

SUPPLEMENTARY DATA

Supplementary methods

Patients, samples and outcome data

All patients aged 60 years and over that had been enrolled into 2 large multi-centre clinical trials were first identified. UKALL14 (NCT01085617) was a phase 3 randomised controlled trial that recruited patients aged 25-65 years (or 19-65 years if *BCR-ABL1* positive) with newly diagnosed ALL between 30/12/2010 and 26/07/2018. Patients were treated with intensive multi-agent chemotherapy, followed by allogeneic stem cell transplantation in first remission where indicated according to risk stratification and donor availability. UKALL60+ (NCT01616238) was a phase 2 trial that recruited patients aged ≥ 60 years at diagnosis (or ≥ 55 years if deemed unfit for more intensive treatment) between 29/01/2013 and 26/11/2018. Treatment protocols ranged from intensive multi-agent chemotherapy to low intensity palliative regimens. All patients with *BCR-ABL1* positive disease received imatinib together with either intensive multi-agent (UKALL14) or low intensity (UKALL60+) chemotherapy.

Event-free survival (EFS) was defined as time to relapse, second tumour or death, censoring at date of last contact. Relapse rate (RR) was defined as time to relapse for those achieving a complete remission, censoring at date of death in remission or last contact. Overall survival (OS) was defined as time to death, censoring at date of last contact. All survival rates are quoted at 5 years. Kaplan-Meier methods were used to estimate survival rates and the two-sided log-rank test was employed to evaluate the equality of the survivorship functions in different subgroups.

B-other ALL cases

B-other ALL refers to a heterogenous subgroup of patients who lack a primary chromosomal abnormality by conventional cytogenetic techniques. Specifically, these included cases with normal, failed or complex karyotypes or those without subgroup-

defining chromosomal abnormalities. Failed karyotypes were required to have had *BCR-ABL1* and *KMT2A* fusions excluded by fluorescence in situ hybridisation (FISH). *ABL1* break apart FISH (Cytocell, Cambridge, UK) was also performed in cases where the *BCR-ABL1* dual colour dual fusion pattern had identified in extra *ABL1* signal, potentially suggesting a variant *ABL1* rearrangement. All FISH patterns were interpreted by two independent observers with a minimum of 100 nuclei scored and an abnormal pattern was reported if detected in at least 10% of nuclei by both observers.

Preparation of SNP array data

Copy number segmentation and visualisation were carried out using Nexus Copy Number 10 (Biodiscovery, El Segundo, CA).

Raw array data from Affymetrix (Santa Clara, CA, USA) arrays were loaded directly to Nexus Copy Number 10 (Biodiscovery, El Segundo, CA, USA) in the form of CEL files. Illumina (San Diego, CA, USA)-generated IDAT files first needed to be converted into a text-based format before being loaded to Nexus. To achieve this, the Illumina-specific SNP array software package – GenomeStudio 2.0 – was used, in accordance with the Nexus protocol for the analysis of Illumina arrays. The IDAT files were loaded to GenomeStudio 2.0 and then converted into text-based format by creating a Final_Report file. This was then loaded onto Nexus to visualise the data and perform copy number segmentation.

Systematic correction of the arrays was then performed. This is a recommended step in the analysis of SNP array data due to the waviness in the probe signals that can often be seen across the genome¹. This is partly related to GC content as probes with high GC content will bind better to their target sequence, producing a higher signal intensity. As such, systematic correction was performed in Nexus using the recommended Illumina and Affymetrix correction files.

Nexus employs a hybrid segmentation algorithm termed Fast Adaptive States Segmentation Technique (FASST2). This is based on HMM-segmentation but does not assume fixed integer levels of copy number, and instead accepts a large number of potential copy number states falling between fixed integer levels.

To account for the variation in probe density between the array platforms, a minimum of 10 probes was required for copy number segments with Affymetrix arrays and 6 probes with Illumina arrays. Constitutional copy number variations were excluded by discarding segments with $\geq 50\%$ overlap with regions reported in the Toronto Database of Genomic Variants. CNAs smaller than 10kb and those that did not contain any genes were also excluded.

Next generation sequencing (NGS) analyses

Separately, regions that contained the breakpoints of selected gene deletions identified by SNP array were also included in the capture library to validate novel abnormalities by a second technique.

BAM files were deduplicated and re-aligned to the reference genome (GRCh37/hg19). Variant calling of single nucleotide variants (SNVs) and indels was performed using GATK HaplotypeCaller and Ensembl VEP (supplementary methods). Deletion breakpoints were confirmed by directly examining sequencing reads using the Integrative Genomics Viewer (IGV) (21) and identifying mate pairs that spanned the deletion breakpoint.

A SureSelect XT2 capture library (Agilent, Santa Clara, CA, USA) was designed using the SureDesign web portal (<https://earray.chem.agilent.com/suredesign/>) to capture either exons or the full sequence of genes implicated in leukaemogenesis (supplementary table 1). DNA samples were first amplified using a REPLI-g mini kit (Qiagen, Hilden, Germany) to yield at least 1 ug of whole genome amplified DNA. Following amplification, double stranded DNA concentrations were measured using the Quant-iT PicoGreen broad-range assay (Invitrogen, Carlsbad, CA, USA) and FLUOstar Omega microplate reader (BGM Labtech, Ortenberg, Germany). SureSelect XT2 libraries were then prepared using 1 ug of input DNA. Mechanical DNA shearing was performed on the Bioruptor pico sonication system (Diagenode, Liège, Belgium) inputting shearing settings as follow – time on: 7 seconds; time off: 90 seconds; number of cycles: 4 – to yield 800-1000 bp fragments. Sample quality and fragment size were then assessed on the 2100 Bioanalyzer (Agilent) to ensure that a fragment peak was visible around 800-1000 bp. Library prep was then performed according to the manufacturer's protocol with two exceptions: i) the ratio of AMPure

