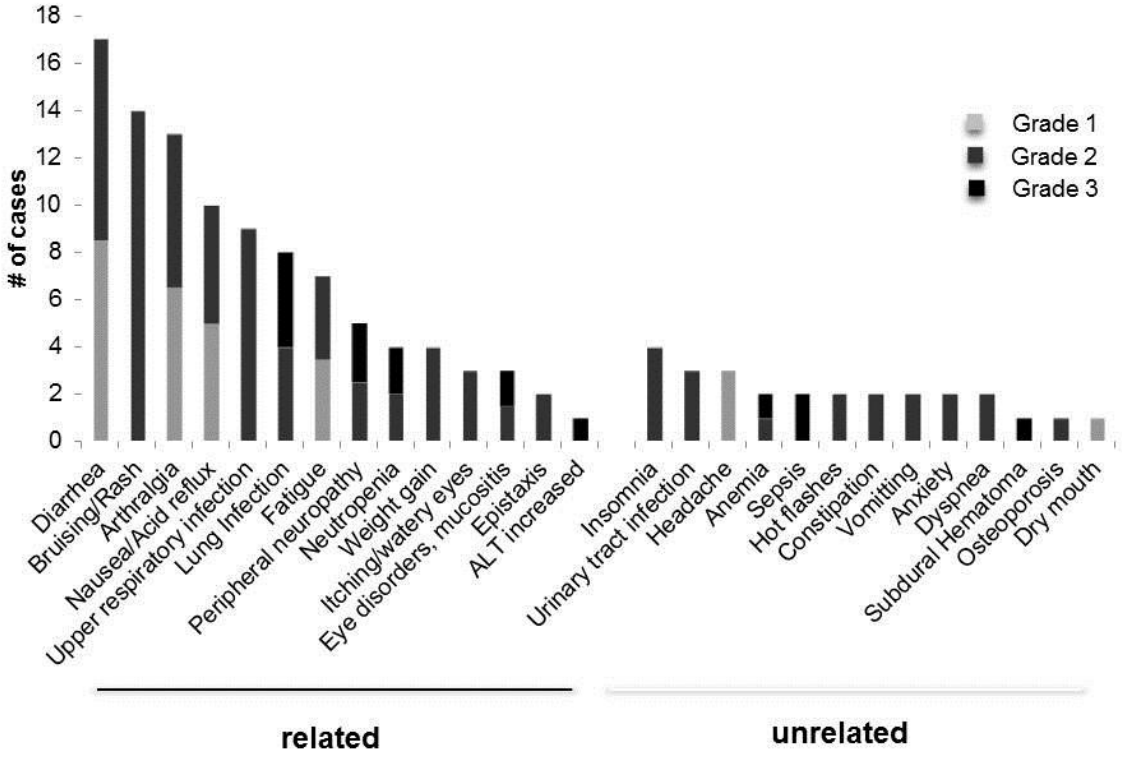
Suppl. Figure S1 ***Changes in spleen sizes during iR treatment.*** CT scan assessment of spleen size at 12 months in 34 evaluable patients on iR therapy.



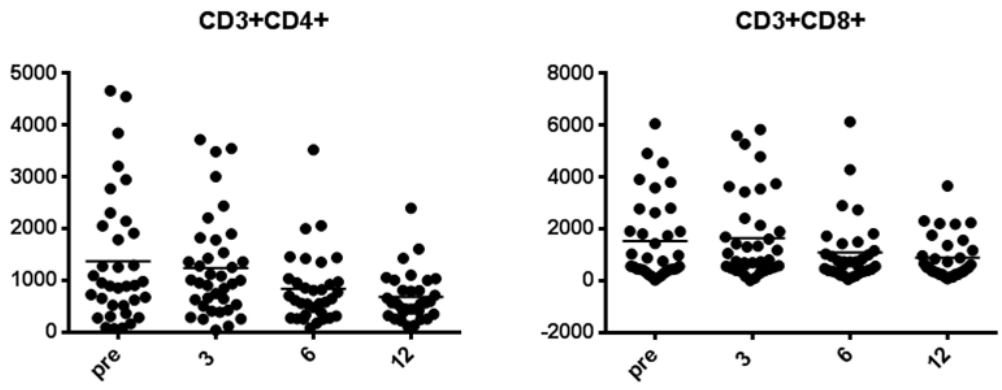
Suppl. Figure S2 ***Changes in haemoglobin levels and platelet counts during iR treatment.*** Trended haemoglobin levels (A) and platelet counts (B) in CLL patients during therapy with ibrutinib and rituximab. The horizontal axis shows the time of treatment. The boxes in each of the graphs depict the range (25% to 75%) and the black lines indicate the median at each of the timepoints.



