doi:10.1038/nature14231

Supplementary Table 1: *Characteristics of ALL patient samples studied*

Case	Cytogenetics	Oncogene		Clinical course	Gender/Age
LAX2	t(9;22)(q34;q11)	*BCR-ABL1;* p210,	T315I	Relapse (Imatinib)	m/38
LAX9	t(9;22)(q34;q11) del(12)(p12;p13)	*BCR-ABL1;* p190,	unmutated	at diagnosis	m/n.k.
SFO2	t(9;22)(q34;q11)	*BCR-ABL1;* p210,	unmutated	at diagnosis	m/7
BLQ1	FISH der(9), der(22)	*BCR-ABL1;* p210,	T315I	Relapse (Imatinib)	m/n.k.
BLQ5	FISH der(9), der(22)	*BCR-ABL1;* p190,	T315I	Relapse (Imatinib)	f/n.k.
BLQ11	FISH der(9), der(22)	*BCR-ABL1;* p210,	T315I	Relapse (Imatinib)	m/n.k.
TXL2	t(9;22)(q34;q11)	*BCR-ABL1;* p210,	unmutated	at diagnosis	m/n.k.
TXL3	t(9;22)(q34;q11)	*BCR-ABL1;* p210,	unmutated	at diagnosis	m/n.k.
ICN1	t(9;22)(q34;q11)	*BCR-ABL1;* p210,	unmutated	at diagnosis	m/n.k.
PDX2	der(9)(q10)t(9;22)(q34;q11)	*BCR-ABL1;* p190,	unmutated	at diagnosis	f/52
PDX14	45~46,XY,del(9)(p21) t(9;22)(q34;q11.2)[cp2]/ 45~46,sl,add(11)(q23), -19, +mar[cp14]/45~46, 46,XY[2]	*BCR-ABL1;* n.d.	unmutated	at diagnosis	m/36
PDX59	46,XY,del(9)(p13),t(9;22) (q34;q11.2)[12]/46,XY, del(9)(p13),der(9)t(9;22) (q34;q11.2),ider(22)(q10) t(9;22)(q34;q11.2) [4]/46,XY[7]	*BCR-ABL1;* p190,	unmutated	at diagnosis	m/6
MXP4	t(9;22)(q34;q11)	*BCR-ABL1;* p210,	unmutated	at diagnosis	f/14
MXP5	t(9;22)(q34;q11)	*BCR-ABL1;* p190,	unmutated	at diagnosis	m/5
ICN3		*MLL-AF4*		Relapse	m/5
ICN12	t(1;19)(q23;p13)	*TCF3-PBX1*		at diagnosis	f/8
ICN13	t(4;11)(q21;q23)	*MLL-AF4*		at diagnosis	f/15
LAX6	t(7;14)(q34;q32)	*IGH-TCRB*		at diagnosis	m/n.k.
LAX7		n.d.		at diagnosis	m/n.k.
LAX7R		*KRAS*^{G12V}		Relapse	m/n.k.
PDX12		n.d.		at diagnosis	n.k.
SFO1		n.d.		Relapse	n.k.
SFO3		n.d.		Relapse	m/n.k.

Notes: All primary samples are bone marrow biopsies, blast content >80%; LAX, Los Angeles; SFO, San Francisco; BLQ, Bologna; TXL, Berlin; ICN, Seoul; PDX, Portland; MXP, Milan; n.d., not determined; n.k., not known; f, female; m, male

Supplementary Table 2: *Characteristics of CML patient samples studied*

Patient	Age at Dx	Age at last F/U	Duration F/U (year)	Therapy	BCR-ABL1 % (IS)[a] at latest evaluation
CP1	73	75	2	Imatinib	<0.0024
CP2	29	29	0.5	Imatinib	<0.0149
CP3	66	67	1	Imatinib	<0.0024
CP4	59	61	2	Imatinib+IFN	<0.22
CP5	18	18	0	Imatinib	<0.11

Notes: CP, chronic phase; Dx, diagnosis; F/U, follow-up. [a]Minimal residual disease quantitative PCR results