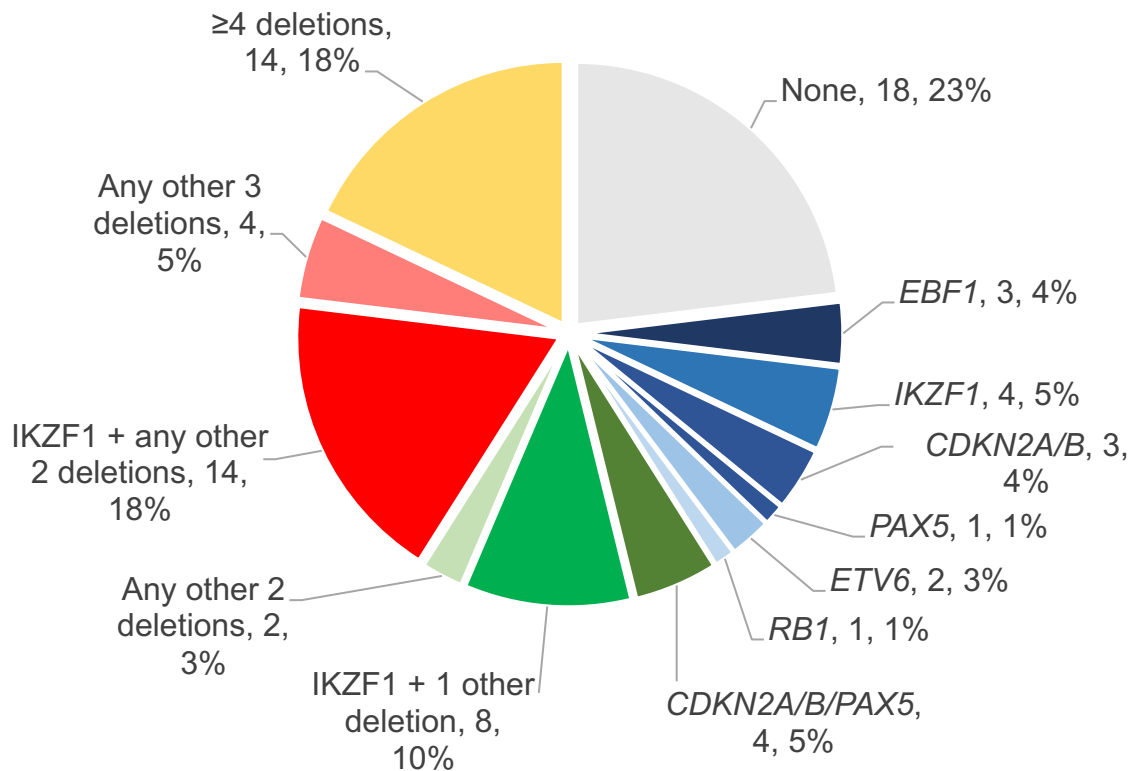
XP beads (Beckman Coulter, Brea, CA, USA): DNA was reduced to 0.7 to optimise bead-binding to the longer DNA fragments in the library and ii) The PCR amplification was performed using the Longamp Taq polymerase enzyme (New England Biolabs, Ipswich MA, USA), which is optimized for amplification of longer DNA fragments.

Each pooled library was sequenced using a mid-output kit on the Illumina NextSeq 550 with 100bp paired end reads. BAM files were generated and then deduplicated and re-aligned to the reference genome (hg19/GRCh37). As no germline DNA was available, variant calling was performed using the GATK HaplotypeCaller³. Ensembl VEP files were produced and calls with a population allele frequency ≥ 0.01 in the Exome Aggregation Consortium (ExAC) database⁴ were excluded as likely germline variants. All non-coding variants, synonymous variants, and those reported as both tolerated and benign in the SIFT⁵ and Polyphen⁶ databases respectively were also excluded. Calls with COSMIC identifiers were examined in the COSMIC database⁷ to identify known somatic mutations in cancer, specifically those in *TP53*.

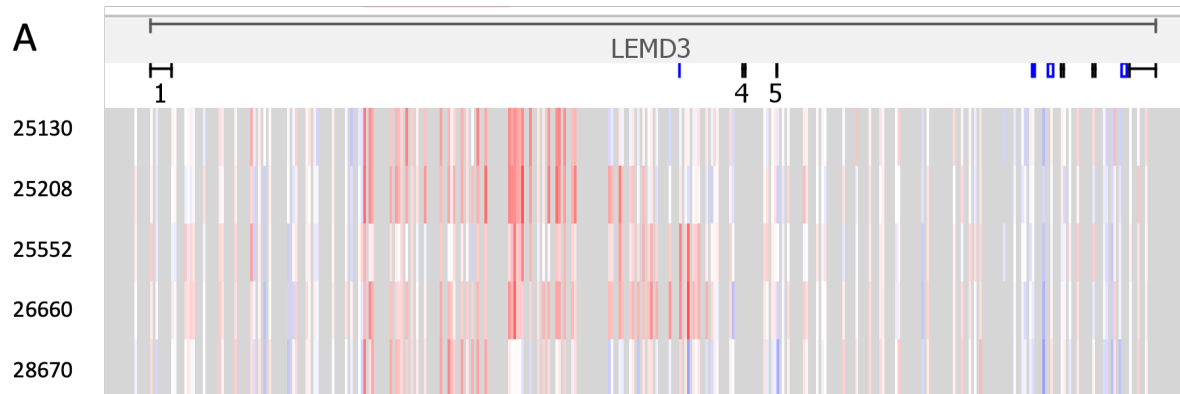
Supplementary references

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Supplementary figures



Supplementary figure S1. Patterns of gene deletions observed across full cohort of 78 SNP arrays. Combinations of deletions grouped by patterns observed. *CDKN2A/B/PAX5* combined deletion commonly represented del(9p).



