

Outcomes of Childhood Noninfant Acute Lymphoblastic Leukemia With 11q23/*KMT2A* Rearrangements in a Modern Therapy Era: A Retrospective International Study

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abstract

PURPOSE We aimed to study prognostic factors and efficacy of allogeneic hematopoietic stem-cell transplantation (allo-HSCT) in first remission of patients with noninfant childhood acute lymphoblastic leukemia (ALL) with 11q23/*KMT2A* rearrangements treated with chemotherapy regimens between 1995 and 2010.

PATIENTS AND METHODS Data were retrospectively retrieved from 629 patients with 11q23/*KMT2A*-rearranged ALL from 17 members of the Ponte-di-Legno Childhood ALL Working Group. Clinical and biologic characteristics, early response assessed by minimal residual disease at the end of induction (EOI) therapy, and allo-HSCT were analyzed for their impact on outcomes.

RESULTS A specific 11q23/*KMT2A* translocation partner gene was identified in 84.3% of patients, with the most frequent translocations being t(4;11)(q21;q23) (n = 273; 51.5%), t(11;19)(q23;p13.3) (n = 106; 20.0%), t(9;11)(p21_22;q23) (n = 76; 14.3%), t(6;11)(q27;q23) (n = 20; 3.8%), and t(10;11)(p12;q23) (n = 14; 2.6%); 41 patients (7.7%) had less frequently identified translocation partner genes. Patient characteristics and early response varied among subgroups, indicating large biologic heterogeneity and diversity in therapy sensitivity among 11q23/*KMT2A*-rearranged ALL. The EOI remission rate was 93.2%, and the 5-year event-free survival (EFS) for the entire cohort was 69.1% ± 1.9%, with a range from 41.7% ± 17.3% for patients with t(9;11)-positive T-ALL (n = 9) and 64.8% ± 3.0% for patients with t(4;11)-positive B-ALL (n = 266) to 91.2% ± 4.9% for patients with t(11;19)-positive T-ALL (n = 34). Low EOI minimal residual disease was associated with favorable EFS, and induction failure was particularly predictive of nonresponse to further therapy and relapse and poor EFS. In addition, EFS was not improved by allo-HSCT compared with chemotherapy only in patients with both t(4;11)-positive B-ALL (n = 64 v 51; P = .10) and 11q23/*KMT2A*-rearranged T-ALL (n = 16 v 10; P = .69).

CONCLUSION Compared with historical data, prognosis of patients with noninfant 11q23/*KMT2A*-rearranged ALL has improved, but allo-HSCT failed to affect outcome. Targeted therapies are needed to reduce relapse and treatment-related mortality rates.

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ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Contemporary risk-adapted treatment on the basis of genetics and minimal residual disease (MRD) has improved survival rates to > 90% in childhood acute lymphoblastic leukemia (ALL).^{1,2} Rearrangements of the *KMT2A* gene (formerly *MLL*), involving > 100 translocation partner genes (TPGs), are detected in approximately 5% of childhood ALL.³⁻⁹ Although *KMT2A* rearrangements confer an inferior outcome in infant ALL, their prognostic impact in children age ≥ 1 year is less clear.⁹⁻¹⁶ In fact, there is no consensus among study groups regarding risk stratification,

significance of different TPGs, and indication for allogeneic hematopoietic stem-cell transplantation (allo-HSCT) in first complete remission (CR1). In our previous study (1983-1994), we found that noninfants with *KMT2A*-rearranged ALL had a superior outcome compared with their infant counterparts irrespective of the type of *KMT2A* rearrangement.^{13,14} However, small numbers precluded meaningful analyses of allo-HSCT, and the impact of MRD was not assessed.^{13,14} To address these issues, we initiated this study of noninfants with 11q23/*KMT2A*-rearranged ALL, treated on contemporary, mostly

CONTEXT

Key Objective

Although 11q23/*KMT2A* rearrangements have poor outcomes in infant acute lymphoblastic leukemia (ALL), their impact in noninfants is unclear. This international collaboration addressed outcomes and prognostic factors of noninfant 11q23/*KMT2A*-rearranged ALL treated with contemporary protocols, including allogeneic hematopoietic stem-cell transplantation for selected subgroups.

