THE LANCET

Supplementary appendix

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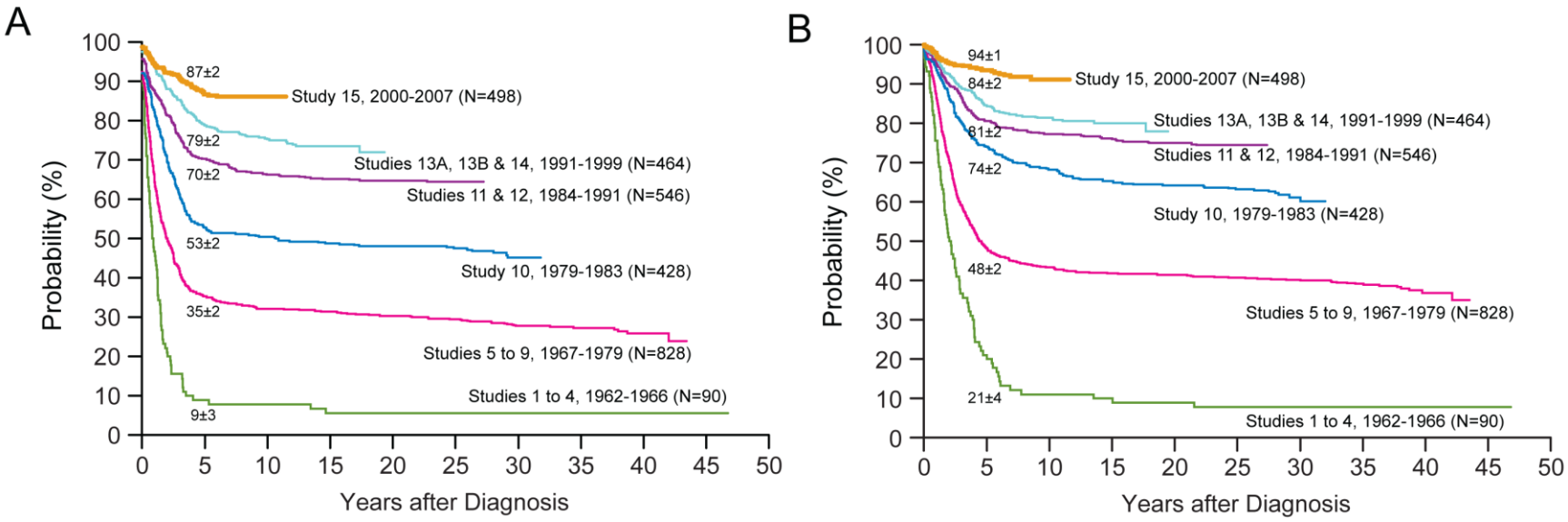


Web Figure 1. Kaplan–Meier estimates of event-free survival (A) and overall survival (B) in 2852 children with newly diagnosed acute lymphoblastic leukaemia treated in 15 consecutive Total studies at St. Jude Children's Research Hospital, 1962 to 2007. Five-year event-free and overall survival estimates (±SE) are shown on the respective curves.

Supplementary Table 1: Inherited gene variants and risk of childhood acute lymphoblastic leukaemia

Gene	Function	Risk allele frequency*	Odds ratio†‡	*P* value‡	References
IKZF1	Transcription factor (differentiation)	0.27	1.69	1.2×10^{-19}	[1-3]
ARID5B	Transcriptional regulator	0.34	1.65	6.69×10^{-19}	[1-3]
CEBPE	Transcription factor (differentiation)	0.52	1.34	2.88×10^{-7}	[1, 3]
CDKN2A (p16)	Negative cell cycle regulator	0.15	1.42	3.01×10^{-11}	[4]

*Frequency in the control (white, Caucasian) population. †These odds ratio values apply to both B and T lymphoblastic leukaemia, and to the main molecular subtypes of the former including *ETV6-RUNX1*$^{+}$ acute lymphoblastic leukaemia and hyperdiploid acute lymphoblastic leukaemia. The exception appears to be with *ARID5B* variants which predominantly impact on hyperdiploid B lymphoblastic leukaemia.[1, 2] ‡All odds ratios and *P* values were obtained from a single study,[1] although similar values have been described in other studies.[2, 3]