B

Patient ID	Sex (M/F)	Age (yrs)	Genetic subgroup	WCC (x10 ⁹ /L)	Deleted segment	Size of deletion (bp)	Outcome
25130	F	62	<i>IGH-CRLF2</i>	33.6	chr12:65,579,942-65,597,922	17,980	Died after 1 month
25208	M	62	<i>BCR-ABL1</i>	205.4	chr12:65,579,942-65,602,114	22,172	Alive after 9 years
25552	M	61	<i>P2RY8-CRLF2</i>	2.9	chr12:65,579,801-65,611,980	32,179	Died after 4 months
26660	F	62	<i>BCR-ABL1</i>	18.2	chr12:65,579,942-65,608,678	28,736	Alive after 7 years
28670	F	61	<i>BCR-ABL1</i>	1.6	chr12:65,579,942-65,591,462	11,520	Died after 2 months

Supplementary figure S2. Focal *LEMD3* deletions. SNP array data shown with each bar representing a probe (A). Red colours indicate negative log₂ ratio (copy number loss), blue colours represent positive log₂ ratio (copy number gain), and white represents no copy number change. Demographic, clinical and genetic data (B) indicating that all affected patients had *BCR-ABL1* or *CRLF2* rearrangements.

Supplementary table S1. Targeted gene sequencing panel.

Gene	Region captured
<i>ABL1</i>	whole gene
<i>ABL2</i>	whole gene
<i>ARID2</i>	whole gene
<i>ASXL1</i>	exons
<i>ATM</i>	exons
<i>CREBBP</i>	exons
<i>CSF1R</i>	whole gene
<i>DGKH</i>	whole gene
<i>DNMT3A</i>	exons
<i>ETV6</i>	whole gene
<i>FLT3</i>	whole gene
<i>FOXO1</i>	exons
<i>IKZF1</i>	whole gene
<i>IKZF2</i>	exons
<i>IKZF3</i>	exons
<i>IL7R</i>	exons
<i>JAK1</i>	exons
<i>JAK2</i>	whole gene
<i>JAK3</i>	exons
<i>KDM6A</i>	whole gene
<i>KMT2C</i>	exons
<i>KRAS</i>	exons
<i>MEF2C</i>	whole gene
<i>MEF2D</i>	whole gene
<i>NF1</i>	whole gene
<i>NOTCH1</i>	exons
<i>NR3C1</i>	exons
<i>NRAS</i>	exons
<i>NT5C2</i>	exons
<i>PAX5</i>	whole gene
<i>PDGFRB</i>	whole gene
<i>PTEN</i>	whole gene
<i>PTPN11</i>	exons
<i>RAG1</i>	whole gene
<i>RB1</i>	exons
<i>RUNX1</i>	exons
<i>SH2B3</i>	exons
<i>TCF3</i>	whole gene
<i>TCF4</i>	whole gene
<i>TET2</i>	exons
<i>TFDP3</i>	exons
<i>TOX</i>	exons
<i>TP53</i>	exons
<i>ZFHX3</i>	exons

Supplementary table S2. Primary chromosomal abnormalities in 210 adults aged ≥60 years recruited to UKALL14 or UKALL60+.

Immunophenotype	Cytogenetics	Number of cases (%)	Percentage male	Median age (yrs)
BCP-ALL	<i>BCR-ABL1</i>	55 (26%)	40%	64
	<i>TCF3-PBX1</i>	3 (1%)	33%	64
	<i>KMT2A-v</i>	12 (6%)	33%	64
	HeH	2 (1%)	100%	64.5
	HoTr	29 (14%)	43%	64
	B-other	88 (42%)	60%	65
T-ALL		11 (5%)	64%	64
No data		10 (5%)	40%	63
Total		210 (100%)	50%	64

Supplementary table S3. Complete cohort of 210 adults aged ≥60 years with ALL included in study.