Knowledge Generated

This study demonstrated great clinical heterogeneity among childhood noninfant 11q23/*KMT2A*-rearranged ALL. Low end of induction minimal residual disease was associated with favorable event-free survival (EFS), and induction failure was predictive of resistant disease, relapse, and poor EFS. In addition, EFS was not improved by transplantation compared with chemotherapy alone in patients with both t(4;11)/*KMT2A::AFF1*-positive B-ALL and 11q23/*KMT2A*-rearranged T-ALL.

Relevance (S. Bhatia)

Allogeneic hematopoietic stem-cell transplantation does not influence outcomes in patients with noninfant 11q23/*KMT2A*-rearranged ALL, presenting the need for alternative targeted therapies.*

*Relevance section written by JCO Associate Editor Smita Bhatia, MD, MPH, FASCO.

MRD-based protocols, including allo-HSCT in CR1 for selected patient cohorts.¹⁷⁻²⁰

PATIENTS AND METHODS

Data on characteristics, treatment, response including MRD, allo-HSCT, and outcomes of patients with 11q23/*KMT2A*-rearranged ALL age 1-18 years and treated between 1995 and 2010 were collected from 17 members of the Ponte-di-Legno Childhood ALL Group (Data Supplement, online only). 11q23/*KMT2A* rearrangements were defined by an 11q23-involving chromosomal aberration detected by conventional cytogenetics and/or *KMT2A*-split signal fluorescence in situ hybridization analyses and/or different polymerase chain reaction–based methodologies and/or Southern blots.^{4,5,7,21-23} The TPG was defined by the most informative method. Patients with 11q23/*KMT2A* deletions were excluded.^{13,14,24-26}

Diagnosis was performed according to standard criteria.^{8,27} CR was defined as < 5% blasts in bone marrow and no extramedullary disease. Detection of MRD, on the basis of either immunoglobulin and T-cell receptor gene rearrangements or flow cytometry, was performed at the end of induction (EOI).²⁸⁻³⁰

Written informed consent was obtained from legal guardian(s) or patients, as appropriate. Trials and registries were conducted according to the Declaration of Helsinki and approval of local ethics committees. For nontrial/nonregistry patients, retrospective data collection was performed with institutional review board approval.

Statistical Analysis

Event-free survival (EFS) was calculated from the date of diagnosis to the date of first event (resistant disease, relapse, second malignant neoplasm, and death) and

censored at the last follow-up for patients without events. Overall survival (OS) was defined as the time from diagnosis to death from any cause or last follow-up. EFS and OS curves were estimated by the Kaplan-Meier method with standard errors calculated by the Greenwood formula and compared by the log-rank test. For allo-HSCT analysis, Kaplan-Meier curves were adjusted to account for the waiting time to allo-HSCT. The influence of allo-HSCT was also analyzed with the inclusion of a time-dependent variable in Cox models and the Mantel-Byar test. Cumulative incidence functions for competing events were constructed by the method of Kalbfleisch and Prentice, including Gray's test. The Cox proportional hazard model was used for multivariable analyses.

RESULTS

Patients With 11q23/*KMT2A* Rearrangements

Among the 686 patients selected, 57 were excluded (Data Supplement). Therapies are shown in the Data Supplement.^{10,11,31-63} The male:female ratio was 1:1; the median age was 4.7 years, and the median leukocyte count was $82.9 \times 10^9/L$; 535 patients (85%) had B-ALL, and 82 (13%) had T-ALL (Table 1 and Data Supplement). EOI MRD was < 0.05% in 56%, 0.05 to < 0.5% in 23%, and $\geq 0.5\%$ in 21% of patients (Table 1).

Among the 619 patients with EOI status data, four (0.6%) died during induction and 38 (6.1%) had induction failure (IF; 19 subsequently achieved CR); thus, the CR rate at EOI was 93.2% and the ultimate CR rate was 96.2%. With a median follow-up of 5.8 years (range, 0.1-17.5 years), the 5-year EFS probability (5y-pEFS) of the total cohort was $69.1\% \pm 1.9\%$ and the 5-year OS probability (5y-pOS) was $76.6\% \pm 1.7\%$. The 5-year probability of cumulative incidence of resistance or relapse (5y-pCIRR) was $22.4\% \pm 1.7\%$ (resistance,

TABLE 1. Characteristics, Treatment Response, and Outcomes of the Entire Cohort With 11q23 Rearrangements and by the Specific Translocations t(4;11), t(11;19), t(9;11), t(6;11), and t(10;11)