Table 2. Key genetic alterations in B lymphoblastic leukaemia, by gene (referenced version)

Gene	Alteration	Frequency	Pathway and consequences	Clinical relevance	References
PAX5	Focal deletions, translocations, sequence mutations	31.7%	Transcription factor needed for B-lymphoid development; mutations impair DNA binding and transcriptional activation	Not associated with adverse outcome	[5-7]
IKZF1	Focal deletions, sequence mutations	15% of paediatric cases More than 80% of *BCR-ABL1* cases and 66% of cases of chronic myeloid leukaemia in lymphoid blast crisis	Transcription factor needed for development of haemopoietic stem cells to lymphoid precursors; deletions and mutations result in loss of function or dominant negative isoforms.	Associated with poor outcomes	[5, 6, 8, 9]
		A third of cases of high-risk *BCR-ABL1*-negative disease		Tripling of cumulative incidence of relapse	[10-12]
	Inherited variants			Increased risk of developing disease	[1, 2]
JAK1, *JAK2*	Pseudokinase and kinase domain mutations	18-35% of Down's-syndrome-associated cases, 11% of high-risk *BCR-ABL1*-negative cases	Mutations cause constitutive JAK-STAT activation; transforms mouse Ba/F3-EpoR haemopoietic cell line		[13-16]
CRLF2	Rearrangement as *IGH@-CRLF2* or *P2RY8-CRLF2* resulting in overexpression	5-16% of paediatric and adult cases and >50% of cases associated with Down's syndrome	Associated with mutant *JAK* in as much as 50% of cases; *CRLF2* and *JAK* mutations cotransform in Ba/F3 cells, causing constitutive STAT activation		[17-20]
		14% of paediatric high-risk cases of B lymphoblastic leukaemia	Associated with *IKZF1* alteration and *JAK* mutations	Associated with poor outcome	[21, 22]
CREBBP	Focal deletion and sequence mutations	19% of relapsed cases of B lymphoblastic leukaemia*	Impaired histone acetylation and transcriptional regulation	Mutations selected for at relapse and associated with glucocorticoid resistance	[23, 24]

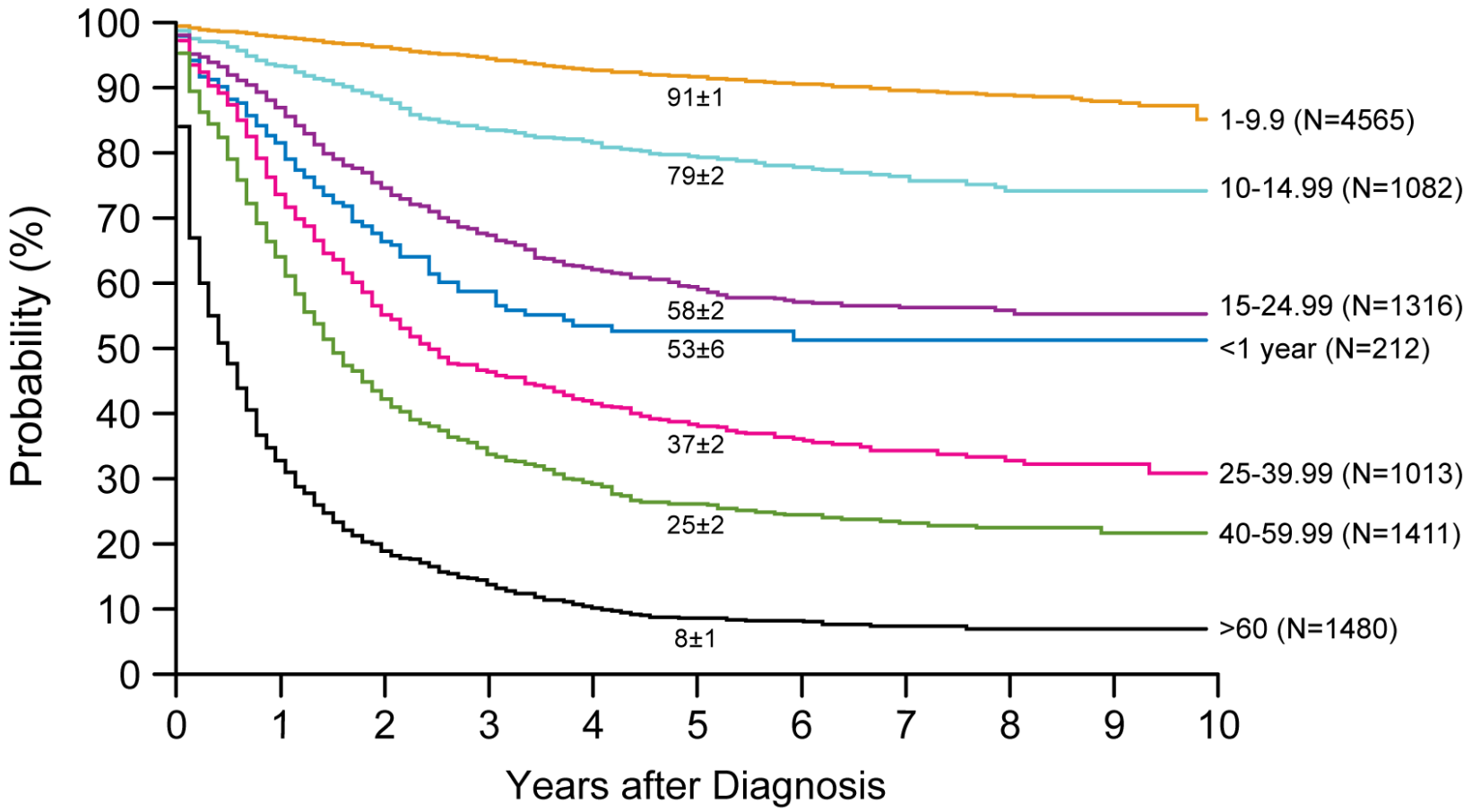
* Also mutated in non-Hodgkin lymphoma.