Patient ID	Sex	Age	Trial	% BM Blasts	SNP array	Genetic subgroup	Genetic risk group	Karyotyping +/- routine FISH	B-other FISH screening	SNP arrays	MLPA	Targeted NGS	Karyotype
24309	Male	63	UKALL14	80	Illumina	Complex	Very high risk	✓	✓	✓	✓		45-48,XY,t(2;18)(p11;q21),-4,-5,der(9)t(1;9)(q2;q2),del(13)(q12q14),del(14)(q1q22),add(16)(q1),i(17)(q10),+21,+1-3mar[cp11]
24813	Female	62	UKALL14	50	Illumina	No data	Standard risk			✓	✓	✓	NDS
24890	Male	65	UKALL14	100	Illumina	B-other	Standard risk	✓		✓	✓	✓	46,XY[10]
24919	Female	64	UKALL14	95	Illumina	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓		46,XX,t(9;22)(q34;q11)[8]/46,XX[2]
24983	Female	60	UKALL14	73	NA	BCR-ABL1	Tyrosine kinase activating	✓					52,XX,+2,+5,add(9)(p1),t(9;22)(q34;q11),+16,+21,+der(22)t(9;22),+mar[3]/52,XX,+2,+5,+5,der(9)add(9)(p1)t(9;22),+16,+21,+der(22)t(9;22),der(22)t(9;22)[5]/46,XX[2]
25082	Female	62	UKALL14	95	Illumina	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓	✓	53,XX,+X,+2,+6,t(9;22)(q34;q11.2),+14,+18,+21,+der(22)t(9;22)[7]/54,idem,+der(22)t(9;22)[3]
25100	Female	63	UKALL14	79	Illumina	KMT2A-v	High risk	✓		✓		✓	46,XX,t(1;11)(p32;q23)[11]
25101	Female	63	UKALL14	NA	Complex	Very high risk	✓	✓					45,XX,-9,del(20)(q11.2q13?3),+mar1,+mar2,+mar3[cp3]/46,XX[22]
25102	Female	63	UKALL14	79	NA	HoTr	Very high risk	✓					38,X,-X,add(1)(p3),-3,-4,-5,-7,-9,add(9)(p1),add(10)(q24),-15,-17,-19,-20,-22,+3mar[cp14]/74-75,idemx2,-2,-6,inc[cp11]
25123	Male	60	UKALL14	92	NA	HoTr	Very high risk	✓					63-71<2n>,XY,+X,+X,+Y,+1,+1,+2,+4,+5,+del(5)(q?15q?33),+6,+6,+10,+10,+11,+11,+12,+12,+15,+18,+18,+19,+19,+22,+22[cp5]/46,XY[5]
25130	Female	62	UKALL14	100	Illumina	CRLF2-r	Very high risk	✓	✓	✓	✓	✓	46,XX[20]
25208	Male	62	UKALL14	66	Illumina	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓	✓	46,XY,-9,t(9;22)(q34;q11),add(10)(q2?2),+der(22)t(9;22)(q34;q11)[2]
25235	Male	63	UKALL14	70	NA	ZNF384-r	Standard risk	✓	✓				FAILED
25237	Female	63	UKALL14	60	NA	No data	Standard risk				✓		46,XX[20]
25246	Male	64	UKALL14	42	Illumina	CRLF2-r	Very high risk	✓	✓	✓	✓	✓	46,XY,der(19)t(1;19)(q12;p13.3)[2]/46,idem,t(5;18)(q33;q23)[8]/46,XY[10]
25247	Male	64	UKALL14	95	Illumina	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓	✓	47,XY,t(9;22)(q34;q11),+10[10]
25267	Female	63	UKALL14	1	Illumina	MEF2D-r	Standard risk	✓	✓	✓	✓	✓	45-47,XX,+1,dic(1;17)(p32;q25),inc[cp3]
25293	Male	63	UKALL14	99	NA	B-other	Standard risk	✓					92,inc[2]/46,XY[18]
25344	Female	61	UKALL14	80	Illumina	B-other	Standard risk	✓	✓	✓	✓		FAILED
25346	Male	64	UKALL14	40	Illumina	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓	✓	46,XY,t(9;22)(q34;q11)[9]
25371	Female	60	UKALL14	50	Illumina	CRLF2-r	Very high risk	✓	✓	✓	✓	✓	46,XX[20]
25373	Male	65	UKALL14	32	Illumina	B-other	Standard risk	✓	✓	✓	✓	✓	46,XY,del(9)(q13q22)[4]/46,XY[14]
25415	Female	64	UKALL14	NA	B-other	Standard risk	Standard risk	✓	✓				46,XX[20]
25426	Female	64	UKALL14	8	NA	B-other	Standard risk	✓	✓				46,XX
25437	Female	64	UKALL14	88	Illumina	HoTr	Very high risk	✓		✓	✓	✓	66-69<3n>,XXX,-1,-3,+der(1;3)(p10;q10)x2,+6,-7,-8,-9,+12,-13,-14,-15,-16,-17,+18,+21,+22,+mar1,+mar2[cp8]/46,XX[2]
25451	Male	63	UKALL14	88	Illumina	ZNF384-r	Standard risk	✓	✓	✓	✓	✓	46,XY[20]
25491	Male	63	UKALL14	92	NA	BCR-ABL1	Tyrosine kinase activating	✓					43,X,-Y,-7,-7,add(9)(p?2),t(9;22)(q34;q11),-10,-11,add(13)(q32),+2mar[cp7]/46,XY[2]
25548	Female	60	UKALL14	16	Illumina	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓		46,XX,t(9;22)(q34;q11)[10]
25552	Male	61	UKALL14	80	Illumina	CRLF2-r	Very high risk	✓		✓	✓	✓	46,XY[20]
25685	Male	62	UKALL14	NA	No data	Standard risk	Standard risk	✓					46,XY[22]
25688	Male	62	UKALL14	82	NA	T-cell	Standard risk	✓					46,XY[23]
25694	Male	60	UKALL14	4	NA	KMT2A-v	High risk	✓					failed
25695	Male	63	UKALL14	80	NA	HoTr	Very high risk	✓					74-79<3n>,XXY,+Y,+1,?add(2)(p1),+add(2)(p1),-3,+4,+5,+6,+9,+add(11)(q2),-12,+14,-15,-15,-16,+18,+19,+21,+21,+21,+1-3mar[cp6]
25709	Female	62	UKALL14	100	NA	KMT2A-v	High risk	✓			✓		46,XX,t(3;4;11)(p13;q21;q23)[10]
25793	Female	67	UKALL60	100	Illumina	BCR-ABL1	Tyrosine kinase activating	✓		✓		✓	46,XX,der(9)t(9;22)(q34;q11)t(9;21)(q34;q22.3),der(21)t(9;22)(9;21),der(22)t(9;22)[8]/46,XX[3]
25794	Female	65	UKALL60	89	NA	HoTr	Very high risk	✓					36,X,-X,-2,-3,-4,-7,-10,-13,-15,-16,-17,inc[6]?72,inc[5]/46,XX[2]
25842	Male	64	UKALL14	NA	HoTr	Very high risk	Very high risk	✓					37-39,XY,-2,-3,-4,-9,-13,-16,-17,-20[cp8]/60-62<3n>,XXY,+Y,-2,-3,-5,-9,-13,-14,-16,-17,-20[cp2]
25893	Female	78	UKALL60	92	Affymetrix	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓		47,XX,+X,?add(3)(q21),t(9)(q10)t(9;22)(q34;q11)[5]/45,XX[5]
25894	Male	63	UKALL60	98	NA	IGH@-r	Standard risk	✓					44,XY,-8,-13,der(14)(8;14)(q11;q32)[13]/44,idem,add(19)(p13.3)[4]/46,XY[3]
25895	Male	67	UKALL60	87	NA	B-other	Standard risk	✓	✓				46,XY[20]
25907	Male	70	UKALL60	96	NA	IGH@-r	Standard risk	✓	✓				47,XY,+X,?(18;22)(q11;q21)[1]/46,XY[3]
25925	Female	61	UKALL14	86	NA	BCR-ABL1	Tyrosine kinase activating	✓					46,XX,?(3;14)(q24;q32),t(9;22)(q34;q11),-11,+mar[1]/47,idem,+der(22)t(9;22)[5]/46,XX[4]
25949	Female	61	UKALL14	90	NA	B-other	Standard risk	✓					FAIL
25953	Female	71	UKALL60	90	Affymetrix	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓		46,XX[10]
25967	Male	60	UKALL14	95	Illumina	Complex	Very high risk	✓	✓	✓	✓	✓	46,XY,+5,-6,dic(7;9)(p13;p11),add(14)(q32),del(17)(p11),+21[18]/46,XY[2]
26062	Male	61	UKALL14	84	Illumina	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓		46,XY,t(9;22)(q34;q11)[5]/48-51,XY,+X,+6,+8,t(9;22)(q34;q11),+16,+der(22)t(9;22)[cp12]/46,XY[2]
26609	Male	83	UKALL60	50	Affymetrix	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓		45,XY,-7,t(9;22;11)(q34;q11;q13)[19]/46,XY[1]
26610	Male	65	UKALL60	63	Affymetrix	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓		46,XY,der(9)del(q)(p1)(9;22)(q34;q11),der(22)t(9;22)(q34;q11)[13]/46,XY[17]
26611	Male	68	UKALL60	83	NA	B-other	Standard risk	✓	✓		✓		47,XY,+X,del(16)(?q1),i(17)(q10)[8]/46,XY[8]
26612	Male	66	UKALL60	3	NA	B-other	Standard risk	✓	✓				46,XY[10]
26613	Male	66	UKALL60	81	NA	Complex	Very high risk	✓					44-45,XY,del(3)(q?2q?2),-7,+8,del(9)(p2?1),-20[cp9]/46,XY[1]
26614	Male	75	UKALL60	98	Affymetrix	B-other	Standard risk	✓		✓	✓	✓	Failed
26621	Female	69	UKALL60	90	Affymetrix	T-cell	Standard risk	✓		✓	✓		FAIL
26659	Male	60	UKALL14	0	Illumina	HoTr	Very high risk	✓		✓			Fail