Parameter	All 11q23-Positive Patients		t(4;11)-Positive Patients		t(11;19)-Positive Patients				t(9;11)-Positive Patients				t(6;11)-Positive Patients		t(10;11)-Positive Patients	
	No.	%	B-ALL		B-ALL		T-ALL		B-ALL		T-ALL		T-ALL		B-ALL	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
All	629	100	266	100	70	100	34	100	65	100	9	100	19	100	14	100
Therapy era																
1995-1999	121	19	70	26	10	14	8	24	7	11	2	22	3	16	2	14
2000-2004	171	27	67	25	15	21	14	41	23	35	2	22	7	37	2	14
2005-2010	337	54	129	48	45	64	12	35	35	54	5	56	9	47	10	71
Sex																
Male	314	50	123	46	32	46	22	65	37	57	3	33	8	42	7	50
Female	315	50	143	54	38	54	12	35	28	43	6	67	11	58	7	50
Age, years																
Median	4.7		9.2		2.3		9.0		1.8		3.4		10.6		1.6	
Range	1.0-17.6		1.0-17.7		1.0-16.1		2.4-16.8		1.0-13.9		1.1-13.3		2.1-17.8		1.0-5.9	
1- < 2	185	29	47	18	32	30	0	0	35	54	3	33	0	0	9	64
2- < 6	158	25	52	20	14	23	9	26	27	42	5	56	3	16	5	36
6- < 10	79	13	43	16	5	14	10	29	2	3	0	0	6	32	0	0
10- < 15	144	23	84	32	16	27	12	35	1	2	1	11	6	32	0	0
≥ 15	63	10	40	15	3	6	3	9	0	0	0	0	4	21	0	0
Leukocyte count (× 10 ⁹ /L)																
Median	82.9		173.5		43.1		144.6		31.5		18.4		24.4		20.5	
Range	0.5-1,148.0		1.0-1,148.0		1.0-1,132.0		6.7-496.0		0.5-684.0		2.0-256.0		2.8-588.0		5.1-288.4	
< 100.0	349	55	87	33	49	70	16	47	48	74	7	78	17	89	13	93
≥ 100.0	280	45	179	67	21	30	18	53	17	26	2	22	2	11	1	7
Immunophenotype																
B-lineage	535	85	266	100	70	100			65	100					14	100
T-lineage	82	13					34	100			9	100	19	100		
Others/unknown	13	2														
Initial CNS involvement																
Yes	37	6	21	8	3	4	2	6	5	8	2	22	0	0	0	0
No	576	94	241	92	65	96	31	94	57	92	7	78	19	100	13	100
Prednisone response																
Available	247	39	110	41	31	44	16	47	23	65	3	33	7	35	6	43
GPR	196	79	90	82	31	100	4	25	19	83	1	33	5	71	5	83
PPR	51	21	22	18	0	0	12	75	4	17	2	67	2	29	1	17

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TABLE 1. Characteristics, Treatment Response, and Outcomes of the Entire Cohort With 11q23 Rearrangements and by the Specific Translocations t(4;11), t(11;19), t(9;11), t(6;11), and t(10;11) (continued)