Supplementary Table 3: *Cell lines used in the study*

Cell line	Disease	Genetic alteration/Oncogenic lesion	Source
BEL-1	ALL	*MLL-AF4*	Dr. R. Tang, Paris
Toledo	B-NHL, Diffuse large B cell lymphoma	Complex karyotype	ATCC
JSC-1	B-NHL, Primary effusion lymphoma	$KSHV^+$ EBV^+, HIV associated	Dr. J. Jung, USC
BCP-1	B-NHL, Primary effusion lymphoma	$KSHV^+$, HIV negative	Dr. J. Jung, USC
BCBL-1	B-NHL, Primary effusion lymphoma	$KSHV^+$, HIV associated, *BCL6* mutation	Dr. J. Jung, USC
APK-1	B-NHL, Primary effusion lymphoma	$KSHV^+$ EBV^+	Dr. J. Jung, USC
KARPAS-422	B-NHL, Diffuse large B cell lymphoma	t(14;18)(q32;q21); *IGH-BCL2* genes altered	DSMZ
JEKO-1	B-NHL, Mantel cell lymphoma	t(11;14)(q13;q32) *IGH-CCND1* *MYC* amplification, *CDKN2A*, *TP53* deletion	DSMZ
U-266	Multiple Myeloma	*CDKN2A*, *TP53* mutation, *PTEN* deletion	DSMZ
JJN-3	Multiple Myeloma	Complex karyotype	DSMZ
MHH-PREB-1	B-NHL, Burkitt's lymphoma	t(8;14)(q24;q32) → *MYC-IGH*	DSMZ
MN-60	B-NHL, Burkitt's lymphoma	t(8;14)(q24;q32) → *MYC-IGH*	DSMZ
MC-116	B-NHL, Burkitt's lymphoma	t(8;14)(q24;q32) → *MYC-IGH*	DSMZ

Supplementary Table 4: *Mouse strains studied*

Mouse strain	Source	Purpose
[a]*Pecam1*$^{-/-}$	Dr. Tak W. Mak	Genetic loss-of-function experiments
Cd300a$^{-/-}$	UCD, MMRRC	Genetic loss-of-function experiments
[b]*Lair1*$^{fl/fl}$	Dr. John E. Coligan	Inducible deletion of Lair1
[c]*Ptpn6*$^{fl/fl}$	Dr. Klaus Rajewsky	Inducible deletion of Ptpn6
[d]*Inpp5d*$^{fl/fl}$	Dr. Silvia Bolland	Inducible deletion of Inpp5d
[e]*Btk*$^{-/-}$	Dr. Anne Satterthwaite	Genetic loss-of-function experiments
[f]*Csk*^{AS}	Dr. Arthur Weiss	Inducible inhibition of Csk
[g]*Rag1*$^{-/-}$	Jackson Laboratories	Genetic loss-of-function experiments
NOD/SCID	Jackson Laboratories	Transplant recipient mice

Notes:

a Duncan GS, Andrew DP, Kaufman SA, Yoshida H, Spellberg J, Pompa JL, Elia A, Wakeham A, Karan-Tamir B, Muller W, Senaldi G, Zukowski M, Mak TW. 1999. Genetic evidence for functional redundancy of Platelet/Endothelial cell adhesion molecule-1 (PECAM-1): CD31-deficient mice reveal PECAM-1-dependent and PECAM-1-independent functions. *J Immunol*. 162: 3022-30.

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c Pao LI, Lam KP, Henderson JM, Kutok JL, Alimzhanov M, Nitschke L, Thomas ML, Neel BG, Rajewsky K. 2007. B cell-specific deletion of protein-tyrosine phosphatase Shp1 promotes B-1a cell development and causes systemic autoimmunity. *Immunity*. 27: 35-48.

d Karlsson MC, Guinamard R, Bolland S, Sankala M, Steinman RM, Ravetch JV. 2003. Macrophages control the retention and trafficking of B lymphocytes in the splenic marginal zone. *J Exp Med*. 198: 333-40.

e Khan WN, Alt FW, Gerstein RM, Malynn BA, Larsson I, Rathbun G, Davidson L, Müller S, Kantor AB, Herzenberg LA, et al. 1995. Defective B cell development and function in Btk-deficient mice. *Immunity*. 3: 283-99.

f Tan YX, Manz BN, Freedman TS, Zhang C, Shokat KM, Weiss A. 2014. Inhibition of the kinase Csk in thymocytes reveals a requirement for actin remodeling in the initiation of full TCR signaling. *Nat Immunol*. 15:186-94.

g Mombaerts P, Iacomini J, Johnson RS, Herrup K, Tonegawa S, Papaioannou VE. 1992. RAG-1-deficient mice have no mature B and T lymphocytes. *Cell*. 68: 869-77.