26660	Female	62	UKALL14	84	illumina	BCR-ABL1	Tyrosine kinase activating	✓			✓	✓	✓	46,XX,t(9;22)(q34;q11.2)[8]/46,XX[37]
26682	Female	63	UKALL60	35	Affymetrix	BCR-ABL1	Tyrosine kinase activating	✓			✓	✓		44,XX,-7,der(9;12)(q10;q10),t(9;22)(q34;q11.2),-13,+mar[8]/46,XX[2]
26706	Male	60	UKALL14	89	illumina	HoTr	Very high risk	✓			✓			39,XY,add(2)(p13),-3,-4,-7,-8,i(9)(q10),-12,-13,-16,-17,+2mar[cp3]
26726	Male	66	UKALL60	88	Affymetrix	HeH	Standard risk	✓			✓	✓		Not Done
26732	Female	64	UKALL14		NA	BCR-ABL1	Tyrosine kinase activating	✓						46,XX[20]
26768	Female	70	UKALL60	89	NA	B-other	Standard risk	✓						46,XX,add(3)(q27)[19]/46,XX[1]
26971	Male	67	UKALL60	50	Affymetrix	B-other	Standard risk	✓	✓		✓	✓		46,XY,add(1)(q1)[5]/46,XY[5]
26990	Female	63	UKALL60	94	NA	B-other	Standard risk	✓	✓					46,XX[20]
26995	Male	70	UKALL60		Affymetrix	B-other	Standard risk	✓	✓		✓	✓		46,XY[20]
27026	Female	63	UKALL14		illumina	BCR-ABL1	Tyrosine kinase activating	✓			✓	✓		67-73,XX,+X,t(9;22)(q34;q11),+ider(22)(9;22)x2,inc[cp5]
27033	Male	72	UKALL60	72	NA	B-other	Standard risk	✓	✓					46,XY[20]
27043	Female	65	UKALL14	90	illumina	BCR-ABL1	Tyrosine kinase activating	✓			✓	✓		46,XX,t(2;9)(p21;p23),add(6)(q21),t(9;22)(q34;q11),add(21)(q21)[8]/46,XX[2]
27071	Female	60	UKALL14	90	illumina	B-other	Standard risk	✓	✓					46,XX[20]
27085	Female	63	UKALL60	92	Affymetrix	BCR-ABL1	Tyrosine kinase activating	✓			✓			46,XX,t(9;22)(q34;q11.2),der(19)(8;19)(q13;p13.3)[8]/46,XX[2]
27121	Female	64	UKALL60		NA	HoTr	Very high risk	✓			✓			36,X,-X,-2,-3,-4,-7,-12,-13,-15,-16,-17[7]/46,XX[3]
27147	Female	69	UKALL60	86	NA	BCR-ABL1	Tyrosine kinase activating	✓						46,XX,t(9;22)(q34;q11)[3]
27181	Male	65	UKALL14	40	illumina	IGH@-r	Standard risk	✓	✓		✓	✓	✓	46,XY,inv(14)(q11q32)[2]/46,XY[18]
27219	Female	65	UKALL60	90	NA	B-other	Standard risk	✓	✓					Failed
27298	Male	66	UKALL60	90	Affymetrix	B-other	Standard risk	✓	✓		✓	✓		46,XY[20]
27333	Female	63	UKALL14	73	illumina	BCR-ABL1	Tyrosine kinase activating	✓			✓	✓		46,XX,t(9;22)(q34;q11.2)[13]/47,XX,der(9;22)(q34;q11.2)add(9)(p13),der(22)(9;22)(q34;q11.2),+der(22)(9;22)[3]/46,XX[4]
27389	Female	73	UKALL60		illumina	KMT2A-v	High risk	✓			✓		✓	47,XXX,t(11;19)(q23;p13)[7]/46,XX[3]
27391	Male	65	UKALL60		Affymetrix	B-other	Standard risk	✓			✓	✓		46,XY[7]
27392	Female	73	UKALL60	72	Affymetrix	HoTr	Very high risk	✓			✓	✓		46,XX[20]
27395	Male	60	UKALL14	98	NA	T-cell	Standard risk	✓						47,XY,+19,inc[4]
27407	Female	69	UKALL60	61	NA	HoTr	Very high risk	✓						64-70<3n>,XX,-X,+1,+2,+2,-3,-4,+5,+6,-7,-9,+10,+11,-13,-13,-15,-16,-17,-18,-19,?der(19)(13;19)(q1;q13),-20,+21,+3-7mar[cp6]
27408	Male	70	UKALL60	0	NA	T-cell	Standard risk	✓						46,XY,t(7;14)(p15;q23)[5]/46,XY[2]
27409	Male	74	UKALL60	8	NA	B-other	Standard risk	✓						Failed
27441	Female	61	UKALL14	90	illumina	No data	Standard risk				✓	✓		NDS
27452	Male	62	UKALL14	40	NA	B-other	Standard risk	✓	✓					46,XY,i(9)(q10)[10]
27490	Male	64	UKALL60	40	Affymetrix	B-other	Standard risk	✓	✓		✓			-92,inc[11]/46,XY[2]