Parameter	All 11q23-Positive Patients		t(4;11)-Positive Patients		t(11;19)-Positive Patients				t(9;11)-Positive Patients				t(6;11)-Positive Patients		t(10;11)-Positive Patients	
	No.	%	B-ALL		B-ALL		T-ALL		B-ALL		T-ALL		T-ALL		B-ALL	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
BM response day 15																
Available	347	55	156	59	39	56	22	65	36	55	4	44	11	58	6	43
< 5% blasts	230	66	109	70	32	82	8	36	27	75	0	0	5	45	4	67
≥ 5%-24% blasts	65	19	31	20	7	18	1	5	8	22	4	100	1	9	1	17
≥ 25% blasts	52	15	16	11	0	0	13	59	1	3	0	0	5	45	1	17
Remission status at EOI																
Available ^a	615	98	259	97	69	99	34	100	63	97	9	100	18	95	14	100
CR	577	94	247	95	67	97	30	88	62	98	8	89	14	78	13	93
Induction failure	38	6	12	5	2	3	4	12	1	2	1	11	4	22	1	7
MRD at EOI																
Available	331	53	128	48	39	56	10	29	38	58	6	67	7	37	12	86
< 0.5%	259	78	93	73	37	95	5	50	36	95	3	50	7	100	10	83
≥ 0.5%	69	21	34	27	1	3	5	50	2	5	3	50	0	0	2	17
Not classifiable ^b	3	1	1	1	1	3	0	0	0	0	0	0	0	0	0	0
MRD at EO1																
Available	331	53	126	47	39	56	10	29	38	43	6	67	7	37	12	86
< 0.05%	186	56	64	51	27	69	3	30	24	63	1	17	5	71	9	75
≥ 0.05%	122	37	59	47	5	13	7	70	11	29	5	83	2	29	2	17
Not classifiable ^b	23	7	5	4	7	18	0	0	3	8	0	0	0	0	1	8
Eligibility for allo-HSCT																
Available ^c	386	61	174	65	41	59	26	76	38	58	7	78	15	79	8	57
Indication	247	64	138	79	18	44	16	62	20	53	7	100	11	73	2	25
No indication	139	36	36	21	23	56	10	38	18	47	0	0	4	27	6	75
allo-HSCT in CR1	107	28	65	37	7	17	10	38	7	18	2	29	5	33	0	0
With indication ^d	102	95	64	98	7	100	8	80	6	86	1	100	5	100	0	0
No/unknown indication ^e	5	5	1	1	0	0	2	20	1	14	1	0	0	0	0	0
Outcomes																
5y-pEFS	193	69.1 (1.9)	92	64.8 (3.0)	19	73.5 (5.4)	3	91.2 (4.9)	19	71.8 (5.7)	5	41.7 (17.3)	6	68.4 (10.7)	3	77.9 (11.3)
5y-pOS	147	76.6 (1.7)	80	70.0 (2.9)	10	84.9 (4.4)	1	97.1 (2.9)	14	81.4 (4.9)	4	53.3 (17.3)	5	72.4 (10.6)	1	92.9 (6.9)
Events																
Death before CR	10	1.6 (0.5)	5	1.9 (0.8)	—	—	—	—	1	1.5 (1.5)	1	11.1 (11.1)	1	5.3 (5.3)	—	—
Resistance to therapy	14	2.2 (0.6)	2	0.8 (0.5)	1	1.4 (1.4)	1	2.9 (2.9)	—	—	—	—	1	5.3 (5.3)	1	7.1 (7.1)

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TABLE 1. Characteristics, Treatment Response, and Outcomes of the Entire Cohort With 11q23 Rearrangements and by the Specific Translocations t(4;11), t(11;19), t(9;11), t(6;11), and t(10;11) (continued)

Parameter	All 11q23-Positive Patients		t(4;11)-Positive Patients		t(11;19)-Positive Patients				t(9;11)-Positive Patients				t(6;11)-Positive Patients		t(10;11)-Positive Patients	
	No.	%	B-ALL		B-ALL		T-ALL		B-ALL		T-ALL		T-ALL		B-ALL	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Death in CR1	39	6.2 (1.0)	19	7.2 (1.6)	4	5.9 (2.9)	1	2.9 (2.9)	5	7.7 (3.3)	2	22.2 (15.1)	1	5.3 (5.3)	—	—
Related to allo-HSCT ^{de}	14	2.2 (0.6)	7	2.7 (1.0)	1	1.5 (1.5)	1	2.9 (2.9)	1	1.5 (1.5)	1	11.1 (11.1)	—	—	—	—
Others	25	4.0 (0.8)	12	4.5 (1.3)	3	4.3 (2.5)	—	—	4	6.2 (3.0)	1	11.1 (11.1)	1	5.3 (5.3)	—	—
Relapse	125	20.2 (1.6)	63	24.2 (2.7)	14	19.2 (4.8)	1	2.9 (2.9)	12	19.0 (5.0)	2	25.0 (17.3)	3	15.8 (8.7)	2	14.9 (10.2)
Isolated BM	82	13.1 (1.4)	45	20.7 (2.5)	7	8.6 (3.4)	1	2.9 (2.9)	4	6.2 (3.0)	1	11.1 (11.2)	2	10.5 (7.3)	1	7.8 (7.8)
Isolated CNS	12	1.9 (0.6)	2	0.8 (0.5)	3	4.4 (2.5)	—	—	3	4.6 (2.6)	—	—	—	—	1	7.1 (7.2)
Isolated testes	11	1.8 (0.5)	3	1.2 (0.7)	3	4.7 (2.7)	—	—	2	3.1 (2.2)	—	—	—	—	—	—
Combined BM/CNS	9	1.5 (0.5)	—	—	1	1.5 (1.5)	—	—	2	3.5 (2.5)	—	—	—	—	—	—
Combined BM/others (without CNS)	5	0.8 (0.4)	2	0.8 (0.6)	—	—	—	—	—	—	—	—	—	—	—	—
Other relapse sites	6	1.0 (0.4)	2	0.8 (0.5)	—	—	—	—	1	1.6 (1.6)	1	13.9 (14.6)	1	5.3 (5.3)	—	—
Secondary neoplasms	5 ^h	1.1 (0.3)	3	1.1 (0.1)	—	—	—	—	1	2.9 (3.0)	—	—	—	—	—	—