Supplementary Table 5: *Retroviral and lentiviral vectors*

Constitutive expression

Construct	Overexpression of	Purpose
Retroviral vector		
MSCV IRES-GFP	GFP	Empty vector control
MSCV IRES-Neo	Neomycin resistance	Empty vector control
MSCV CD8-CD79A IRES-GFP	CD8-CD79A(Igα)	Reconstitution of ITAM signalling
MSCV LMP2A IRES-GFP	LMP2A	Reconstitution of ITAM signalling
MSCV BCR-ABL1 IRES-Neo	BCR-ABL1	Leukemic transformation (*Ph*$^+$ ALL, CML)
MSCV Myr-Syk IRES-GFP	Myr-Syk	Reconstitution of Syk signalling
MSCV Myr-Btk IRES-GFP	Myr-Btk	Reconstitution of Btk signalling
MSCV Syk IRES-GFP	Syk	Reconstitution of Syk, wildtype
MSCV Syk(Y348E/Y352E) IRES-GFP	Syk(Y348E/Y352E)	Reconstitution of Syk, mutant
MSCV Syk(Y348F/Y352F) IRES-GFP	Syk(Y348F/Y352F)	Reconstitution of Syk, mutant
MSCV Syk(K402A) IRES-GFP	Syk(K402A)	Reconstitution of Syk, kinase-dead
MSCV TEL-SYK IRES-GFP	TEL-SYK	Reconstitution of TEL-SYK
MSCV TEL-SYK(K402A) IRES-GFP	TEL-SYK(K402A)	Reconstitution of TEL-SYK, kinase-dead
pQCXI LUC-BLAST	Firefly-Luciferase	Luciferase bioimaging
MSCV Ptpn11(D61A) IRES-GFP	Ptpn11(D61A)	Reconstitution of Ptpn11
MSCV delta SH2 Ptpn6 IRES-GFP	SH2 deleted Ptpn6	Reconstitution of Ptpn6
MSCV Ptpn6(D419A) IRES-GFP	Ptpn6(D419A)	Ptpn6 vector control
MSCV CD8-Inpp5d IRES-GFP	CD8-Inpp5d	Reconstitution of Inpp5d
MSCV Inpp5d(D675A) IRES-GFP	Inpp5d(D675A)	Inpp5d vector control
MSCV Pecam1 IRES-GFP	Pecam1	Reconstitution of Pecam1, wildtype
MSCV Pecam1(Y679/702F) IRES-GFP	Pecam1(Y679/702F)	Reconstitution of Pecam1, mutant
MSCV Cd300a IRES-GFP	Cd300a	Reconstitution of CD300a, wildtype
MSCV Cd300a mutant (Y-A) IRES-GFP	Cd300a(Y231/255/267/293A)	Reconstitution of CD300a, mutant
MSCV Lair1 IRES-GFP	Lair1	Reconstitution of Lair1, wildtype
MSCV Lair1(Y228/257F) IRES-GFP	Lair1(Y228/257F)	Reconstitution of Lair1, mutant
Lentiviral vectors		
pcl6 LUC-BLAST	Firefly-Luciferase	Luciferase bioimaging
pcl6 LMP2A IRES-Puro	LMP2A	Reconstitution of ITAM signaling

Inducible expression

Construct	Overexpression of	Purpose
Retroviral vector		
MSCV ERT2 IRES-Puro	Puromycin resistance	Empty vector control
MSCV ERT2 IRES-GFP	GFP	Empty vector control
pRetroX-Tet3G	Tet-On	Empty vector control
MSCV Cre ERT2 IRES-Puro	Cre; Puromycin resistance	Inducible activation of Cre
MSCV Cre ERT2 IRES-GFP	Cre; GFP	Inducible activation of Cre
pRetroX-TRE3G-Cebpa	Tet-On; Cebpa	Inducible expression of Cebpa