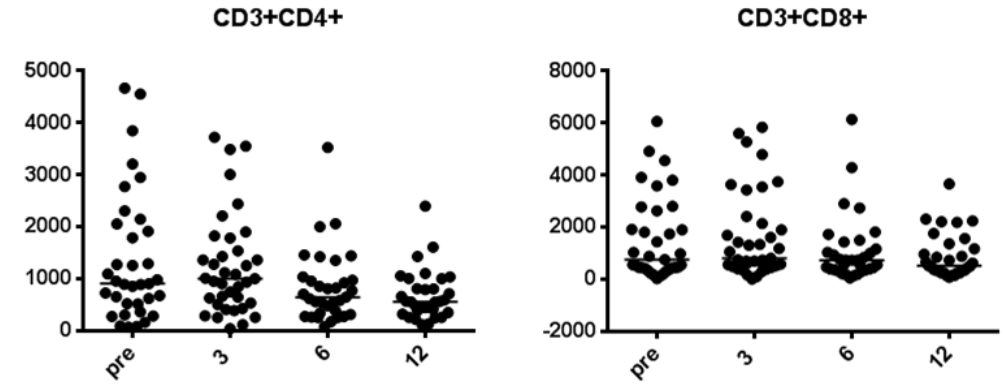
Suppl. Figure S3: Changes in weight during iR therapy.



Suppl. Figure S4 ***Related and unrelated toxicities during iR therapy.*** The different grades of related (left hand side) and unrelated (right hand side) toxicities are indicated in different shades of grey, as indicated.



Suppl. Figure S5 ***CD4 and CD8 T cell counts in individual patients before and during iR therapy.*** The dots represent individual absolute T cell numbers, and the bar represents the mean at each time point displayed on the horizontal axis (in months).



Suppl. Figure S6 ***CD4 and CD8 T cell counts in individual patients before and during iR therapy.*** The dots represent individual absolute T cell numbers, and the bar represents the median at each time point displayed on the horizontal axis (in months).

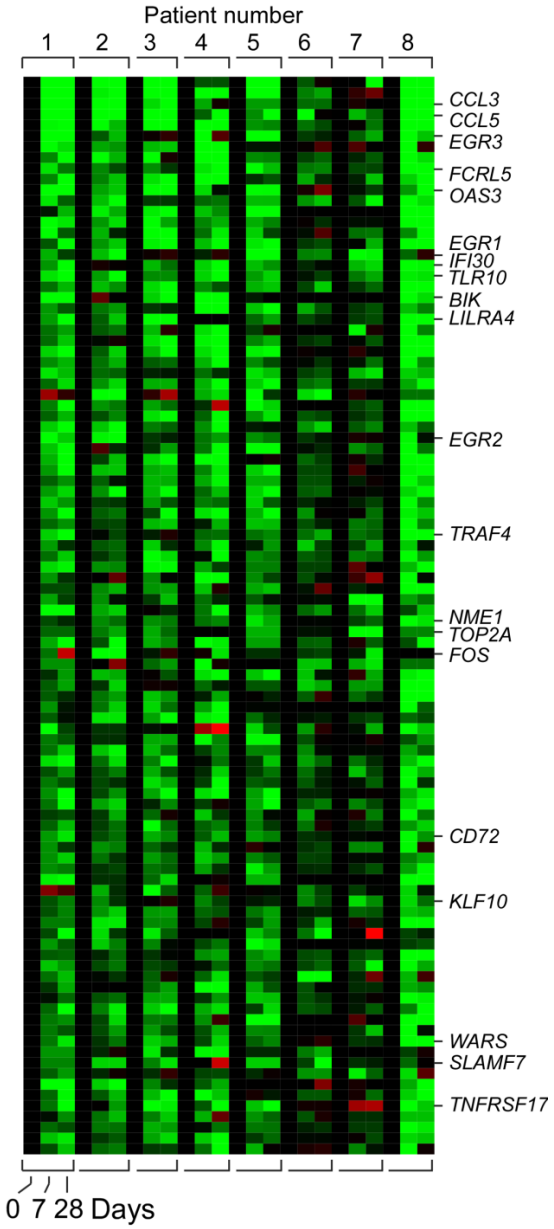


Figure S7 ***DNA microarray analysis identifies homogenous gene expression changes in CLL cells during iR therapy.*** These heatmaps depict genes that are down regulated in eight different CLL cell samples after 7 and 28 days of iR therapy. The changes in gene expression are depicted for each gene relative to its expression level at baseline before iR therapy ("Day 0"). Shades of green indicate down-regulation of a given gene.

