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Genetic and genomic analysis of acute lymphoblastic leukaemia in older adults reveals a distinct profile of abnormalities: analysis of 210 patients from the UKALL14 and UKALL60+ clinical trials

by Thomas Creasey , Emilio Barretta, Sarra L. Ryan, Ellie Butler, Amy A. Kirkwood, Daniel Leongamornlert, Elli Papaemmanuil, Pip Patrick, Laura Clifton-Hadley, Bela Patel, Tobias Menne, Andrew K. McMillan, Christine J. Harrison, Clare J Rowntree, Nick Morley, David I. Marks, Adele K. Fielding, and Anthony V. Moorman

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Genetic and genomic analysis of acute lymphoblastic leukaemia in older adults reveals a distinct profile of abnormalities: analysis of 210 patients from the UKALL14 and UKALL60+ clinical trials

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Author contributions.

TC and AVM designed the study. TC, AVM, EB and EB collected and assembled the data. TC, AVM, EB, EB and SLR performed data analysis and interpretation. CJH and AVM were responsible for administrative support. AKF was chief investigator of the UKALL14 and UKALL60+ clinical trials. AAK, DL, EP, PP, LCH, BP, TM, AKM, CJR, NM, DIM, AKF participated in recruitment of patients and provided study materials. TC and AVM developed the first drafts of the manuscript. All authors contributed to the review and amendments of the manuscript and approved the final version for submission.

Disclosures

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Abstract

Despite being predominantly a childhood disease, the incidence of ALL has a second peak in adults aged 60 years and over. These older adults fare extremely poorly with existing treatment strategies and very few studies have undertaken a comprehensive genetic and genomic characterisation to improve prognosis in this age group.

We performed cytogenetic, single nucleotide polymorphism (SNP) array and next generation sequencing (NGS) analyses on samples from 210 patients aged ≥60 years from the UKALL14 and UKALL60+ clinical trials. *BCR-ABL1* positive disease was present in 26% (55/210) of patients, followed by low hypodiploidy/near triploidy in 13% (28/210). Cytogenetically cryptic rearrangements in *CRLF2*, *ZNF384* and *MEF2D* were detected in 5%, 1% and 1% of patients respectively. Copy number abnormalities were common and deletions in ALL driver genes were seen in 77% of cases. *IKZF1* deletion was present in 51% (40/78) of samples tested and the *IKZF1^{plus}* profile identified in over a third (28/77) of BCP-ALL cases. The genetic good risk abnormalities high hyperdiploidy (n=2), *ETV6-RUNX1* (no cases) and ERG deletion (no cases) were exceptionally rare in this cohort. RAS pathway mutations were seen in 17% (4/23) of screened samples. *KDM6A* abnormalities, including biallelic deletions, were discovered in 5% (4/78) of SNP array and 9% (2/23) of NGS samples, and represent a novel, potentially therapeutically actionable lesions using EZH2 inhibitors.

Outcome remained poor with five-year event-free (EFS) and overall survival (OS) rates of 17% and 24% respectively across the cohort indicating a need for novel therapeutic strategies.

Introduction

Acute lymphoblastic leukaemia (ALL) presents most commonly in early childhood (1). However, the disease has a bimodal incidence with a second smaller peak in adults aged 60 years old and over (2). Optimal care of these older adults (≥ 60 years) remains an area of unmet clinical need. Although they comprise only 30-35% of diagnoses each year in adults, around 60% of disease-related deaths occur within this age group, and they are the only ALL patients not to have benefitted from the stepwise improvements in prognosis driven through successive clinical trials in children and younger adults (2, 3).

Primary chromosomal abnormalities are one of the hallmarks of ALL and greatly influence treatment decisions and prognosis (4, 5). Although *BCR-ABL1* is well recognised as the most common genetic subgroup in adult ALL (5), to date, only limited biological characterisation of older patients beyond the conventionally defined risk groups has been performed. One recent study reported a comprehensive genomic profile of 1,988 subjects with BCP-ALL using a combination of transcriptome, whole genome and exome sequencing and identified 23 genetic subtypes (6). Despite this impressive cohort, only 103 patients aged 60 years and over at diagnosis were included. Such efforts focussed on older individuals are needed to improve prognostication and to identify novel therapeutic targets (7, 8).

A proportion of patients do not harbour a cytogenetically visible disease-defining lesion, but have a gene expression profile similar to *BCR-ABL1* positive disease (Ph-like/*BCR-ABL*-like ALL) (9, 10). Approximately 50% of children and young adults with this entity have cytogenetically-cryptic *IGH-CRLF2* or *P2RY8-CRLF2* rearrangements, which activate JAK-STAT signalling (11, 12). Other recurrent gene rearrangements include ABL-class fusions (affecting *ABL1*, *ABL2*, *PDGFRB* or *CSF1R*) in 9-13% of Ph-like cases and the JAK-STAT pathway activating rearrangements of *JAK2* or *EPOR* in 7-10% and 3-6% of patients respectively (11, 12). To date, most studies have focussed on paediatric and young adult (<60 years) cohorts (11, 13), although one study reported the Ph-like signature in 24% of older BCP-ALL patients in a restricted subgroup lacking large scale aneuploidy (12).

Separately, *ZNF384* and *MEF2D* rearrangements have been reported in 2-6% of paediatric BCP-ALL cases, and form distinct clinical entities (14, 15).

Focal copy number abnormalities (CNAs) frequently target genes that are involved in B-cell development or cell cycle regulation These secondary abnormalities drive transformation of a preleukaemic clone into overt disease and include deletions of *EBF1* on 5q33.3, *IKZF1* on 7p12.2, *CDKN2A* and *CDKN2B* on 9p21.3, *PAX5* on 9p13.2, *ETV6* on 12p13.2, *BTG1* on 12p21.33 and *RB1* on 13q14.2 (16).

Importantly, particular combinations of CNAs have an impact on prognosis (17-19). The *IKZF1*^{plus} profile is based on the co-occurrence of *IKZF1* deletion with deletions of *CDKN2A*, *CDKN2B*, *PAX5* or the pseudoautosomal region 1 (PAR1) on Xp22.33/Yp11.31 (resulting in *P2RY8-CRLF2* fusion) in the absence of *ERG* deletion (17). This copy number profile is associated with a significantly poorer outcome in childhood ALL patients, highlighting the prognostic importance of large-scale copy number analyses.

To date, the genetic and genomic landscape of ALL has been primarily restricted to younger patients with few analyses focussed on older individuals. Here, we apply cytogenetic, copy number and next generation sequencing techniques to investigate whether the primary and secondary genetic abnormalities of ALL in older adults are distinct to those encountered in their younger counterparts. We additionally sought to identify novel druggable targets, a particular priority for such patients due to the high toxicity and low success rates they experience from traditional chemotherapeutic approaches (20).

Methods

Patients and samples

Patients aged 60 years and over were identified for genetic profiling studies from two large UK-wide multicentre clinical trials (UKALL14 and UKALL60+) (supplementary methods).

Baseline cytogenetic analyses, typically consisting of a diagnostic karyotype and fluorescence *in situ* hybridisation (FISH) for *BCR-ABL1* fusion and *KMT2A* translocations, were performed in accredited diagnostic genetic laboratories throughout the UK and then centrally reviewed and entered into the Leukaemia Research Cytogenetics Group (LRCG) database.

The study was approved by the institutional review board of each treatment centre and all patients gave written informed consent for data collection and genetic studies as specified by the trials' protocols.

Detection of primary genetic subgroups

Diagnostic karyotype and FISH results from the regional genetic centres were first examined and patients were coded into one of six subgroups – *BCR-ABL1*, *TCF3-PBX1*, *KMT2A* fusions, high hyperdiploidy (HeH) (51-65 chromosomes), low hypodiploidy/near triploidy (HoTr) (30-39 or 60-78 chromosomes) or T-ALL. RT-PCR was performed to identify the presence of Bcr-Abl p190, p210 and p230 oncoproteins in *BCR-ABL1* positive cases. Next, all BCP-ALL cases lacking a primary chromosomal abnormality, hereafter termed B-other ALL, were identified. B-other cases with available fixed cell samples were further investigated by the LRCG to determine the occurrence of cytogenetically cryptic abnormalities using dual colour break-apart FISH probes for *CRLF2*, *PDGFRB/CSF1R*, *ABL2*, *IGH*, *ZNF384*, *MEF2D* (Cytocell, Cambridge, UK) and *JAK2* (Kreatech Diagnostics, Amsterdam, Netherlands). Separately, multiplex ligation-dependent probe amplification (MLPA) using the IKZF1-P335 kit (MRC Holland, The Netherlands) was performed on cases with available DNA as previously described (21) and permitted the detection of *P2RY8-CRLF2* fusion that occurs through PAR1 deletion on Xp22.33/Yp11.31.

Copy number analysis

SNP arrays were performed on DNA extracted from diagnostic bone marrow samples obtained at trial enrolment. SNP arrays were performed at the Newcastle Genomics Centre, Newcastle-upon-Tyne Hospitals NHS Foundation Trust using the Affymetrix Cytoscan HD (Affymetrix, Santa Clara, CA) or Illumina CytoSNP 850k (Illumina, San Diego, CA) arrays according to the manufacturers' protocols.

Deletions in *IKZF1*, *CDKN2A*, *CDKN2B*, *PAX5*, *RB1*, *ETV6*, *EBF1*, *BTG1* ('driver genes') were specifically identified from the SNP array results, with loss of any part of the gene considered significant. All arm-level and focal CNAs were then examined to detect recurrent abnormalities.

Next generation sequencing (NGS)

Separately, targeted NGS analyses were performed on selected samples using a custom SureSelect XT2 target enrichment kit (Agilent, Santa Clara, CA). Samples were selected based on availability of DNA and the presence of CNAs by SNP array. The capture library was designed to target either the coding regions or full sequence of 44-genes that are well known to be implicated in ALL (supplementary table S1). Libraries were prepared in accordance with the manufacturer's protocol and sequenced on the NextSeq 550 (Illumina, San Diego, CA) using 100 bp paired end chemistry (supplementary methods).

Survival analysis

Survival analysis was restricted to patients enrolled in UKALL14 because all these patients received similar intensive treatment with curative intent (22). Patients were grouped according to primary chromosomal abnormalities as described previously (23). Briefly, patients with complex karyotypes, HoTr or JAK-STAT activating rearrangements were classed as very high risk (VHR); patients with any *KMT2A* fusions were classed as high risk (HR); patients with *BCR-ABL1* and other kinase activating fusions were classed as tyrosine kinase activating (TKA) abnormalities; all other BCP-ALL patients were classed as standard risk (SR) and T-ALL patients were analysed separately. All p-values were two-sided and, because of multiple testing, values <0.01 were considered statistically significant. All analyses were performed using Intercooled Stata (StataCorp, College Station, TX) and R version 3.4.3 (http://www.R-project.org).