27508	Male	61	UKALL14	92	NA	HoTr	Very high risk	✓						64-66<3n>,XX,-Y,-3,-7,+12,+13,-15,-16,+21[cp3]/80-86<4n>,X,-X,-Y,-Y,-3,-4,-5,-6,-7,-7,-9,-10,+12,+13,-15,-16,+17,-19,-20,-22[cp6]/45,X,-Y[1]
27509	Male	69	UKALL60	60	Affymetrix	BCR-ABL1	Tyrosine kinase activating	✓			✓	✓		45,XY,der(7;9)(q10;q10)(9;22)(q34;q11.2),der(22)(9;22)(q34;q11.2)[11]
27537	Female	67	UKALL60	87	Affymetrix	HoTr	Very high risk	✓			✓	✓		69,XX,+1,+1,+2,+4,+4,+5,+6,+6,+8,+10,+10,+11,+11,+12,+14,+14,+18,+18,+19,+21,+21,+22,+mar[3]/46,XX[5]
27554	Female	78	UKALL60	75	Affymetrix	B-other	Standard risk	✓	✓		✓	✓		46,XX,add(12)(q13)[3]/46,XX[27]
27555	Male	64	UKALL60	0	Affymetrix	HoTr	Very high risk	✓			✓	✓		67<2n>,XY,+X,+Y,+1,+1,+2,+4,+5,+6,+?del(6)(q25),+8,+add(9)(p21),+10,+11,+11,+12,+14,+18,+19,+21,+21,+22,+22,inc[1]/46,XY[10]
27556	Female	75	UKALL60	50	NA	B-other	Standard risk	✓	✓					46,XX[9]
27557	Male	61	UKALL14	21	NA	T-cell	Standard risk	✓						46,XY[20]
27579	Female	60	UKALL60	55	NA	BCR-ABL1	Tyrosine kinase activating	✓						46,XX,t(2;9;22)(p21;q34;q11.2)[6]/46,XX[4]
27583	Female	61	UKALL60	95	Affymetrix	BCR-ABL1	Tyrosine kinase activating	✓			✓	✓		51,XX,+X,+4,t(9;22)(q34;q11.2),+14,+17,+der(22)(9;22)[10]
27584	Female	76	UKALL60	90	Affymetrix	BCR-ABL1	Tyrosine kinase activating	✓			✓	✓		46,XX,t(9;22)(q34;q11)[7]/45,idem,-7[3]/46,XX[1]
27585	Female	66	UKALL60	62	Affymetrix	BCR-ABL1	Tyrosine kinase activating	✓			✓	✓		46,XX,t(9;22)(q34;q11)[11]
27596	Male	62	UKALL60	64	Affymetrix	HoTr	Very high risk	✓			✓	✓		38-39,XY,-3,-4,-5,-7,-9,-15,-16,inc[cp4]/46,XY[16]
27640	Male	67	UKALL60	97	NA	B-other	Standard risk	✓	✓					45,XY,dic(7;9)(p1?1;p1?1)/46,XY[12]
27642	Female	72	UKALL60	90	Affymetrix	T-cell	Standard risk	✓			✓	✓	✓	Failed
27668	Male	68	UKALL60	60	NA	BCR-ABL1	Tyrosine kinase activating	✓						Fail
27752	Female	73	UKALL60	48	Affymetrix	B-other	Standard risk	✓	✓		✓	✓		46,XX[20]
27754	Female	63	UKALL14		illumina	BCR-ABL1	Tyrosine kinase activating	✓			✓	✓		Fail
27810	Female	79	UKALL60	90	NA	No data	Standard risk							NDS
27811	Male	64	UKALL14		NA	HoTr	Very high risk	✓						63-65,XY,+X,+Y,+1,+4,+5,+6,+8,+10,+11,+12,+18,+18,+19,+21,+21,+22,+22,+1-5mar[cp9]/46,XY[1]
27812	Male	65	UKALL14	99	illumina	TCF3-PBX1	Standard risk	✓			✓	✓		46,XY,der(19)(1;19)(q23;p13)[10]/46,XY[2]
27819	Female	65	UKALL60	90	Affymetrix	B-other	Standard risk	✓	✓		✓	✓		46,XX[20]
27833	Female	73	UKALL60	98	Affymetrix	IGH@-r	Standard risk	✓	✓		✓	✓	✓	Failed
27836	Male	63	UKALL14	61	illumina	BCR-ABL1	Tyrosine kinase activating	✓			✓	✓		45,XX,-7,t(9;22)(q34;q11.2),t(12;21)(p13;q22)[5]/46,XY,idem,+der(22)(9;22)(q34;q11.2)[5]
27887	Female	68	UKALL60	80	NA	BCR-ABL1	Tyrosine kinase activating	✓						46,XX,t(9;22)(q34;q22)[8]/46,XX[2]
27919	Female	82	UKALL60	11	NA	B-other	Standard risk	✓						Fail
27930	Male	60	UKALL60	82	NA	B-other	Standard risk	✓						46,XY[20]
27978	Male	66	UKALL60	30	NA	No data	Standard risk	✓						No sample
28011	Male	61	UKALL14		illumina	CRLF2-r	Very high risk	✓	✓		✓	✓		46,XY,-2,add(7)(q3),add(12)(p11),+mar[3]/46,XY[19]
28032	Female	69	UKALL60	98	NA	T-cell	Standard risk	✓						47,XX,+19[7]/46,XX[3]. ish der(8)(IGHx1), 14(IGHx1)