Supplementary Table 6: *Flow cytometry antibodies*

Flow cytometry antibodies for human cells

Surface antigen	Clone ID	Company
CD19	HIB19	BD Biosciences
CD79A	ZL74	AbD serotec
CD79B	CB3-1	BD Biosciences
PECAM1	WM59	BD Biosciences
CD300A	MEM-260	ABCAM
LAIR1	DX26	BD Biosciences
BTLA	J168-540	BD Biosciences
CD22	HIB22	BD Biosciences
FCRL2	Polyclonal (AF2048)	R & D systems
CEACAM1	283340	R & D systems

Flow cytometry antibodies for mouse cells

Surface antigen	Clone ID	Company
Cd19	1D3	BD Biosciences
B220	RA3-6B2	BD Biosciences
Cd13	R3-242	BD Biosciences
c-kit	2B8	BD Biosciences
Sca-1	D7	BD Biosciences
Pecam1	MEC 13.3	BD Biosciences
Lair1	113	eBioscience
Mac1	M1/70	BD Biosciences

Supplementary Table 7: *Western blot antibodies*

Antigen	Clone ID	Company
ACTB	Polyclonal (ab8227)	ABCAM
ARF-Mo	Polyclonal (ab80)	ABCAM
P21	C-19	Santa Cruz
P27	F-8	Santa Cruz
P53	1C12	Cell Signaling
p-PTPN6 (Tyr564)	D11G5	Cell Signaling
PTPN6	C14H6	Cell Signaling
p-INPP5D (Tyr1020)	Polyclonal (3941)	Cell Signaling
INPP5D	P1C1	Santa Cruz
p-ERK1/2 (Thr202/Tyr204)	D13.14.4E	Cell Signaling
ERK1/2	Polyclonal (9102)	Cell Signaling
p-PLCγ1 (Tyr783)	Polyclonal (2821)	Cell Signaling
PLCγ1	D9H10	Cell Signaling
p-PLCγ2 (Tyr1217)	Polyclonal (3871)	Cell Signaling
PLCγ2	Polyclonal (3872)	Cell Signaling
p-BTK (Tyr223)	Polyclonal (5082)	Cell Signaling
BTK	Polyclonal (3533)	Cell Signaling
p-SRC (Tyr416)	D49G4	Cell Signaling
LYN	C13F9	Cell Signaling
Oxidized PTP Active Site	335636	R & D systems
p-SYK (Tyr352)	65E4	Cell Signaling
SYK	Polyclonal (2712)	Cell Signaling
p-CD79A (Y182)	Polyclonal (5173)	Cell Signaling
CD79A	HM47/A9	Abcam
p-BLNK (Y96)	Polyclonal (3601)	Cell Signaling
BLNK	Polyclonal (3587)	Cell Signaling
LMP2A	14B7	Abcam
PAX5	D19F8	Cell Signaling
C/EBPα	D56F10	Cell Signaling

Supplementary Table 8: *Sequences of oligonucleotides*

Genotyping PCR primers for mouse cells

Pecam1 wt_F	5'-ATTATCCGCTCTGCACTGGTATTC-3'
Pecam1 wt_R	5'-AGGTAAGGACCTACAGGTGTGTTC-3'
Pecam1 null_F	5'-CCTCGTGCTTTACGGTATCGCCGC-3'
Pecam1 null_R	5'-AGGTAAGGACCTACAGGTGTGTTC-3'
Cd300a wt_F	5'-GAAGGGTGCTGAAGGGTGATTGAC-3'
Cd300a wt_R	5'-CTCATCACACATAATGTACTCCCAG-3'
Cd300a null_F	5'-GCAGCGCATCGCCTTCTATC-3'
Cd300a null_R	5'-GCCAGGTATGACATGAACATGTG-3'
Lair1_A	5'-TCCACTAAGCCTGAGATGACAGC-3'
Lair1_B	5'-GTTTGCTGAGGGAGTCCTGATTC-3'
Lair1_C	5'-TTCAAGTCATCCAGTGGCAGTTG-3'
Inpp5d-58_F	5'- GTGGAGCAAAGCTAACTCTAG-3'
Inpp5d-59_R	5'-GTTTCTTTATCCGCTATGTCC-3'
Inpp5d-78_R	5'-GGTATCGATAAGCTTCGAGGG-3'
Ptpn6_F	5'-ACCCTCCAGCTCCTCTTC-3'
Ptpn6_R	5'-TGAGGTCCCGGTGAAACC-3'