Results

Patient demographics and baseline cytogenetics

We identified a total of 210 patients aged ≥60 years from the UKALL14 (n=95) and UKALL60+ (n=115) clinical trials. Median patient age was 64 years (range 60-83) and 24% (n=50) were over 70 years at diagnosis. Male: female ratio was 1:1. In total, 90% (n=189) had confirmed BCP-ALL and 5% (n=11) had T-cell disease. The remaining 5% (n=10) did not have a diagnostic immunophenotype centrally recorded. Patient numbers decreased with advancing age but no significant difference was seen in the genetic subgroups represented in different age groups (p=0.47) (figures 1A and 1B). The most prevalent abnormality was *BCR-ABL1*, present in 28% (55/200) of evaluable patients. Of these, the p210, p190 and p230 isoforms were present in 40% (22/55), 33% (18/55) and (<1%) 1/55 of patients respectively. Two patients had both p190 and p210 isoforms identified and the Bcr-Abl isoform was unknown in the remaining 22% (12/55) patients. Low hypodiploidy/near triploidy (HoTr) was the second most prevalent primary chromosomal abnormality and was identified in 14% (28/200) of patients (supplementary table S2) and *KMT2A-v* rearrangements were discovered in a further 6% (12/200) of patients. Of the patients with BCP-ALL, 47% (88/189) did not have a primary chromosomal abnormality identified by routine cytogenetic and FISH analyses performed in regional cytogenetic centres (B-other ALL).

Of the eleven patients with T-ALL, *TLX1* (n=1) and *TLX3* (n=1) rearrangements were identified. The other 9 patients either had no rearrangements identified (n=5) or were not tested (n=4).

Individual patient demographic, clinical and genetic data are shown in supplementary table S3.

Gene rearrangements in B-other ALL patients

Patients with B-other ALL included those with normal (n=21), failed (n=25) or complex karyotypes (n=5). Patients with dic(9;12) (n=2), *IGH* translocation (n=5) or other non-subgroup defining chromosomal abnormalities (n=30) were also included

in the B-other category. Fixed cell samples were available for 74% (65/88) of B-other patients and gene rearrangements were identified in 21% (19/65) (table 2). Not all samples could be screened for all abnormalities due to availability of material for multiple FISH experiments.

CRLF2 rearrangements were identified in 17% (8/48) of successfully screened cases. The *CRLF2* rearrangement partners were *IGH* (n=5), *P2RY8* (n=2) and unknown (n=1). Two additional patients had *P2RY8-CRLF2* fusion identified by MLPA, through the presence of PAR1 deletion (table 1). *IGH* translocations were present in 26% (14/53) of B-other samples tested. Of these, five cases accounted for patients with *IGH-CRLF2* translocations detailed above, and three cases had separate primary genetic abnormalities identified (one *ZNF384* translocation and two *P2RY8-CRLF2* fusions). In the remaining six samples, the *IGH* partners were *CEBPA* (n=1), *CEBPD* (n=1), *CEBPE* (n=1), *BCL2* (n=1) and unknown (n=2). *ZNF384* and *MEF2D* rearrangements were each identified in 8% (3/40) and 3% (1/39) of screened B-other cases respectively.

In total, *CRLF2*, *IGH*, and *ZNF384* rearrangements were present in 5%, 3% and 1% of the complete patient cohort respectively (figure 1C). No variant *ABL1* (0/83), *PDGFRB* (0/56), *JAK2* (0/53) or *ABL2* (0/52) rearrangements were detected.

Copy Number Alterations

SNP arrays were performed on diagnostic bone marrow samples from 78 of the 210 patients (49 from UKALL14 and 29 from UKALL60+) using the Illumina CytoSNP 850k (n=51) and Affymetrix Cytoscan HD (n=27) arrays. The SNP array cohort was reasonably representative of the complete patient cohort, although *BCR-ABL1* positive patients were slightly over-represented (supplementary table S4).

Deletions were more frequent than gains in all cytogenetic subgroups apart from high hyperdiploidy. Following the exclusion of probable constitutional CNVs as described in supplementary methods, a median of 7 deletions (range 0-52) and 1 gain (range 0-29) were seen per patient sample.

In the 68/78 patients without primary ploidy shift (defined as HoTr and HeH), large deletions on 9p were the most prevalent arm-level CNA, seen in 22% (15/68) of cases (figure 2 and supplementary table S5). An additional copy of the Philadelphia

chromosome was present in 12% (8/68) of patients (26% of *BCR-ABL1+* cases) and 1q gains and monosomy 7 were each present in 10% (7/68) of samples.

Of the CNAs in known driver genes, *IKZF1* deletions were the most frequent abnormality, present in 51% (40/78) of cases. These were focal intragenic deletions in 19 cases, most commonly involving exons 4-7 (n=11) or exons 2-7 (n=4). Rarer *IKZF1* deletions involved exons 4-8 (n=2), exons 2-8 (n=1) and one patient had biallelic *IKZF1* loss involving exons 2-7 and 2-8. Focal *IKZF1* deletions were almost exclusively seen in patients with *BCR-ABL1* (n=13) or *CRLF2* rearrangements (n=5) (supplementary table S6). In the remaining cases, *IKZF1* loss resulted from monosomy 7 (n=16) or del(7p) (n=5) (figure 2 and supplementary table S6).

The pattern of gene deletions varied by *BCR-ABL1* status with a higher frequency of *IKZF1* deletion in *BCR-ABL1* positive ALL as previously described (24) and a higher frequency of *ETV6* and *RB1* deletions in *BCR-ABL1* negative ALL (table 2). Most deletions were heterozygous with the exception of *CDKN2A/B* which were homozygous in 50% of cases.

In total, 23% (18/78) of patients had no deletions in driver genes, 18% (14/78) had one deletion, 18% (14/78) had two deletions, 23% (18/78) had 3 deletions and 18% (14/78) had four or more gene deletions (supplementary figure S1). *IKZF1* deletions in particular co-occurred with other gene deletions much more commonly than in isolation (46% vs 5%). The $IKZF1^{plus}$ profile (17) was present in 36% (28/77) of the BCP-ALL samples, specifically in *BCR-ABL1*+ (n=13), B-other (n=8) and HoTr (n=7) patients.

We detected recurrent focal CNAs in several other genes, which to date have not been defined in the pathogenesis of ALL. Focal deletions in *LEMD3* on 12q14.3 and *KDM6A* on Xp11.3 were each seen in 6% (5/78) and 5% (4/78) of cases respectively. Demographic, genetic and outcome features of affected cases are shown in table 3. *LEMD3* deletions ranged from 11-32kb in size (supplementary table S7 and supplementary figure S2), although were confined to intron 2 of the gene in three of these. *KDM6A* deletions ranged from 56-316 kb in size and were homozygous or hemizygous in 3/4 cases (supplementary table S7). Deletion

breakpoints for all *LEMD3* and *KDM6A* deletions were visually confirmed in IGV in the cases analysed by NGS.

Mutational landscape

Twenty three patient samples covering all major genetic subgroups (supplementary table S3) were successfully sequenced using the 44-gene targeted panel. Across these samples, 25 single nucleotide variants (SNVs) and 8 indels were identified (figure 3). At least one gene in the NGS panel was mutated in 74% (17/23) of patients. Pathogenic mutations in the RAS signalling pathway were identified in 17% (4/23) of cases. *KRAS* p.G12D and *KRAS* p.R68W variants were seen in patients with *KMT2A* and *EP300-ZNF384* rearrangements respectively. *NRAS* p.G12S and p.G12D were present in one B-other case and one patient with unidentified genetic subgroup respectively. With the exception of the *KRAS* p.R68W variant, all RAS pathway mutations are reported in the COSMIC database (25).

Two patient samples with HoTr were included. Consistent with the underlying chromosomal abnormality, a pathogenic *TP53* variant (*TP53* p.R282W) was detected in one of these (26, 27). Two indels in *NF1* and a *FLT3* missense variant (*FLT3* p.V194M) were also seen, the latter being reported as a tolerated passenger mutation in AML (28).

Known pathogenic variants were also seen in *JAK2* (*JAK2* p.R683T in a patient with *IGH-CRLF2*), *CREBBP* (*CREBBP* p.L1499Q in a patient with *IGH-BCL2*), *CSF1R* (*CSF1R* p.V32G in a patient with *P2RY8-CRLF2*). Additionally, previously unreported *KDM6A* mutations were discovered in two *BCR-ABL1*+ patients (*KDM6A* p.Y215H and p.K987Q).

We also investigated whether mutations associated with clonal haematopoiesis of indeterminate potential (CHIP) (most commonly affecting *DNMT3A*, *TET2* and *ASXL1*) were present in older adults with ALL (29, 30). These are found in 10% of adults over the age of 65 years without haematological diseases, but are associated with an increased risk of subsequently developing myelodysplastic syndrome or acute myeloid leukaemia (30). Overall, these were discovered in only 13% (3/23) of cases with single variants in each of *DNMT3A*, *TET2* and *ASXL1*.

***KDM6A* alterations**

Overall *KDM6A* was disrupted in 6 cases, with focal deletions in 5% (4/78) of SNP array samples (table 3) and mutations in 9% (2/23) of NGS samples (figure 3). Interestingly, the deletions resulted in homozygous or hemizygous *KDM6A* loss in 3 of the 4 cases (figure 4A and supplementary table S7). Biallelic *KDM6A* deletions were seen in the two female patients with HoTr ALL, albeit by two different mechanisms. By cytogenetics and SNP array, patient #29407 had lost one copy of chromosome X and had a focal *KDM6A* deletion in the remaining homologue. In comparison, patient #25437 had two focal but subtly distinct intragenic *KDM6A* microdeletions on each X chromosome (figure 4B). As *KDM6A* is not in a pseudoautosomal region, the male patient (#28011) had a deletion affecting the only *KDM6A* allele, resulting in hemizygous loss. The *KDM6A* mutations detected by NGS were present in exons 8 (*KDM6A* p.Y215H) and 20 (*KDM6A* p.K987Q) (figure 5C) and are not reported in the literature although the SIFT (31) and Polyphen (32) *in silico* prediction tools described deleterious and probably damaging consequences respectively, consistent with loss of function. Patients with *KDM6A* deletions had a poor outcome and all four affected patients died 5-18 months after diagnosis (table 2). The two patients with *KDM6A* mutations similarly both died within 2 months of diagnosis.

Patient outcome by genetic subtype

All 95 UKALL14 patients had outcome data available for analysis. Five-year EFS and OS rates were 17% and 24% respectively (figure 5 and supplementary table S8). Even though the outcome of these older patients was poor there was evidence that tumour genetics remained a strong risk factor (figure 5), as we have previously demonstrated for younger adults (23). Patients with genetic SR had the best outcome with 84% entering remission and 5-year EFS and OS rates of 28% and 41% respectively. In comparison, over a third of patients with VHR genetics did not go into remission and all 28 patients with genetic HR or VHR disease died within 5 years of diagnosis.

Regarding patients with B-other ALL with gene rearrangements identified, all three patients with *ZNF384* rearranged-ALL survived >2 years from diagnosis whereas 6/8

of those with *CRLF2* rearrangements and 4/6 of those with *IGH* translocations (excluding *CRLF2* partners) died within 2 years (table 1).

Of the 40 patients with *IKZF1* deletions, no significant difference in outcome was identified between those with focal deletions of exons 4-7 (generating the dominant negative IK6 isoform) (33) compared with patients with other *IKZF1* deletions (supplementary table S9).