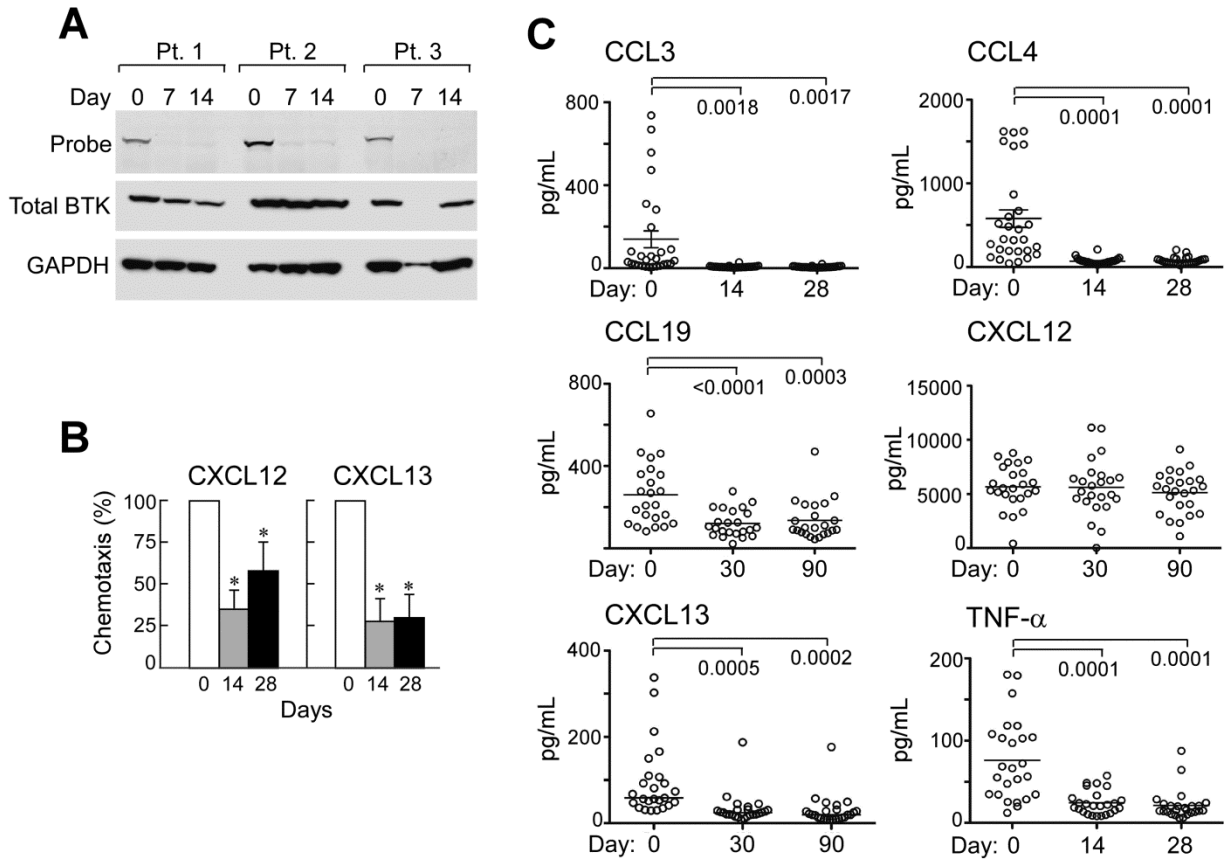


Figure S8 ***Correlative studies*** (A) CLL cells before and during treatment with ibrutinib that were incubated with a BTK affinity probe PCI-33380. Full occupancy of BTK is shown after 7 days of treatment for 3 independent high-risk CLL patients. (B) Migration of CLL cells before and during treatment with ibrutinib towards 200 ng/mL CXCL12 or 1 μg/mL CXCL13. The bar diagram represents the mean chemotaxis (±SEM) of CLL cells from 6 different patients before and after 14 and 28 days of treatment. Chemotaxis toward both chemokines was significantly inhibited. (C) Alters cytokine and chemokine secretion of CLL patients after ibrutinib treatment. The bar diagrams represent the mean CLL patient plasma concentrations for various cytokines and chemokines. Displayed are the means (± SEM) from 28 different patient samples. The secretion of some chemokines was significantly inhibited by ibrutinib treatment, with $P \leq .0005$, as indicated by the asterisks describing the comparison of results from each patient during treatment to the results from the relevant sample before treatment.

E. References

1. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993; 85(5): 365-76.
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3. Burger JA, Burger M, Kipps TJ. Chronic Lymphocytic Leukemia B Cells Express Functional CXCR4 Chemokine Receptors That Mediate Spontaneous Migration Beneath Bone Marrow Stromal Cells. Blood. 1999; 94(11): 3658-67.