Supplementary table S4. Demographic and genetic details of patients analysed by SNP array.

	SNP array cohort (n=78)	Complete cohort (n=210)	p-value
Demographics			
Median age (range)	64 (60-83)	64 (60-83)	
Female	58% (45)	50% (105)	0.29
Male	42% (33)	50% (105)	0.29
Genetic subgroups			
<i>BCR-ABL1</i>	40% (31)	26% (55)	0.03
HoTr	12% (9)	13% (28)	0.84
<i>KMT2A</i> fusion	6% (5)	6% (12)	0.78
<i>TCF3-PBX1</i>	1% (1)	1% (3)	1
HeH	1% (1)	1% (3)	1
B-other	36% (28)	42% (88)	0.42
T-ALL	1% (1)	5% (11)	0.19
Unknown	3% (2)	5% (10)	0.52

Supplementary table S5: Frequency of recurrent arm-level CNAs in cases lacking primary ploidy shift (n=68)

Abnormality	% of cases (n=68)	Subgroups represented (n)
del(9p)	22% (15)	<i>BCR-ABL1</i> (11), B-other (4)
gain of Ph*	12% (8)	<i>BCR-ABL1</i> (8)
gain 1q	10% (7)	B-other (4), <i>BCR-ABL1</i> (2), <i>TCF3-PBX1</i> (1)
-7	10% (7)	<i>BCR-ABL1</i> (5), B-other (2)
del(7p)	9% (6)	<i>BCR-ABL1</i> (4), B-other (2)
gain 21q	7% (5)	<i>BCR-ABL1</i> (2), B-other (3)
del(17p)	7% (5)	B-other (4), <i>BCR-ABL1</i> (1)
del(12p)	6% (4)	B-other (2), <i>BCR-ABL1</i> (1), T-ALL (1)
gain 14q	4% (3)	<i>BCR-ABL1</i> (3)
-9	4% (3)	<i>BCR-ABL1</i> (3)
+5	3% (2)	B-other (1), <i>BCR-ABL1</i> (1)
+2	3% (2)	<i>BCR-ABL1</i> (2)
+6	3% (2)	<i>BCR-ABL1</i> (1), <i>KMT2A-v</i> (1)
gain 8q	3% (2)	<i>BCR-ABL1</i> (1), B-other (1)
+11	3% (2)	B-other (1), <i>BCR-ABL1</i> (1)
del(13q)	3% (2)	<i>BCR-ABL1</i> (2)