Discussion

To our knowledge, our study provides the largest genetic and genomic characterisation to date of older adults with ALL.

The landscape of primary chromosomal abnormalities and CNAs is distinct from that observed in children and younger adults. T-ALL was only seen in 5% of cases, which is less than half the rate seen in younger adults (34).

Overall, a quarter of patients had *BCR-ABL1* positive ALL, although the frequency of this did not increase further over the age of 60 years. This corroborates the findings from a large analysis of three German Multicentre study group for adult ALL (GMALL) trials where the proportion of *BCR-ABL1* positive cases reached a plateau after 45 years of age (35). In comparison, our study highlights that low hypodiploidy/near triploidy becomes more common with advancing age, whereby it is encountered in <2% of childhood patients (36), 4-9% of adults aged 25-60 (23) rising to around 15% of adults aged 60 years and over in our cohort. Other high risk cytogenetic subgroups, specifically *KMT2A* fusions and complex karyotypes were present in 6% and 3% of patients respectively, which is similar to that seen in younger adults (5, 23). We found a lower frequency of *CRLF2* rearrangements than reported by two US studies that included older adults (12, 37). This could be related to the higher prevalence of Hispanic ancestry in the US, and the associated inheritance of *GATA3* risk alleles, which confer an elevated risk of *CRLF2* rearranged ALL (38). In comparison to younger patients, ABL-class fusions were notably absent in our cohort. Other studies have similarly identified very low

frequencies of ABL-class fusions in older individuals. Indeed, only 2 cases were identified in 103 adults aged ≥60 years in a recent large US study (6). Data from the GMALL group similarly demonstrates a rapid decrease in the frequency of Ph-like ALL in older age groups (39).

Although we limited our survival analysis to UKALL14 patients, we highlight that prognosis remains very poor in older adults with ALL (figure 5). However, consistent with recent studies, patients with *ZNF384* rearrangements seemed to have a favourable outcome (23).

Copy number abnormalities in key genes recurrently disrupted in ALL were discovered in the majority of patients. *IKZF1* loss was present in over half of all cases tested by SNP array, occurring in 68% of *BCR-ABL1* positive and 40% of *BCR-ABL1* negative ALL. The high rate of *IKZF1* loss in *BCR-ABL1* positive ALL is consistent with much of the published literature (24, 40). However, the frequency of *IKZF1* deletion in the older patients with *BCR-ABL1* negative ALL was double that reported in younger adults (40% vs 19%) (41). This discrepancy is at least in part driven by the increased frequency of low hypodiploid cases, as these usually only retain 1 copy of chromosome 7. However, *IKZF1* deletions were still encountered in 36% (10/28) of B-other cases. Deletions in other key driver genes in BCP-ALL (*CDKN2A/B*, *PAX5*, *RB1*, *ETV6* and *EBF1*) were also encountered more frequently than in younger patients (23).

The high risk *IKZF1^{plus}* copy number profile was identified in over a third of patients, although its prognostic impact in older adults still needs to be elucidated. Interestingly, no focal *ERG* deletions, which are associated with a favourable outcome, were detected (42). Overall, these data confirm that all genetic biomarkers typically associated with a good prognosis, namely *ETV6-RUNX1* fusion, high hyperdiploidy and *ERG* deletions are exceedingly rare in older adults with ALL, contributing to the adverse outcomes of this patient population. By virtue of the techniques used, we recognise that we were not able to identify certain novel subgroups, such as the recently described PAX5-driven subtypes (6) or *DUX4* rearrangements, although the latter are associated with *ERG* deletions in the majority of cases (43).

Importantly, our study highlighted therapeutically actionable targets that would merit further investigation in older adults. We identified *KDM6A* deletions and mutations in 5% (4/78) and 9% (2/23) of screened patients respectively. *KDM6A* (also known as *UTX*) on Xp11.3 is an H3K27me3 demethylase, involved in epigenetic regulation through repression of PRC2/EZH2 activity. Recurrent *KDM6A* mutations have been identified in T-ALL, and shown to have gender-specific tumour suppressor effect (44). *KDM6A* escapes X-inactivation in females and therefore retains biallelic expression. Hence, loss of tumour suppressor function through *KDM6A* abnormalities disproportionately affects males and has been postulated to explain the skewed gender-distribution of T-ALL. To our knowledge, our study is the first to demonstrate *KDM6A* disruption in a significant proportion of older adults with ALL, most of whom had B-cell disease. Most interestingly, we have highlighted homozygous *KDM6A* deletions in female patients, and no evidence of skewed gender distribution. Loss of KDM6A function, resulting in EZH2 overactivity, has been shown to play an important pathogenic role in urothelial bladder cancer (45) and functional analyses have demonstrated susceptibility of KDM6A-null cell lines to the FDA-approved EZH2 inhibitor tazemetostat (45). Our findings therefore identify a proportion of patients who may respond to EZH2 inhibition, a treatment as yet untested in ALL.

We also discovered recurrent small focal intragenic deletions in *LEMD3* in 6% (5/78) of cases. *LEMD3* regulates bone morphogenic protein (BMP) and transforming growth factor beta (TGF-B) signalling and to date has not been implicated in cancer (46). The significance of these deletions remains speculative, particularly as some were confined to introns.

Recurrent RAS pathway mutations were identified in almost one fifth of patients (4/23), all of whom had *BCR-ABL1* negative ALL. These activate RAS signalling and are potentially therapeutically actionable through MEK inhibition (e.g. selumetinib).

Older adults with ALL fare extremely poorly with current chemotherapeutic approaches. A number of studies have demonstrated the disproportionate treatment toxicities experienced by this patient group, leading to treatment omissions or delays (20). Our analysis confirms the additional challenges posed by the high proportion of poor risk genetic subgroups. Moving forward, the comprehensive identification of druggable targets such as *KDM6A* abnormalities, JAK-STAT activating

rearrangements or RAS pathway mutations presents an opportunity to expand therapeutic options, likely to most benefit this patient population. As a paradigm, significant progress has been made in the management of *BCR-ABL1* positive disease through these approaches, culminating in a promising chemotherapy-free protocol (47). Further dedicated clinical trials that include comprehensive genomic profiling of older adults, combined with targeted treatments and/or immunotherapy and a reduction in the traditional chemotherapy backbone will be key to improving the dismal outcome of these patients.

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Tables

Patient ID	Trial	Abnormality	WCC ($x10^9$/L)	Outcome
25130	UKALL14	*IGH-CRLF2*	33.6	Died after 1 month
25371	UKALL14	*IGH-CRLF2*	47.7	Alive >5 years
28235	UKALL60	*IGH-CRLF2*	5.3	Relapsed and died after 2 years
30102	UKALL60	*IGH-CRLF2*	Not known	Relapsed and died after 5 months
30299	UKALL60	*IGH-CRLF2*	Not known	Died after 4 months
25246	UKALL14	*P2RY8-CRLF2*	6.3	Died within 1 month
28039	UKALL60	*P2RY8-CRLF2*	Not known	Died after 9 months
25552	UKALL14	*P2RY8-CRLF2*	2.9	Died after 4 months
28011	UKALL14	*P2RY8-CRLF2*	3.5	Died after 16 months
30297	UKALL60	*CRLF2-r*	Not known	Alive >2 years
30487	UKALL14	*IGH-CEBPA*	11.7	Alive after 1 year
25894	UKALL60	*IGH-CEBPD*	0.8	Alive >5 years
27181	UKALL14	*IGH-CEBPE*	1.2	Died after 3 months
27833	UKALL60	*IGH-BCL2*	14.5	Died after 2 years
25907	UKALL60	*IGH-r*	2	Died after 1 year
29808	UKALL60	*IGH-r*	Not known	Relapsed and died after 1 year
25451	UKALL14	*EP300-ZNF384*	34.2	Relapsed and died >5 years
25235	UKALL14	*ZNF384-r*	3.5	Alive >5 years
30085	UKALL60	*ZNF384-r*	Not known	Alive >2 years
25267	UKALL14	*MEF2D-r*	1.4	Alive >5 years

Table 1. Clinical and outcome data for all B-other patients with gene rearrangements detected by FISH or MLPA. Outcome of patients with *CRLF2* rearrangement was very poor with only 2/10 alive 2 years after diagnosis. In comparison, 2/3 patients with *ZNF384* rearrangements were still alive after 5 years with only 1 relapse that occurred nearly 7 years after diagnosis.

Gene	Cases with deletion (n)	Deletion frequency by *BCR-ABL1* status			Heterozygous deletions	Homozygous deletions
		BCR-ABL1+ **cases (n=31)**	***BCR-ABL1-*** **cases (n=47)**	**p-value**		
IKZF1	51% (40)	68% (21)	40% (19)	0.02	41	2
CDKN2A	46% (36)	39% (12)	51% (24)	0.36	18	18
CDKN2B	46% (36)	39% (12)	51% (24)	0.36	21	15
PAX5	41% (32)	48% (15)	36% (17)	0.35	32	0
RB1	23% (18)	10% (3)	32% (15)	0.03	17	1
ETV6	21% (16)	6% (2)	30% (14)	0.02	16	0
EBF1	21% (16)	19% (6)	21% (10)	1	15	1
BTG1	13% (10)	6% (2)	17% (8)	0.3	9	1

Table 2. Frequency of individual deletions in known driver genes split by *BCR-ABL1* status. Significant differences identified between rate of *IKZF1*, *ETV6* and *RB1* deletions between *BCR-ABL1* positive (*BCR-ABL*+) and *BCR-ABL1* negative (*BCR-ABL1*-) cases.

Gene	Patient ID	Sex (M/F)	Age (yrs)	Genetic subgroup	WCC ($x10^9$/L)	Outcome
LEMD3	25208	M	62	*BCR-ABL1*	205.4	Alive after 9 years
LEMD3	25130	F	62	*IGH-CRLF2*	33.6	Died after 1 month
LEMD3	28670	F	61	*BCR-ABL1*	1.6	Died after 2 months
LEMD3	26660	F	62	*BCR-ABL1*	18.2	Alive after 7 years
LEMD3	25552	M	61	*P2RY8-CRLF2*	2.9	Died after 4 months
KDM6A	28011	M	61	B-other	3.5	Died after 16 months
KDM6A	29407	F	60	HoTr	2.9	Died after 5 months
KDM6A	25437	F	64	HoTr	1.4	Died after 14 months
KDM6A	27642	F	72	T-ALL	Not known	Died after 18 months

Table 3. Demographic, clinical and outcome data of all cases with focal *LEMD3* or *KDM6A* deletions. All patients with *KDM6A* deletions died within 18 months of diagnosis.

Figure legends

Figure 1. Distribution of primary chromosomal abnormalities by age groups across 210 adults aged ≥60 years. Primary genetic abnormalities shown by 5-year age-groups, displayed by number (A) and proportion of cases (B) in each age group. Frequency of final genetic subgroups is shown following screening of B-other ALL cases for gene rearrangements (C).