Supplementary Table 2: Clinical tests with prognostic and therapeutic implications

Test	Findings	Prognostic risk	Potential treatment*
At diagnosis			
Immunophenotyping	Early T cell precursor phenotype	High	AML-directed therapy, JAK inhibitor
	CRLF2 overexpression[†]	High[‡]	JAK inhibitor[§]
Cytogenetics/RT-PCR	Hyperdiploidy (>50 chromosomes)	Standard	
	t(12;21)(p13;q22)/*ETV6-RUNX1* (*TEL-AML1*)	Standard	
	Hypodiploidy (<44 chromosomes)	High	
	t(9;22)(q34;q11)/*BCR-ABL1*	High	ABL1 kinase inhibitor
	11q23/*MLL* gene rearrangement	High[#]	Epigenetic therapy (eg, DNA methyltransferase inhibitor, histone methyltransferase inhibitor, histone deacetylace inhibitor), FLT3-inhibitor
	iAMP21	High[¶]	
	t(17;19)(q22;p13)/*TCF3-HLF*	High	
Molecular analysis[†]	*IKZF1* alterations	High	ABL1 kinase, PDGFRB, or JAK inhibitor
	CRLF2 rearrangement	High[‡]	JAK inhibitor[§]
	JAK1 or *JAK2* mutation	High	JAK inhibitor
	BCR-ABL1-like phenotype	High	ABL1 kinase, PDGFRB, or JAK inhibitor
	NUP214-ABL1	High	ABL1 kinase inhibitor
	BCR-JAK2	High	JAK inhibitor
	IL7R mutation	High	JAK inhibitor
	CREBBP mutation	High	Histone deacetylase inhibitor
	TP53 mutation	High	
During treatment			
Minimal residual disease	Positive	High	

*Clinical trials have not proven the efficacy of any therapies except ABL1 kinase inhibitor in acute lymphoblastic leukaemia with t(9;22)(q34;q11)/*BCR-ABL1*. [†]These tests have not been incorporated into routine clinical practice. [‡]The subsets with *IKZF1* alteration and/or BCR-ABL1-like gene expression profile. [§]The subsets with *JAK* mutations. [#]Especially in infants and adult patients. [¶]Poor outcome when treated on standard-risk regimens.