Abbreviations: 5y-pEFS, probability of 5-year event-free survival; 5y-pOS, probability of 5-year overall survival; ALL, acute lymphoblastic leukemia; allo-HSCT, allogeneic hematopoietic stem-cell transplantation; BM, bone marrow; CNS, central nervous system; COG, Children's Oncology Group; CR, complete remission; CR1, first complete remission; EOJ, end of induction; GPR, good prednisone response; MRD, minimal residual disease; PPR, poor prednisone response.

^aDeath in induction before CR: n = 4; CR status at EOJ not available: n = 10.

^bSemiquantitative MRD results that could not be assigned to either category with the cutoff value applied.

^cInformation on eligibility for allo-HSCT was not available for the following protocols: COG: AALL0232 and AALL0331; DFCI: 00001 and 05001; FRALLE: F2000; NOPHO: NOPHO 2000 and NOPHO 92; and SJCRH: Total XIIIIB/BH, Total XV, and Total XVI.

^dHLA-matched donor, n = 59; HLA-mismatched donor, n = 14; and unknown HLA compatibility, n = 29.

^eHLA-matched donor, n = 4; unknown HLA compatibility, n = 1.

^fUnless indicated otherwise, the data refer to patients with available information on the respective criteria.

^gCumulative incidences (standard error in brackets) are indicated at 5 years except for the secondary neoplasms that were calculated at 10 years.

^hAcute myeloid/myelomonocytic leukemia, n = 2; renal cell carcinoma, n = 1; melanoma, n = 1; and CNS tumor, n = 1.

2.2% ± 0.6%; relapse, 20.2% ± 1.6%). Two thirds of relapses were isolated bone marrow relapses (5y-CI, 13.1% ± 1.4%); 5y-CI rates of isolated testicular, isolated central nervous system, or combined central nervous system relapse were 3.6% ± 1.1%, 1.8% ± 0.5%, and 1.5% ± 0.5%, respectively. The 5y-CI of death in CR1 was 6.2% ± 1.0%; approximately one third were allo-HSCT-related (14 of 39; 36%; [Table 1](#) and [Figs 1A-1C](#)). Five patients developed a second malignant neoplasm as a first event (10-year cumulative incidence, 1.9% ± 0.5%).

A specific TPG was reported in 530 of 629 patients (84.3%), with the most frequent translocations being t(4;11)(51.5%), t(11;19)(20.0%), t(9;11)(14.3%), t(6;11)(3.8%), and t(10;11)(2.6%; [Table 1](#)); 7.7% had other TPGs (Data Supplement). Some TPGs were lineage-restricted (t(4;11): 266 of 267 B-ALL; t(10;11): 14 of 14 B-ALL; t(6;11): 19 of 20 T-ALL), whereas others were variable (t(11;19): 70 of 104 B-ALL; t(9;11): 65 of 74 B-ALL; [Table 1](#)).

t(4;11)(q21;q23)/*KMT2A::AFF1*. Patients with t(4;11)-positive ALL were significantly older with 46.6% age ≥ 10 years compared with 13.3% of other patients with 11q23/*KMT2A*-rearranged B-ALL ($P < .001$), with age peaks in early childhood and adolescence ([Table 1](#) and Data Supplement). The male:female ratio showed a female preponderance in younger patients (< 10 years 0.71, ≥ 10 years 1.07). Patients with t(4;11)-positive B-ALL had leukocyte counts ≥ 100 × 10⁹/L more often than other patients with 11q23/*KMT2A*-rearranged B-ALL (67.3% v 26.7%; $P < .001$), which was more pronounced in adolescents (< 10 years 56.3%, ≥ 10 years 79.8%).