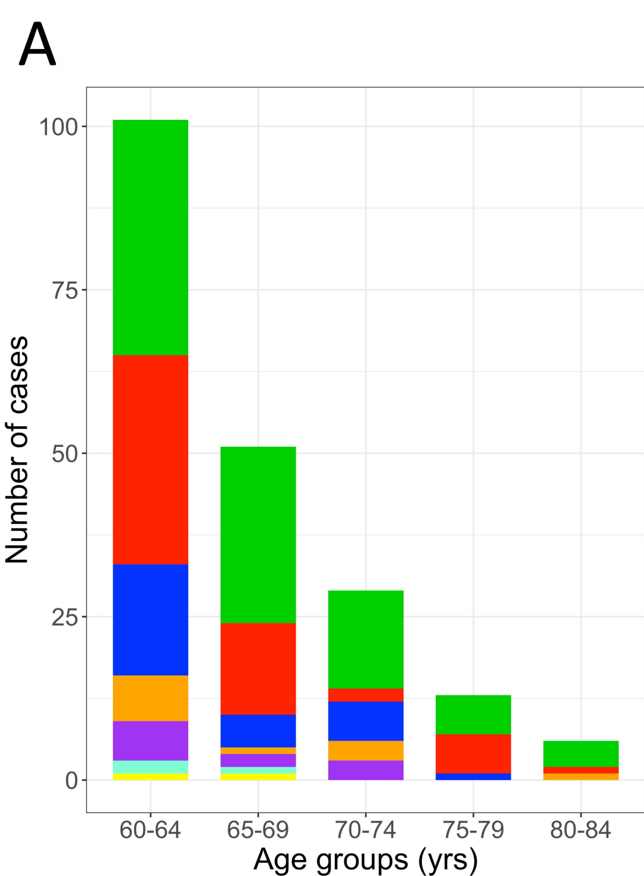
HoTr: low hypodiploidy/near triploidy; HeH: high hyperdiploidy; T-cell: T-cell ALL; B-other: BCP-ALL with no primary chromosomal abnormality identified.

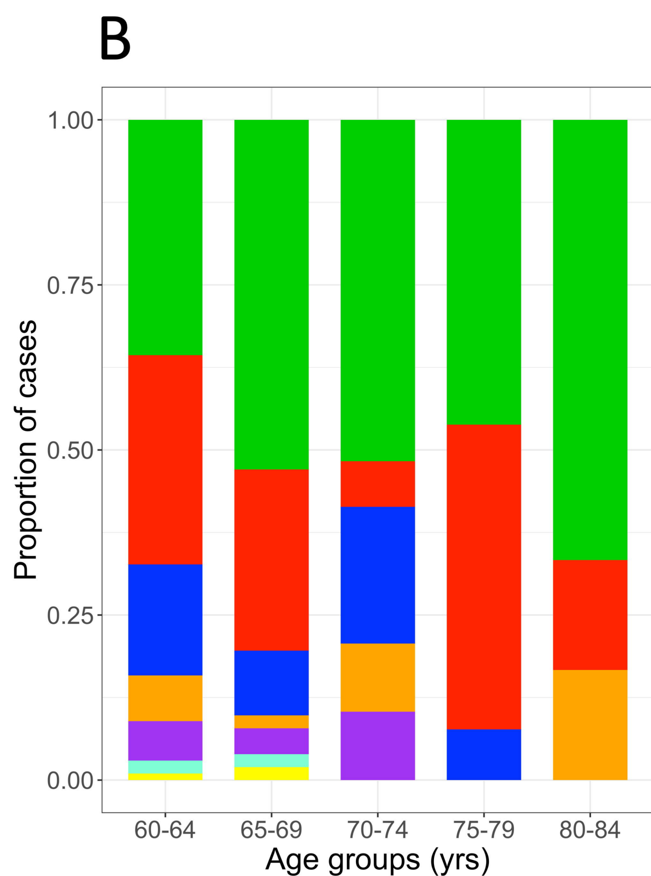
Figure 2. Complete copy number profile based on SNP array results from all 78 patients included in SNP array cohort. Only CNAs present in at least 3 patient samples are displayed.

Figure 3. Mutations detected by 44-gene NGS panel in 23 patients. Only patient samples with at least one mutation displayed (n=17). In total, 24 single nucleotide variants (SNV), 7 frameshift insertions and 1 frameshift deletion were identified. Two genes had both SNVs and indels within the same case ("multi-hit").

Figure 4. *KDM6A* aberrations detected by SNP array and NGS. *KDM6A* deletions identified by SNP array in 4 patient samples (A). Each bar represents a probe on the SNP array. 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. Homozygous *KDM6A* deletion in patient 25437, demonstrating two slightly distinct *KDM6A* deletions measuring 110kb and 87kb respectively and resulting in biallelic loss of exons 3-6 (B). Small gain also noted following segment of homozygous deletion. *KDM6A* protein plot displaying two mutations detected by NGS (C).

Figure 5. Overall survival and event-free survival for 95 adults aged ≥60 years recruited to UKALL14. Overall survival (A) and event free survival (B) for all patients combined; overall survival (C) and event free survival (D) split by genetic risk group with VHR and HR combined into single group. Patients with complex karyotypes, low hypodiploidy/near triploidy or *CRLF2* rearrangements were classed as very high risk (VHR); patients with any *KMT2A* fusions were classed as high risk (HR); patients with *BCR-ABL1* and other kinase activating fusions were classed as tyrosine kinase activating (TKA) abnormalities (all *BCR-ABL1* positive in this study); all other BCP-ALL patients were classed as standard risk (SR). Patients with SR or *BCR-ABL1* had improved overall survival (p=0.001) and event free survival (p=0.002) compared to patients with HR or VHR disease.





Cytogenetic subgroups
B-other
BCR-ABL1
HoTr
KMT2A fusion
T-cell
TCF3-PBX1
HeH

C

No data, 10, 5%

BCR-ABL1, 55, 26%

B-other (uncharacterised), 68, 32%

TCF3-PBX1, 3, 1%

KMT2A, 12, 6%

HeH, 2, 1%

MEF2D, 1, 1%

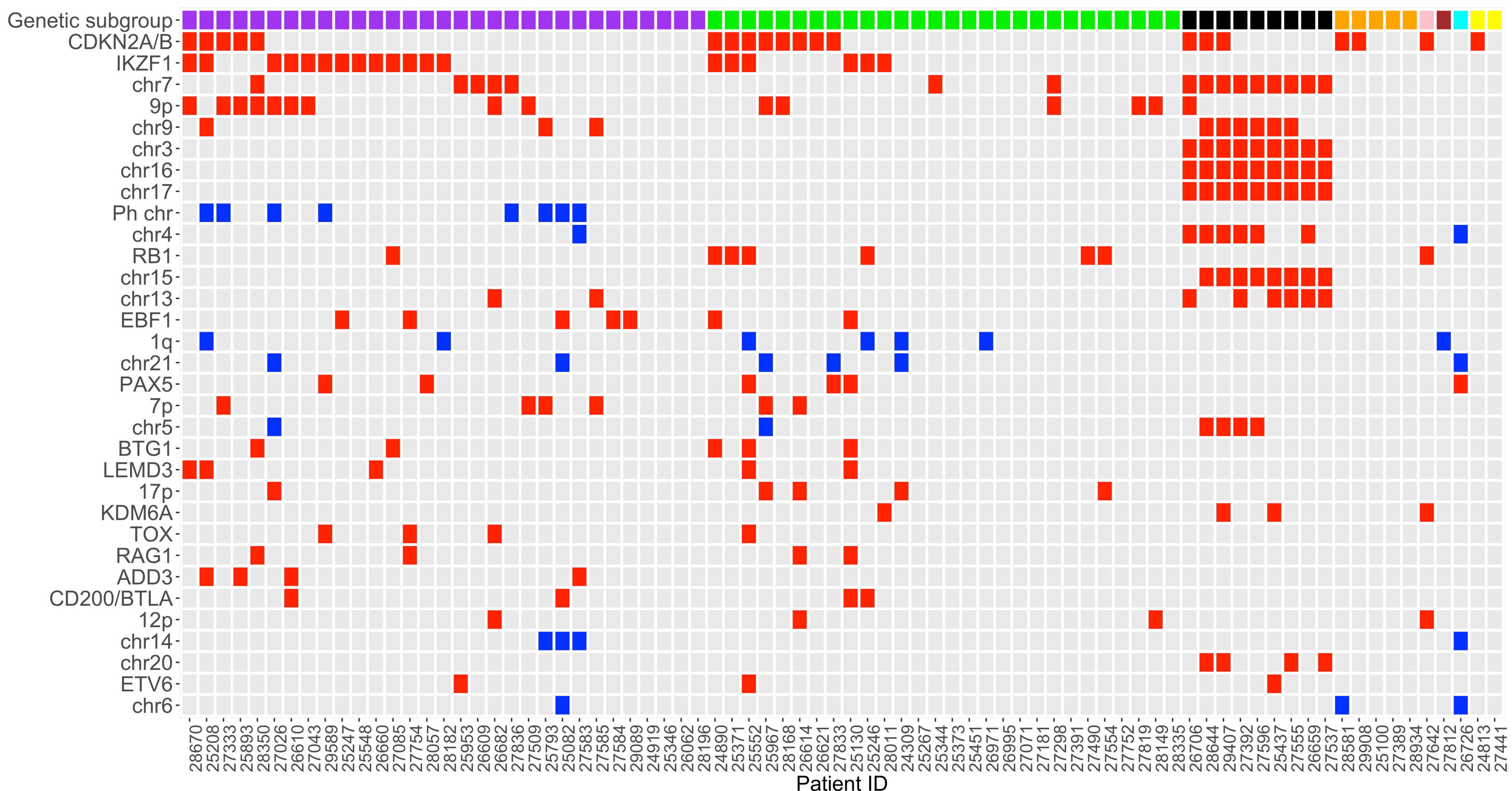
ZNF384, 3, 1%

HoTr, 29, 14%

IGH, 6, 3%

CRLF2, 10, 5%

T-cell, 11, 5%


Genetic subgroup
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IKZF1
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chr9
chr3
chr16
chr17
Ph chr
chr4
RB1
chr15
chr13
EBF1
1q
chr21
PAX5
7p
chr5
BTG1
LEMD3
17p
KDM6A
TOX
RAG1
ADD3
CD200/BTLA
12p
chr14
chr20
ETV6
chr6
28670 25208 27333 25893 28350 27026 26610 27043 29589 25247 25548 26660 27085 27754 28057 28182 25953 26609 26682 27836 27509 25793 25082 27583 27585 27584 29089 24919 25346 26062 28196 24890 25371 25552 25967 28168 26614 26621 27833 25130 25246 28011 24309 25267 25344 25373 25451 26971 26995 27071 27181 27298 27391 27490 27554 27752 27819 28149 28335 26706 28644 29407 27392 27596 25437 27555 26659 27537 28581 29908 25100 27389 28934 27642 27812 26726 24813 27441
Patient ID
Deletion
Gain
Normal
BCR-ABL1
B-other
HoTr
KMT2A-v
T-ALL
TCF3-PBX1
HeH
Unknown

Genetic subgroup
KDM6A
JAK2
FLT3
NF1
IKZF1
ETV6
PAX5
KRAS
NRAS
CSF1R
TP53
ATM
ABL1
ARID2
CXCR4
DNMT3A
IL7R
KMT2C
ASXL1
CREBBP
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RUNX1
TET2