Supplementary table S6. Characteristics of all *IKZF1* deletions

Patient	<i>IKZF1</i> deletion	Genetic subgroup
28670	ex.2-7	<i>BCR-ABL1</i>
25208	ex.2-7 and 2-8	<i>BCR-ABL1</i>
27026	ex.4-7	<i>BCR-ABL1</i>
26610	ex.4-7	<i>BCR-ABL1</i>
27043	ex.4-7	<i>BCR-ABL1</i>
29589	ex.2-7	<i>BCR-ABL1</i>
25247	ex.4-7	<i>BCR-ABL1</i>
25548	ex.4-7	<i>BCR-ABL1</i>
26660	ex.4-8	<i>BCR-ABL1</i>
27085	ex.2-7	<i>BCR-ABL1</i>
27754	ex.4-7	<i>BCR-ABL1</i>
28057	ex.4-7	<i>BCR-ABL1</i>
28182	ex.4-7	<i>BCR-ABL1</i>
24890	ex.4-7	B-other
25371	ex.2-7	<i>CRLF2-r</i>
25552	ex.4-7	<i>CRLF2-r</i>
25130	ex.2-8	<i>CRLF2-r</i>
25246	ex.4-8	<i>CRLF2-r</i>
28011	ex.4-7	<i>CRLF2-r</i>
28350	del(7p)-7	<i>BCR-ABL1</i>
25953	del(7p)-7	<i>BCR-ABL1</i>
26609	del(7p)-7	<i>BCR-ABL1</i>
26682	del(7p)-7	<i>BCR-ABL1</i>
27836	del(7p)-7	<i>BCR-ABL1</i>
25344	del(7p)-7	B-other
27298	del(7p)-7	B-other
26706	del(7p)-7	HoTr
28644	del(7p)-7	HoTr
29407	del(7p)-7	HoTr
27392	del(7p)-7	HoTr
27596	del(7p)-7	HoTr
25437	del(7p)-7	HoTr
27555	del(7p)-7	HoTr
26659	del(7p)-7	HoTr
27537	del(7p)-7	HoTr
27333	del(7p)-7	<i>BCR-ABL1</i>
25793	del(7p)-7	<i>BCR-ABL1</i>
27585	del(7p)-7	<i>BCR-ABL1</i>
25967	del(7p)-7	Complex
26614	del(7p)-7	B-other

Supplementary table S7. Genomic details of *LEMD3* and *IKZF1* deletions

Gene	Patient ID	Deleted segment	Size of deletion (bp)	Deletion type	Deleted exons
<i>LEMD3</i>	25208	chr12:65,579,942-65,602,114	22172	Heterozygous	None
<i>LEMD3</i>	25130	chr12:65,579,942-65,597,922	17980	Heterozygous	None
<i>LEMD3</i>	28670	chr12:65,579,942-65,591,462	11520	Heterozygous	None
<i>LEMD3</i>	26660	chr12:65,579,942-65,608,678	28736	Heterozygous	ex. 2
<i>LEMD3</i>	25552	chr12:65,579,801-65,611,980	32179	Heterozygous	ex. 2-3
<i>KDM6A</i>	28011	chrX:44,810,083-44,867,059	56967	Hemizygous	ex. 3-4
<i>KDM6A</i>	29407	chrX:44,778,209-44,905,069	126860	Homozygous	ex. 3-8
<i>KDM6A</i>	25437	chrX:44,775,342-44,885,557	110215	Homozygous	ex. 3-6
<i>KDM6A</i>	27642	chrX:44,860,967-45,176,870	315903	Heterozygous	ex. 5-29

Supplementary table S8. Outcome of UKALL14 patients >60 years according to UKALL14 genetic risk categories. High risk patients were those with KMT2A fusions; Very high risk were those with complex karyotype, low hypodiploidy/near triploidy, or CRLF2 rearrangement; TKA fusion patients were all BCR-ABL+; Standard risk patients were all other BCP-ALL patients

	Total	Standard Risk	High Risk	Very High Risk	BCR-ABL1+	T-Cell
Total	95 (100)	33 (35)	7 (7)	21 (22)	28 (29)	6 (6)
White Cell Count						
<30	69 (73)	29 (88)	1 (14)	19 (90)	15 (54)	5 (83)
30-100	16 (17)	3 (9)	2 (29)	2 (10)	9 (32)	0 (0)
>100	10 (11)	1 (3)	4 (57)	0 (0)	4 (14)	1 (17)
Complete Remission						
Yes	70 (76)	27 (84)	5 (71)	12 (63)	21 (75)	5 (83)
No	22 (24)	5 (16)	2 (29)	7 (37)	7 (25)	1 (17)
Did not start treatment	3	1	0	2	0	0
5yr Survival Rates						
OS	24% (15-35)	41% (22-59)	0%	0%	24% (10-42)	0%
EFS	17% (9-27)	28% (12-47)	0%	0%	15% (4-33)	0%

Supplementary table S9. Patient outcomes according to type of *IKZF1* deletion

	Total	<i>IKZF1</i> ex.4-7 deletion	Other <i>IKZF1</i> deletions
Total	40 (100)	11 (28)	29 (73)
3-year survival rates			
Overall	19% (7-35)	10% (1-36)	24% (7-45)
Event-Free	11% (3-26)	0%	18% (4-38)
Relapse Rate	52% (26-83)	100%	28% (10-64)
Hazard Ratio			
Overall	-	1.37 (0.58-3.23), 0.467	1
Event-Free	-	1.56 (0.68-3.58), 0.298	1
Relapse Rate	-	2.46 (0.49- 12.36), 0.275	1