AML, acute myeloid leukaemia; JAK, Janus kinase; iAMP21, intrachromosomal amplification of chromosome 21; PDGFRB, platelet-derived growth factor receptor, beta polypeptide; RT-PCR, reverse-transcriptase polymerase chain reaction.



Web Figure 2. Kaplan-Meier estimates of overall survival according to age at diagnosis in 11079 patients with acute lymphoblastic leukaemia newly diagnosed after January 1, 2000 who were registered in the Surveillance, Epidemiology and End Results (SEER) Program of the United States National Cancer Institute. Age in years is shown at right. Five-year overall survival estimates (±SE) are listed on the respective curves.

Supplementary Table 3: Antileukaemic drugs in current clinical trials

Class	Agent	Target	Indication
Purine nucleoside analogue			
	Clofarabine[25]	Ribonucleotide reductase; DNA polymerase; mitochondria	All ALL
	Nelarabine[26]	Ribonucleotide reductase; DNA synthesis	T-ALL
	Forodesine	Purine nucleoside phosphorylase	T-ALL
Vinca alkaloid			
	Vincristine sulfate liposome[27]	Tubulin	All ALL
Kinase inhibitor			
ABL1 kinase inhibitor			
	Dasatinib;[28] Nilotinib;[29] Imatinib;[30] Ponatinib	ABL1 kinase; platelet-derived growth factor receptor B	*BCR-ABL1*-positive ALL; *BCR-ABL1*-like ALL (eg, *NUP214-ABL1*)
Aurora kinase inhibitor			
	Alisertib	Aurora A kinase	*BCR-ABL1*-positive ALL
Janus kinase (JAK) inhibitor			
	Ruxolitinib; TG101348; CYT387	JAK	JAK-mutated ALL; *BCR-ABL1*-like ALL (eg, *BCR-JAK2*; mutated *IL7R*)
Tyrosine kinase inhibitor			
	Lestaurtinib; Midostaurin; Sorafenib; Quizartinib; Tandutinib; Sunitinib	FMS-like tyrosine kinase 3	*MLL*-rearranged ALL; hyperdiploid ALL
Other molecular or signaling inhibitor			
Proteasome inhibitor			
	Bortezomib[31]	Ubiquitin-proteasome pathway	All ALL
Mammalian target of rapamycin (mTOR) inhibitor			
	Sirolimus; Temsirolimus; Everolimus	mTOR	All ALL
Farnesyltransferase inhibitor			
	Tipifarnib; Lonafarnib	Ras, lamin A	All ALL
γ-Secreatase inhibitor			
	RO4929097	γ-Secretase	T-ALL
Angiogenesis inhibitor			
	Bevacizumab	Vascular endothelial growth factor	All ALL

Apoptosis inducer		
Obatoclax; Oblimersen	Bcl-2	All ALL
Chemokine receptor (CXCR4) antagonist		
Plerixafor	CXCL12 (SDF1)/CXCR4 axis	All ALL
Epigenetic therapy		
DNA methyltransferase inhibitor		
Azacitidine; Decitabine	DNA methyltransferase	All ALL
Histone methyltransferase inhibitor		
EPZ-5676	DOT1L	*MLL*-rearranged ALL
Histone deacetylase inhibitor		
Vorinostat; Panobinostat; Depsipeptide; Valproic acid	Histone deacetylase	All ALL
Immune therapy		
Monoclonal antibody		
Blinatumomab[32]	CD19 (engages CD3 T cells)	CD19-positive ALL
SAR3419	CD19	CD19-positive ALL
DT2219ARL	CD19 and 22	CD19/CD22-positive ALL
Rituximab[33]	CD20	CD20-positive ALL
Epratuzumab;[34] Moxetumomab; Inotuzumab ozogamicin[35]	CD22	CD22-positive ALL
Alemtuzumab[36]	CD52	CD52-positive ALL
Cellular therapy		
Natural killer cells	Killer immunoglobulin-like receptor (KIR)-ligand	Donor KIR-recipient ligand mismatch
T cells with CD19-specific chimeric antigen receptor	CD19	CD19-positive ALL

ALL, acute lymphoblastic leukaemia

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