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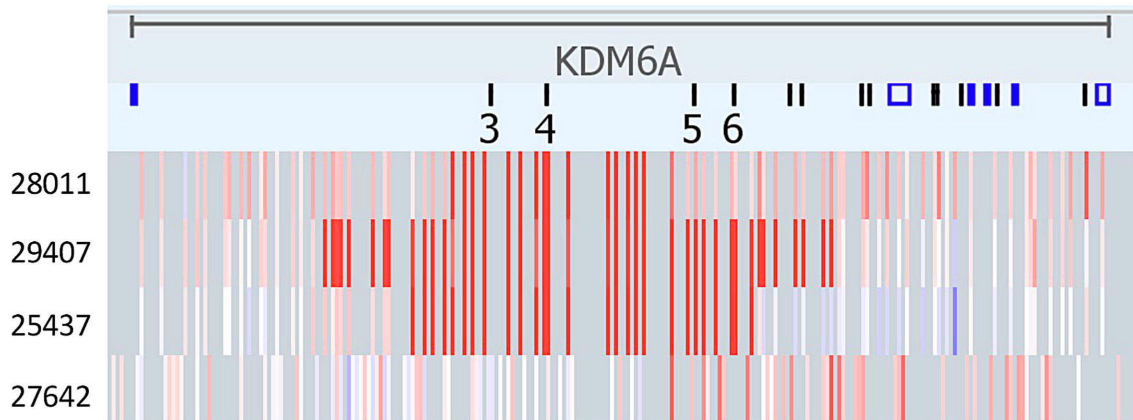
Patient ID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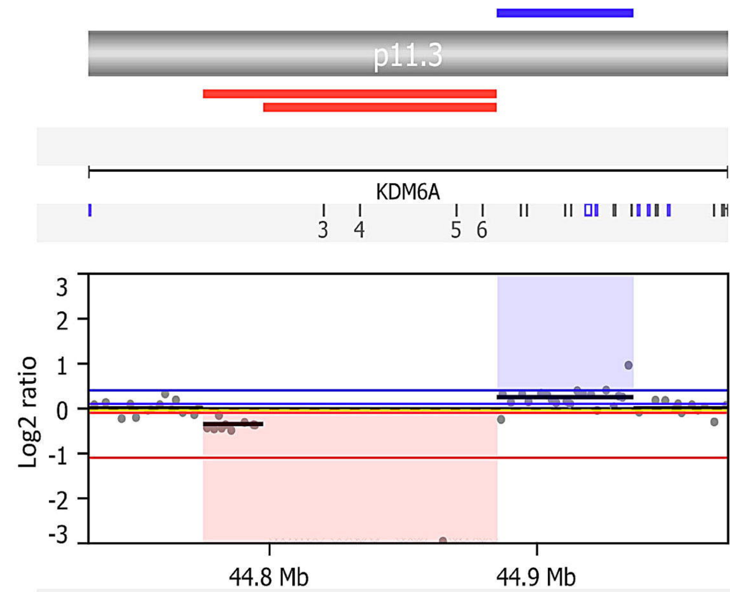
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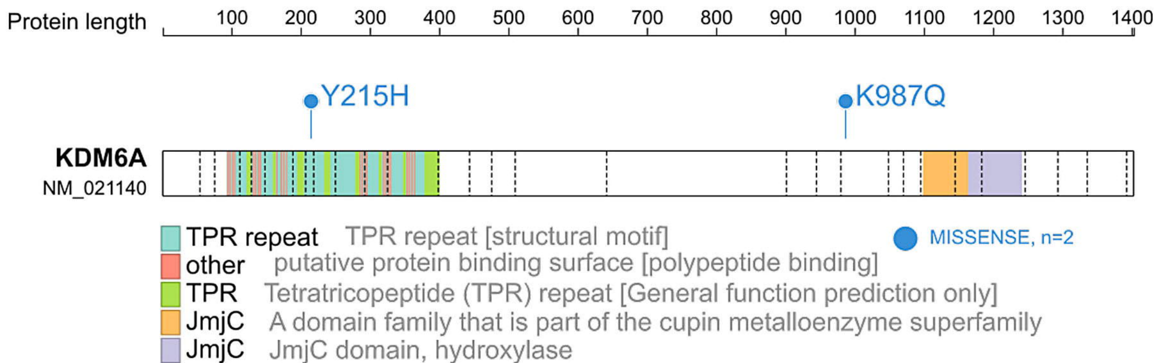
44.9 Mb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500
600
700
800
900
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1100
1200
1300
1400
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NM_021140
TPR repeat TPR repeat [structural motif]
other putative protein binding surface [polypeptide binding]
TPR Tetratricopeptide (TPR) repeat [General function prediction only]
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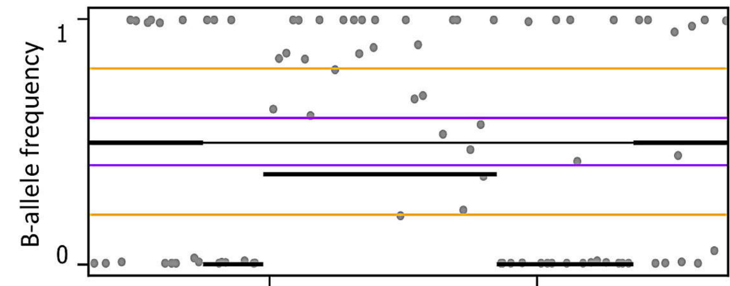
JmjC JmjC domain, hydroxylase
MISSENSE, n=2


B-allele frequency
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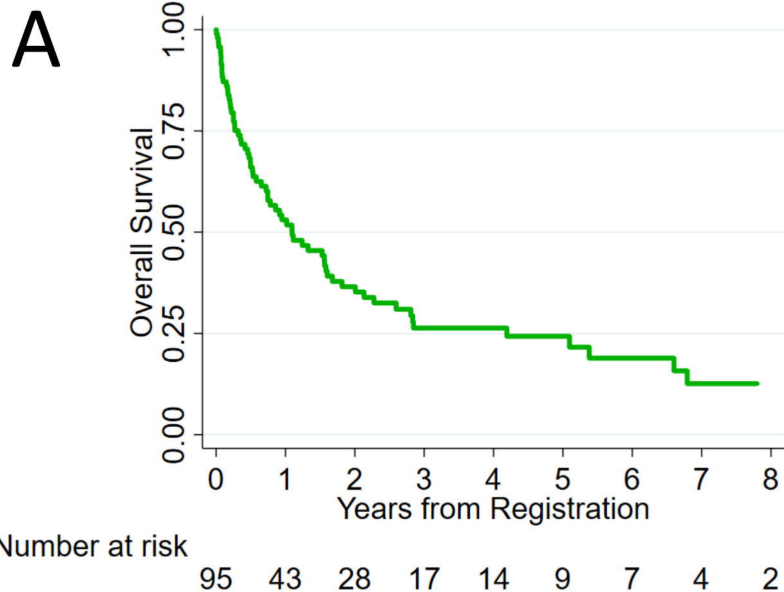
A
Overall Survival
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0.50
0.25
0.00
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Years from Registration
Number at risk
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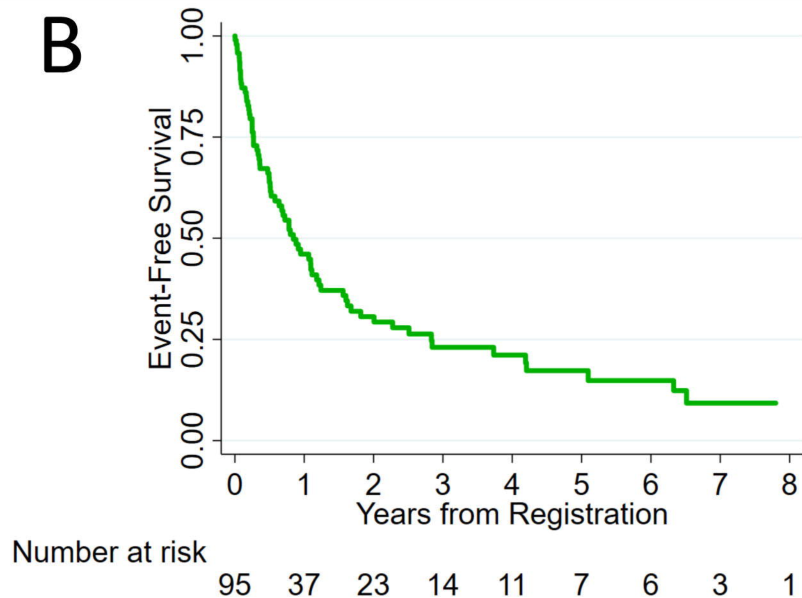
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Event-Free Survival
1.00
0.75
0.50
0.25
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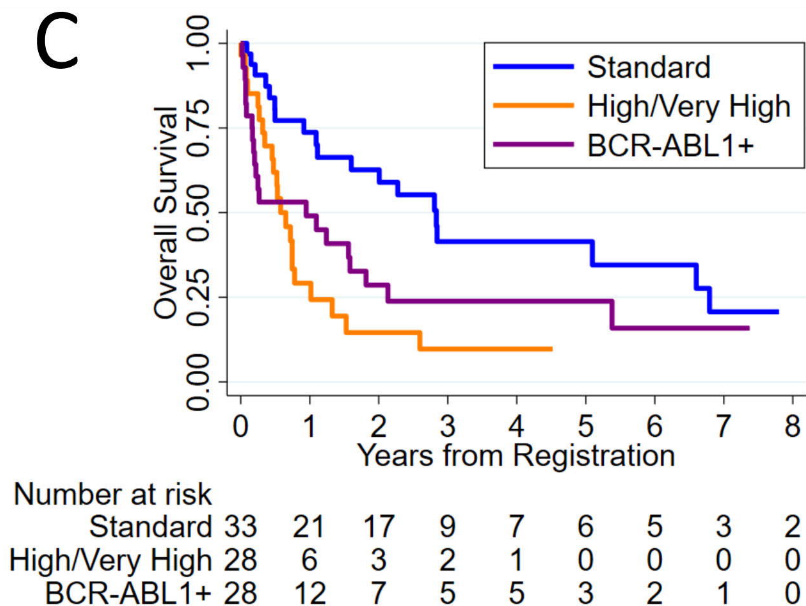
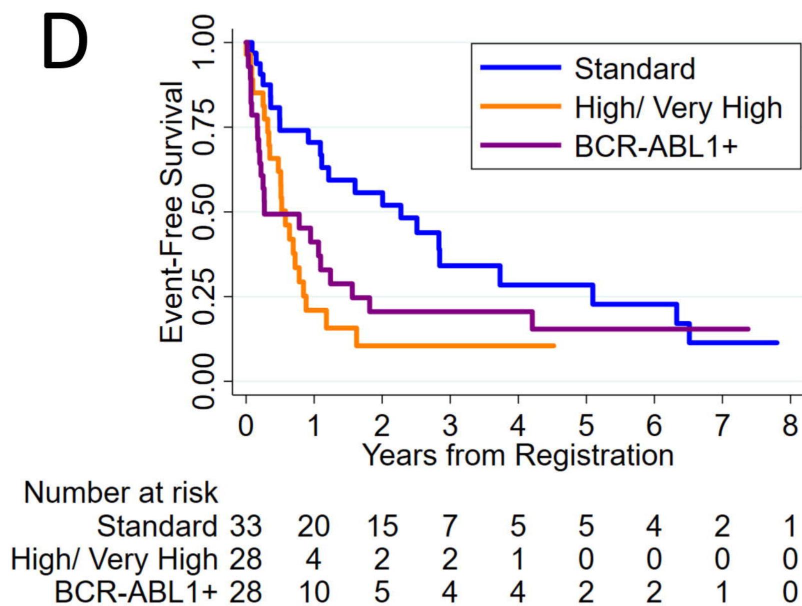
0 1 2 3 4 5 6 7 8
Years from Registration
Number at risk
95 37 23 14 11 7 6 3 1