Supplementary Table 9: *GEO accession numbers for gene expression microarray data*

GEO accession	GEO description	Figure
GSE12453	Gene expression in IGH-BCL2, IGH-MYC-rearranged B cell	Extended 3a
GSE16131, GSE4475, GSE36000	Lymphoma and classical Hodgkin's disease	Extended 3a
[a]NA	Gene expression in normal pre-B cells; Data from Van Zelm *et al.*, J Immunol. 2005	Extended 3a
[b]NA	Gene expression in various ALL subtypes including Ph^{+} ALL; Data from Ross *et al.*, Blood. 2003 http://www.stjuderesearch.org/data/ALL3/rawFiles.html	Extended 3a

Notes:

a. van Zelm MC, van der Burg M, de Ridder D, Barendregt BH, de Haas EF, Reinders MJ, Lankester AC, Révész T, Staal FJ, van Dongen JJ. Ig gene rearrangement steps are initiated in early human precursor B cell subsets and correlate with specific transcription factor expression. *J Immunol*. 2005 Nov 1;175(9):5912-22.

b. Ross ME, Zhou X, Song G, Shurtleff SA, Girtman K, Williams WK, Liu HC, Mahfouz R, Raimondi SC, Lenny N, Patel A, Downing JR. Classification of pediatric acute lymphoblastic leukemia by gene expression profiling. *Blood*. 2003 Oct 15;102(8):2951-9.

Supplementary Table 10: *Clinical outcome data in this study*

Clinical trial	Malignancy	Patients NO.	GEO ID	Reference
COG P9906	ALL	207	GSE11877	Kang *et al.* Blood 2010; Harvey *et al.* Blood 2010
ECOG E2993	ALL	191	GSE34861	Geng *et al.* Cancer Discov 2012
ECOG E2993	ALL	54	GSE5314	Juric *et al.* J Clin Oncol 2007

COG ALL:

Kang H, Chen IM, Wilson CS, Bedrick EJ, Harvey RC, Atlas SR, Devidas M, Mullighan CG, Wang X, Murphy M, Ar K, Wharton W, Borowitz MJ, Bowman WP, Bhojwani D, Carroll WL, Camitta BM, Reaman GH, Smith MA, Downing JR, Hunger SP, Willman CL. Gene expression classifiers for relapse-free survival and minimal residual disease improve risk classification and outcome prediction in pediatric B-precursor acute lymphoblastic leukemia. *Blood*. 2010 Feb 18;115(7):1394-405.

Harvey RC, Mullighan CG, Wang X, Dobbin KK, Davidson GS, Bedrick EJ, Chen IM, Atlas SR, Kang H, Ar K, Wilson CS, Wharton W, Murphy M, Devidas M, Carroll AJ, Borowitz MJ, Bowman WP, Downing JR, Relling M, Yang J, Bhojwani D, Carroll WL, Camitta B, Reaman GH, Smith M, Hunger SP, Willman CL. Identification of novel cluster groups in pediatric high-risk B-precursor acute lymphoblastic leukemia with gene expression profiling: correlation with genome-wide DNA copy number alterations, clinical characteristics, and outcome. *Blood*. 2010 Dec 2;116(23):4874-84.

ECOG ALL:

Geng H, Brennan S, Milne TA, Chen WY, Li Y, Hurtz C, Kweon SM, Zickl L, Shojaee S, Neuberg D, Huang C, Biswas D, Xin Y, Racevskis J, Ketterling RP, Luger SM, Lazarus H, Tallman MS, Rowe JM, Litzow MR, Guzman ML, Allis CD, Roeder RG, Müschen M, Paietta E, Elemento O, Melnick AM. Integrative epigenomic analysis identifies biomarkers and therapeutic targets in adult B-acute lymphoblastic leukemia. *Cancer Discov*. 2012 Nov;2(11):1004-23.

Juric D, Lacayo NJ, Ramsey MC, Racevskis J, Wiernik PH, Rowe JM, Goldstone AH, O'Dwyer PJ, Paietta E, Sikic BI. Differential gene expression patterns and interaction networks in BCR-ABL-positive and -negative adult acute lymphoblastic leukemias. *J Clin Oncol*. 2007 Apr 10;25(11):1341-9.