C
Overall Survival
1.00
0.75
0.50
0.25
0.00
Standard
High/Very High
BCR-ABL1+
0 1 2 3 4 5 6 7 8
Years from Registration
Number at risk
Standard 33 21 17 9 7 6 5 3 2
High/Very High 28 6 3 2 1 0 0 0 0
BCR-ABL1+ 28 12 7 5 5 3 2 1 0


D
Event-Free Survival
1.00
0.75
0.50
0.25
0.00
Standard
High/ Very High
BCR-ABL1+
0 1 2 3 4 5 6 7 8
Years from Registration
Number at risk
Standard 33 20 15 7 5 5 4 2 1
High/ Very High 28 4 2 2 1 0 0 0 0
BCR-ABL1+ 28 10 5 4 4 2 2 1 0

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 genome[1]. 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 ≥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

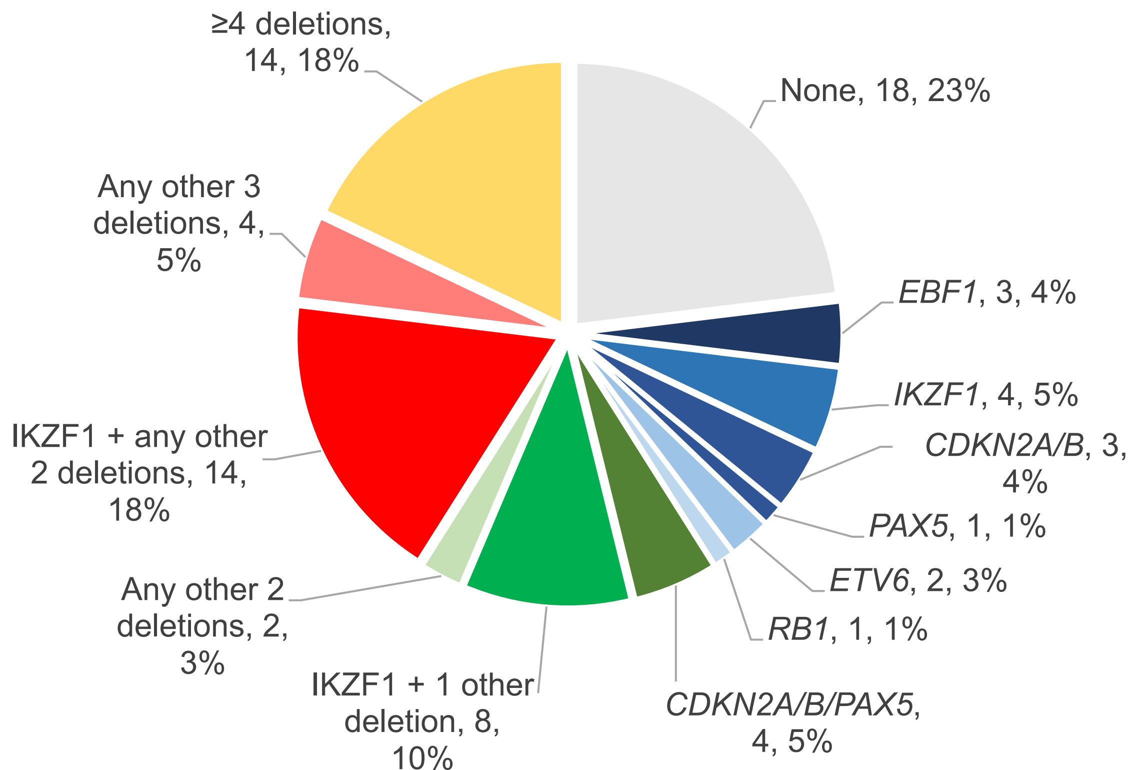
XP beads (Beckman Coulter, Brea, CA, USA): DNA was reduced to 0.7 to optimise bead-binding to the longer DNA fragments in the library and ii) The PCR amplification was performed using the Longamp Taq polymerase enzyme (New England Biolabs, Ipswich MA, USA), which is optimized for amplification of longer 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 HaplotypeCaller[3]. Ensembl VEP files were produced and calls with a population allele frequency $\geq$0.01 in the Exome Aggregation Consortium (ExAC) database[4] were excluded as likely germline variants. All non-coding variants, synonymous variants, and those reported as both tolerated and benign in the SIFT[5] and Polyphen[6] databases respectively were also excluded. Calls with COSMIC identifiers were examined in the COSMIC database[7] to identify known somatic mutations in cancer, specifically those in *TP53*.

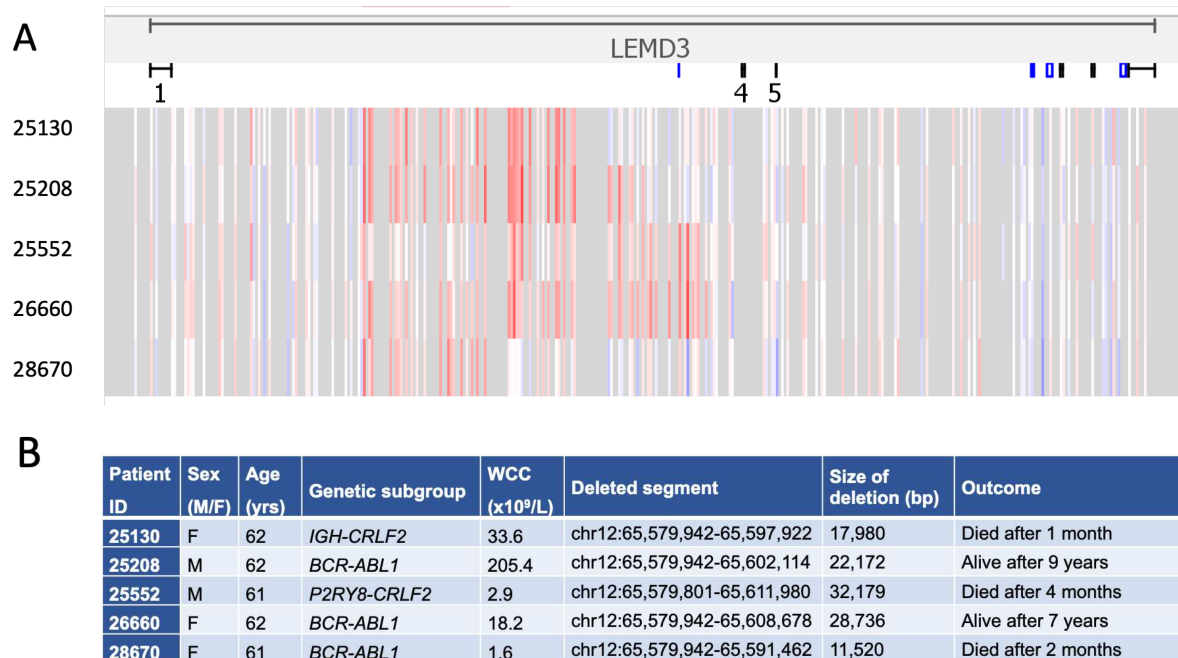
Supplementary references

1. Diskin SJ, Li M, Hou C, et al. Adjustment of genomic waves in signal intensities from whole-genome SNP genotyping platforms. *Nucleic acids research*. 2008;36(19):e126-e126.
2. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020.
3. Poplin R, Ruano-Rubio V, DePristo MA, et al. Scaling accurate genetic variant discovery to tens of thousands of samples. *bioRxiv*. 2017:201178.
4. Karczewski KJ, Weisburd B, Thomas B, et al. The ExAC browser: displaying reference data information from over 60 000 exomes. *Nucleic acids research*. 2017;45(D1):D840-D845.
5. Sim N-L, Kumar P, Hu J, Henikoff S, Schneider G, Ng PC. SIFT web server: predicting effects of amino acid substitutions on proteins. *Nucleic Acids Research*. 2012;40(W1):W452-W457.
6. Adzhubei IA, Schmidt S, Peshkin L, et al. A method and server for predicting damaging missense mutations. *Nature methods*. 2010;7(4):248-249.
7. Tate JG, Bamford S, Jubb HC, et al. COSMIC: the Catalogue Of Somatic Mutations In Cancer. *Nucleic acids research*. 2019;47(D1):D941-D947.

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).



Patient ID	Sex (M/F)	Age (yrs)	Genetic subgroup	WCC (x10⁹/L)	Deleted segment	Size of deletion (bp)	Outcome
25130	F	62	*IGH-CRLF2*	33.6	chr12:65,579,942-65,597,922	17,980	Died after 1 month
25208	M	62	*BCR-ABL1*	205.4	chr12:65,579,942-65,602,114	22,172	Alive after 9 years
25552	M	61	*P2RY8-CRLF2*	2.9	chr12:65,579,801-65,611,980	32,179	Died after 4 months
26660	F	62	*BCR-ABL1*	18.2	chr12:65,579,942-65,608,678	28,736	Alive after 7 years
28670	F	61	*BCR-ABL1*	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
ABL1	whole gene
ABL2	whole gene
ARID2	whole gene
ASXL1	exons
ATM	exons
CREBBP	exons
CSF1R	whole gene
DGKH	whole gene
DNMT3A	exons
ETV6	whole gene
FLT3	whole gene
FOXO1	exons
IKZF1	whole gene
IKZF2	exons
IKZF3	exons
IL7R	exons
JAK1	exons
JAK2	whole gene
JAK3	exons
KDM6A	whole gene
KMT2C	exons
KRAS	exons
MEF2C	whole gene
MEF2D	whole gene
NF1	whole gene
NOTCH1	exons
NR3C1	exons
NRAS	exons
NT5C2	exons
PAX5	whole gene
PDGFRB	whole gene
PTEN	whole gene
PTPN11	exons
RAG1	whole gene
RB1	exons
RUNX1	exons
SH2B3	exons
TCF3	whole gene
TCF4	whole gene
TET2	exons
TFDP3	exons
TOX	exons
TP53	exons
ZFHX3	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	***BCR-ABL1***	55 (26%)	40%	64
	TCF3-PBX1	3 (1%)	33%	64
	KMT2A-v	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)(q1q2),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	✓	✓				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						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,-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)t(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	✓					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),i(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)t(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,?t(18;22)(q11;q21)[1]/46,XY[3]
25925	Female	61	UKALL14	86	NA	BCR-ABL1	Tyrosine kinase activating	✓					46,XX,?t(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)t(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)t(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)t(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)t(9;22)(q34;q11.2)add(9)(p13),der(22)t(9;22)(q34;q11.2),+der(22)t(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)t(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)t(9;22)(q34;q11.2),der(22)t(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)(q?25),+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)t(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)t(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)t(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)

28033	Female	63	UKALL60	92	NA	KMT2A-v	High risk	✓					46,XX,t(4;11)(q21;q23),inc[5]
28034	Male	74	UKALL60	4	NA	No data	Standard risk						Not analysed
28039	Male	76	UKALL60	88	NA	CRLF2-r	Very high risk	✓	✓		✓		45,XY,-7,-15,-17,+mar[10]/46,XY[1]
28050	Male	66	UKALL60	98	NA	B-other	Standard risk	✓	✓				Fail
28051	Male	66	UKALL60	28	NA	BCR-ABL1	Tyrosine kinase activating	✓					46,XY,t(9;22)(q34;q11)[3]/46,XY[5]
28057	Female	64	UKALL14		Illumina	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓	✓	46,XX,t(9;22)(q34;q11),inc[3]/46,XX,inc[2]
28076	Male	63	UKALL60	80	NA	B-other	Standard risk	✓					46,XY[20]
28091	Female	64	UKALL14	76	NA	T-cell	Standard risk	✓					Failed
28092	Female	71	UKALL60	80	NA	HoTr	Very high risk	✓					37,XX,del(2)(q21)(q31),-3,-4,-5,-7,-9,-13,-16,-17,-20[7]/46,XX[3]
28093	Male	72	UKALL60		NA	B-other	Standard risk	✓					Fail
28104	Female	64	UKALL60		NA	TCF3-PBX1	Standard risk	✓					46,XY[20]
28105	Female	78	UKALL60	90	NA	B-other	Standard risk	✓					46,XX,del(12)(p?13)[3]/46,XX[7]
28135	Female	79	UKALL60	75	NA	BCR-ABL1	Tyrosine kinase activating	✓					45,XX,-7,t(9;22)(q34;q11)[10]
28149	Female	64	UKALL14	80	Illumina	B-other	Standard risk	✓		✓	✓		46,XX,dic(9;12)(p13;p12)[5]/46,XX[5]
28150	Male	65	UKALL60	95	NA	BCR-ABL1	Tyrosine kinase activating	✓					45,XY,add(3)(p21),add(6)(q21),-7,-9,-21,add(22)(q11),+2mar,inc[cp6]/46,XY[14]
28168	Male	65	UKALL14		Illumina	B-other	Standard risk	✓	✓	✓	✓		45,XY,inv(2)(p1?5q1?3),dic(9;12)(p13;p13)[10]/46,XY[1]
28182	Female	60	UKALL14	90	Illumina	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓	✓	46,XX,t(9;22)(q34.1;q11)[2]/46,idem,der(5)t(1;5)(q23;q21)[7]/46,XX[1]
28194	Male	66	UKALL60		NA	B-other	Standard risk	✓	✓				Failed
28196	Male	61	UKALL14	99	Illumina	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓		46,XY,add(9)(q34),der(17)t(17;22)(q21;q11),der(22)t(9;22)(q34;q11)[4]/46,XY,add(4)(q31),add(5)(q31),add(9)(q34),der(17)t(7;22)(q21;q11),der(22)t(9;22)(q34;q11)[6]
28235	Female	65	UKALL60	90	NA	CRLF2-r	Very high risk	✓	✓				46,XX,der(19)t(1;19)(q12;q13)[4]/46,XX[6]
28310	Female	66	UKALL60	36	NA	B-other	Standard risk	✓	✓				45~46,XX,add(9)(p13)[4]/45~46,sl,del(13)(q1?3q3?2)[3]/44~45,sdl1,i(17)(q10)[cp2]/46,XX[9]
28312	Female	67	UKALL60	94	NA	BCR-ABL1	Tyrosine kinase activating	✓					45,XX,t(9;22)(q34;q11.2),add(9)(p?21),-11,der(12)t(11;12)(q23;p13)[7]/46,XX[1]
28317	Male	80	UKALL60	72	NA	B-other	Standard risk	✓	✓				46,XY[20]
28334	Male	64	UKALL14	27	NA	HoTr	Very high risk	✓					39,XY,del(3)(q1?2),-4,-10,-13,-15,-17,-18,-20,-22,+mar[1]/67~69<4n>,XXYY,-2,-2,del(3q)x2,-4,-4,-5,-6,-7,-7,-9,-10,-11,-12,-13,-13,-14,-14,-15,-15,-17,-18,-19,-19,+1~5mar[cp4]/46,XY[5]
28335	Male	63	UKALL14		Illumina	B-other	Standard risk	✓		✓	✓	✓	Failed
28350	Female	62	UKALL14	72	Illumina	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓	✓	45,XX,-7,ins(9;?)(q13;?),t(9;22)(q34;q11.2)[9]/46,XX[6]
28361	Male	67	UKALL60	70	NA	HoTr	Very high risk	✓					36<2n>,XY,del(2)(q33q37),-3,-4,-5,-7,-9,-13,-15,-16,-17,-20[6]/46,XY[4]
28370	Male	81	UKALL60		NA	KMT2A-v	High risk	✓					45,X,-Y,t(11;19)(q23;p13.3)[9]/45,X,-Y[5]
28403	Male	71	UKALL60	92	NA	KMT2A-v	High risk	✓					47,XY,+X,t(4;11)(q21;q23)[3]/47,idem,del(17)(p11.2)[5]/47,idem,add(17)(p11.2)[2]
28404	Female	63	UKALL60	77	NA	HoTr	Very high risk	✓					66~68<3n>X,-X,-X,+1,-2,-3,-4,+5,+6,-7,+8,-9,+10,-12,-15,-16,-17,+18,+21,+21,+22,inc[cp8]/46,XX[2]
28406	Male	74	UKALL60	81	NA	HoTr	Very high risk	✓					65~67,XX,-Y,+2[2],-3[4],-4,-5,+6,-7,+8[4],-9,+10,+11[4],-13[3],-14,-15,der(16)t(11;16)(q1?2;p12)[3],-17,+19[4],-20,+21,+22[cp5]/64~65,XX,-Y,-3,-4,-5,+6,-7,+8,-9,+10,+11,-13,-14,-15,-16,der(16)t(11;16)(q1?2;p12)[3],-17,+19,-20,+21,+22[cp4]/44,X,-Y,der(13;14)(q10;q10)?c[10]/45,XY,der(13;14)(q10;q10)?c[1]
28456	Male	62	UKALL14	100	NA	B-other	Standard risk	✓					Failed
28581	Female	65	UKALL14	88	Illumina	KMT2A-v	High risk	✓		✓	✓	✓	47,XX,t(4;11)(q21;q23),+6[11]
28620	Male	60	UKALL14	91	NA	BCR-ABL1	Tyrosine kinase activating	✓					Failed
28644	Female	64	UKALL14	95	Illumina	HoTr	Very high risk	✓		✓			37<2n>,XX,-3,-4,-5,-7,-9,add(14)(q32),-15,-16,-17,-20[5]/68<3n>,XX,-X,-4,-5,-6,-7,+8,-9,+14,-15,-17,+18,+19,+21,+22,+mar[cp3]/46,XX[5]
28670	Female	61	UKALL14	94	Illumina	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓	✓	45,XX,t(2;7)(p1;p1),der(3)t(3;5)(q13;q15),-5,der(9)add(9)(p1)t(9;22)(q34;q11),add(11)(q15),add(12)(p1),der(22)t(9;22)(q34;q11)[4]/46,XX[6]
28905	Male	60	UKALL14	85	NA	B-other	Standard risk	✓	✓				46,XY[20]
28934	Female	60	UKALL14	90	Illumina	KMT2A-v	High risk	✓		✓	✓		46,XX,der(4)t(4;11)(q21;q23)ins(4;13)(q21;q1?q34),der(11)t(4;11)
28945	Female	64	UKALL14	89	NA	B-other	Standard risk	✓	✓				45,X,-X,add(9)(p2)[10]
29089	Female	60	UKALL14	90	Illumina	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓		46,XX,t(9;22)(q34;q11.2)[9]/46,XX[1]
29202	Male	61	UKALL14	99	NA	B-other	Standard risk	✓					45,XY,del(4)(q21q25),der(9)add(9)(p13)add(9)(q22),-16[10]
29407	Female	60	UKALL14	94	Illumina	HoTr	Very high risk	✓		✓		✓	31~35,X,-X,-2,dic(8;13)(q10;q10),+19,-20[cp3]/57~67,XX,+1,+1,+2,+4,+6,+6,dic(8;13)(q10;q10)x2,+10,+11,+11,+i(11)(q10),+12,+14,+14,+18,+18,+19,+19,+21,+21,+22,+22,+1~6mar[cp11]/46,XX[1]
29453	Male	63	UKALL14	60	NA	T-cell	Standard risk	✓					NDS
29454	Female	65	UKALL14	90	NA	B-other	Standard risk	✓					46,XX,del(9)(q13q22)[6]/46,XX[4]
29481	Female	69	UKALL60	7	NA	B-other	Standard risk	✓					46,XX[20]
29517	Male	65	UKALL14	92	NA	BCR-ABL1	Tyrosine kinase activating	✓					46,XY,t(9;22)(q34;q11.2),add(21)(p11)[5]/46,XY[5]
29519	Female	61	UKALL14	86	NA	B-other	Standard risk	✓					82~84,XXXX,+X,-3,-7,-7,-8,-9,-9,+12,-15,-15,-16,-17,-18,-20,-20,+21,+21[cp10]
29589	Male	61	UKALL14	82	Illumina	BCR-ABL1	Tyrosine kinase activating	✓		✓	✓		47,XY,+2,t(9;22)(q34;q11.2)[4]/48,XY,+2,t(9;22)(q34;q11.2),+der(22)t(9;22)(q34;q11.2)[9]/46,XY[7]
29655	Female	65	UKALL60	60	NA	BCR-ABL1	Tyrosine kinase activating	✓					Not reported
29710	Male	67	UKALL60	93	NA	B-other	Standard risk	✓	✓				49,XY,+8,+2mar[6]/46,XY[4]
29741	Male	77	UKALL60	77	NA	BCR-ABL1	Tyrosine kinase activating	✓					46,XY,t(9;22)(q34;q11.2)[1]/46,XY[12]
29808	Male	66	UKALL60	96	NA	IGH@-r	Standard risk	✓					46,XY,add(2)(q?37),add(8)(q13),add(14)(q32)[10]/46,XY[7]
29809	Male	63	UKALL60	64	NA	BCR-ABL1	Tyrosine kinase activating	✓					46,XX,t(9;22)(q34;q11.2)[5]/46,XX[5]
29848	Female	68	UKALL60	13	NA	B-other	Standard risk	✓					Failed

29849	Female	70	UKALL60	79	NA	HoTr	Very high risk	✓					39~40,XX-3,-4,-7,-9,-17,-20,?add(20)(q13.3),-22,i(22)(q10),+mar[cp7]/73~76<3n>XXX,+X,+1,-3,-4,+6,-7,+8,-9,+10,+12,+13,+14-17,?add(20)(q13.3),-22,i(22)(q10),+2~4mar[cp3]/109~110<5n>,XXXXX,+X,-3,-4,-4,-5,+6,+6,-7,-7,+8,-9,+10,-17,-17,-20,?add(20)(q13.3),?add(20)(q13.3),-22,-22,-22,i(22)(q10),i(22)(q10),+2~3mar[cp3]/46,XX[7]
29881	Male	63	UKALL60	90	NA	BCR-ABL1	Tyrosine kinase activating	✓					Not done
29882	Female	71	UKALL60	70	NA	HoTr	Very high risk	✓					63~67,XX,+X,+1,+1,+2,+4,+4,+6,+7,+8,+8,+10,+10,+11,+11,+12,+12,+14,+14,+21,+21,+22,+22[cp6]/46,XX[4]
29908	Female	62	UKALL14		Illumina	KMT2A-v	High risk	✓		✓		✓	46,XX,t(4;11)(q21;q23),inc[2]/46,XX[1]
29958	Male	79	UKALL60	45	NA	BCR-ABL1	Tyrosine kinase activating	✓					Not Done
30031	Female	73	UKALL60	90	NA	BCR-ABL1	Tyrosine kinase activating	✓					50,XX,+2,del(9)(p13p22),t(9;22)(q34;q11),+11,+21,+der(22)t(9;22)(q34;q11)[8]/46,XX[2]
30063	Male	69	UKALL60	85	NA	No data	Standard risk						Failed. arr(1-22XY)cx, (7)x1, (17)x1
30066	Male	63	UKALL14		NA	HeH	Standard risk	✓					47,XY,+8[4]/52,XY,+6,+7,+8,+12,+17,+22[6]
30085	Male	67	UKALL60	68	NA	ZNF384-r	Standard risk	✓	✓				46,XY[20]
30086	Female	69	UKALL60	90	NA	B-other	Standard risk	✓	✓				46,XX[?]
30102	Female	67	UKALL60	95	NA	CRLF2-r	Very high risk	✓	✓				46,XX,del(9)(p1p2)[9]/46,XX[1]
30103	Female	64	UKALL14		NA	BCR-ABL1	Tyrosine kinase activating	✓					46,XX,t(9;22)(q34;q11.2)[1]/46,idem,add(6)(q27),del(9)(p13)[4]/46,XX[3]
30175	Female	63	UKALL14		NA	B-other	Standard risk	✓					46,XX[16]
30236	Male	73	UKALL60	55	NA	T-cell	Standard risk	✓					45,XY,add(17)(p11.2)[3]/46,XY[17]
30237	Female	74	UKALL60	93	NA	B-other	Standard risk	✓					Failed. arr(1-22,X)x2
30297	Female	64	UKALL60	74	NA	CRLF2-r	Very high risk	✓	✓				46,XX,t(X;9)(p22;p13),der(15)t(1;15)(q21;p13)[cp8]/46,XX[4]
30298	Female	69	UKALL60	90	NA	B-other	Standard risk	✓					46,XX,der(7)ins(7;?)(q22;?)[7]/46,XX[3]
30299	Female	74	UKALL60		NA	CRLF2-r	Very high risk	✓	✓				Not reported
30300	Female	74	UKALL60	95	NA	KMT2A-v	High risk	✓					46,XX,t(4;11)(q21;23)[10]
30315	Female	69	UKALL60	83	NA	HoTr	Very high risk	✓					33~38,XX,-3,-7,-8,-13,-14,-15,-18[cp4]/46,XX[9]
30331	Female	77	UKALL60	92	NA	HoTr	Very high risk	✓					36~37,X,-X,-3,-4,-5,-7,-9,-13,-16,-17,-20,-21,+1~2mar[cp5]
30334	Male	60	UKALL14		NA	B-other	Standard risk	✓					46,XY[20]
30347	Male	70	UKALL60	50	NA	B-other	Standard risk	✓					46,XY[20]
30378	Male	71	UKALL60	43	NA	B-other	Standard risk	✓	✓				Fail
30389	Female	83	UKALL60	85	NA	B-other	Standard risk	✓					92<4n>,XXXX,-3,+12,+12,-17[3]/46,XX[7]
30390	Male	73	UKALL60	71	NA	HoTr	Very high risk	✓					70<3n>,XYY,+1,-3,-4,+5,+6,-7,+8,+11,-12,-13,+14,-15,-16,-17,+18,+20,+21[2]/46,XY[6]
30402	Female	62	UKALL60	90	NA	TCF3-PBX1	Standard risk	✓					46,XX,del(6)(q16q21)[4]/46,idem,der(19)t(1;19)(q23;p13.3)[4]/46,XX[2]
30403	Male	71	UKALL60		NA	B-other	Standard risk	✓					46,XY[20]
30419	Female	64	UKALL60		NA	B-other	Standard risk	✓					46,XX[12]
30426	Male	72	UKALL60		NA	B-other	Standard risk	✓					46,XY[5]
30428	Female	61	UKALL14		NA	HoTr	Very high risk	✓					60,XX,+1,+1,+4,+6,+8,+8,+11,+13,+18,+19,+21,+21+22,+22,inc[cp3]/46,XX[7]
30438	Male	81	UKALL60	91	NA	Complex	Very high risk	✓	✓				45,XY,add(1)(q3),add(2)(p1),-6,-7,add(9)(p2),add(11)(q21),add(12)(p13),del(13)(q12q14),add(16)(p13),+mar[10]
30476	Male	71	UKALL60	59	NA	B-other	Standard risk	✓					Failed
30487	Male	60	UKALL14		NA	IGH@-r	Standard risk	✓					47,XY,+X,t(14;19)(q32;q13)[8]/46,XY[2]
30521	Male	66	UKALL60	79	NA	BCR-ABL1	Tyrosine kinase activating	✓					46,XY,t(9;22)(q34;q11)[10]/46,XY[2]
30556	Male	75	UKALL60	95	NA	B-other	Standard risk	✓					47,XY,+5[2]
30557	Female	78	UKALL60	94	NA	BCR-ABL1	Tyrosine kinase activating	✓					46,XX,+1,t(9;22)(q34;q11.2),der(16)t(1;16)(q11;q11)[13]/46,XX[1]
30623	Male	64	UKALL14		NA	KMT2A-v	High risk	✓					46,XY,der(4)(?11qter->11q23::4p1?4->4q21::11q23->11qter),der(11)t(4;11)(q21;q23),add(15)(q2?2)[12]
30641	Male	62	UKALL60	85	NA	B-other	Standard risk	✓					46,XY,?del(9)(p21p21)[4]/46,XY[16]
30721	Female	61	UKALL14		NA	No data	Standard risk						54,+X,+X,+6,+6,+11,+11,der(11;21)(p10;q10)x2,+22,+22[8]/46,XX[2]
31085	Female	62	UKALL14		NA	No data	Standard risk						67<3n>,XX,-X,-1,-5,+6,-7,+8,-9,+12,-13,-15,-16,+19,+21,+21,+1~2mar[cp8]/46,XX[4]
31095	Male	64	UKALL14		NA	T-cell	Standard risk	✓					Fail
31145	Male	62	UKALL14		NA	BCR-ABL1	Tyrosine kinase activating	✓					46,XY,t(9;22)(q34;q11.2)[2]/44,XY,-7,der(9)t(7;9)(p13;p22)t(9;22),der(13)t(7;13)(q32;q14),-18,der(22)t(9;22)[7]/46,XY[1]

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			
BCR-ABL1	40% (31)	26% (55)	0.03
HoTr	12% (9)	13% (28)	0.84
KMT2A fusion	6% (5)	6% (12)	0.78
TCF3-PBX1	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)	*BCR-ABL1* (11), B-other (4)
gain of Ph*	12% (8)	*BCR-ABL1* (8)
gain 1q	10% (7)	B-other (4), *BCR-ABL1* (2), *TCF3-PBX1* (1)
-7	10% (7)	*BCR-ABL1* (5), B-other (2)
del(7p)	9% (6)	*BCR-ABL1* (4), B-other (2)
gain 21q	7% (5)	*BCR-ABL1* (2), B-other (3)
del(17p)	7% (5)	B-other (4), *BCR-ABL1* (1)
del(12p)	6% (4)	B-other (2), *BCR-ABL1* (1), T-ALL (1)
gain 14q	4% (3)	*BCR-ABL1* (3)
-9	4% (3)	*BCR-ABL1* (3)
+5	3% (2)	B-other (1), *BCR-ABL1* (1)
+2	3% (2)	*BCR-ABL1* (2)
+6	3% (2)	*BCR-ABL1* (1), *KMT2A-v* (1)
gain 8q	3% (2)	*BCR-ABL1* (1), B-other (1)
+11	3% (2)	B-other (1), *BCR-ABL1* (1)
del(13q)	3% (2)	*BCR-ABL1* (2)

Supplementary table S6. Characteristics of all *IKZF1* deletions

Patient	*IKZF1* deletion	Genetic subgroup
28670	ex.2-7	*BCR-ABL1*
25208	ex.2-7 and 2-8	*BCR-ABL1*
27026	ex.4-7	*BCR-ABL1*
26610	ex.4-7	*BCR-ABL1*
27043	ex.4-7	*BCR-ABL1*
29589	ex.2-7	*BCR-ABL1*
25247	ex.4-7	*BCR-ABL1*
25548	ex.4-7	*BCR-ABL1*
26660	ex.4-8	*BCR-ABL1*
27085	ex.2-7	*BCR-ABL1*
27754	ex.4-7	*BCR-ABL1*
28057	ex.4-7	*BCR-ABL1*
28182	ex.4-7	*BCR-ABL1*
24890	ex.4-7	B-other
25371	ex.2-7	*CRLF2-r*
25552	ex.4-7	*CRLF2-r*
25130	ex.2-8	*CRLF2-r*
25246	ex.4-8	*CRLF2-r*
28011	ex.4-7	*CRLF2-r*
28350	del(7p)/-7	*BCR-ABL1*
25953	del(7p)/-7	*BCR-ABL1*
26609	del(7p)/-7	*BCR-ABL1*
26682	del(7p)/-7	*BCR-ABL1*
27836	del(7p)/-7	*BCR-ABL1*
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	*BCR-ABL1*
25793	del(7p)/-7	*BCR-ABL1*
27585	del(7p)/-7	*BCR-ABL1*
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
LEMD3	25208	chr12:65,579,942-65,602,114	22172	Heterozygous	None
LEMD3	25130	chr12:65,579,942-65,597,922	17980	Heterozygous	None
LEMD3	28670	chr12:65,579,942-65,591,462	11520	Heterozygous	None
LEMD3	26660	chr12:65,579,942-65,608,678	28736	Heterozygous	ex. 2
LEMD3	25552	chr12:65,579,801-65,611,980	32179	Heterozygous	ex. 2-3
KDM6A	28011	chrX:44,810,083-44,867,059	56967	Hemizygous	ex. 3-4
KDM6A	29407	chrX:44,778,209-44,905,069	126860	Homozygous	ex. 3-8
KDM6A	25437	chrX:44,775,342-44,885,557	110215	Homozygous	ex. 3-6
KDM6A	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 hypodiplopidy/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	***IKZF1* ex.4-7 deletion**	**Other *IKZF1* 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