Consistent with their inferior early response, t(4;11)-positive patients had a worse 5y-pEFS (64.6% ± 2.9%) and 5y-pOS (70.0% ± 2.8%) and higher 5y-pCIRR (24.9% ± 2.7%) compared with other patients with 11q23-rearranged B-ALL (73.5% ± 3.3%, $P = .039$; 84.5% ± 2.7%, $P < .001$; 19.4% ± 3.0%, $P = .13$, respectively; [Table 1](#) and [Figs 1D-1F](#)). Survival postrelapse was particularly poor in t(4;11)-positive B-ALL with a 5y-pOS of 12.9% ± 4.5% (n = 63, 53 deaths) compared with 38.1% ± 11.4% in other 11q23-rearranged B-ALL (n = 32, 16 deaths; $P = .0011$; Data Supplement).

t(11;19)(q23;p13.3)/*KMT2A::MLLT1*. There was a higher proportion of patients with leukocyte counts ≥ 100 × 10⁹/L at presentation in patients with t(11;19)-positive T-ALL (n = 34) compared with patients with B-ALL (n = 70; 52.9% v 30.0%; $P = .023$, [Table 1](#)). Age distribution also differed significantly ([Table 1](#) and Data Supplement). Response to induction therapy was poor in patients with t(11;19)-positive T-ALL ([Table 1](#)) despite their excellent outcome: 5y-pEFS 91.2% ± 4.9%, 5y-pOS 97.1% ± 2.9%, and 5y-pCIRR 5.9% ± 4.1% v 73.5% ± 5.4% ($P = .032$), 84.9% ± 4.4% ($P = .076$), and 20.6% ± 5.0% ($P = .04$), respectively, in those with t(11;19)-positive B-ALL ([Table 1](#) and [Figs 1D-1I](#)).

Comparison of patients with t(11;19)-positive B-ALL with patients with t(4;11)-positive B-ALL revealed similar age

peaks in early childhood and adolescence (Data Supplement). Patients with t(11;19)-positive B-ALL had significantly less hyperleukocytosis ($P < .001$) and better early response than patients with t(4;11)-positive B-ALL ([Table 1](#)). Although not translating into a lower rate of resistance/relapse ($P = .47$), EFS tended to be higher ($P = .14$) and OS was significantly better ($P = .007$) in patients with t(11;19)-positive than in patients with t(4;11)-positive B-ALL ([Figs 1D-1F](#)).

t(9;11)(p21-q23)/*KMT2A::MLLT3*. Nine patients with t(9;11)-positive T-ALL had inferior EOI MRD results and worse 5y-pEFS (41.7% ± 17.3%) and 5y-pOS (53.3% ± 17.3%) rates compared with the 65 patients with t(9;11)-positive B-ALL (71.8% ± 5.7%, $P = .022$; 81.4% ± 4.9%, $P = .044$; [Table 1](#) and [1D-1E](#) and [1G-1H](#)). However, the 5y-pCIRR (25.0% ± 17.3% v 19.0% ± 5.0%) was not significantly different ($P = .67$) between the two cohorts ([Table 1](#) and [Fig 1F/1I](#)).

The age distribution of t(9;11)-positive B-ALL was different from that of patients with t(4;11)-positive B-ALL, with 83.1% and 23.7% of patients age < 3 years, respectively ($P < .001$; Data Supplement). Patients with t(9;11)-positive ALL were significantly less often to have leukocyte counts ≥ 100 × 10⁹/L compared with those with t(4;11)-positive B-ALL (26.2% v 67.3%; $P < .001$, [Table 1](#)). EOI MRD was significantly lower in t(9;11)-positive patients compared with patients with t(4;11)-positive B-ALL (MRD: < v ≥ 0.5%; $P = .005$, [Table 1](#)). EFS, OS, and CIRR of patients with t(9;11)-positive ALL were superior to those with t(4;11)-positive B-ALL although the differences were not significant ([Figs 1D-1F](#)).

t(6;11)(q27;q23)/*KMT2A::MLLT4*. This small group comprised only 19 patients with T-ALL who were distributed across all ages (Data Supplement). Only 10.5% had leukocyte counts of ≥ 100 × 10⁹/L compared with 22.2% in patients with t(9;11)-positive T-ALL and 52.9% in patients with t(11;19)-positive T-ALL ($P = .006$, [Table 1](#)).

The IF rate was 22.2%, the 5y-pEFS was 68.4% ± 10.7%, the 5y-pOS was 72.4% ± 10.6%, and the 5y-pCIRR was 21.1% ± 9.6% ([Table 1](#) and [Figs 1G-1I](#)). These outcomes were significantly inferior to those with t(11;19)-positive T-ALL ($P = .030$, .0083, .10), but EFS and OS were superior to those with t(9;11)-positive T-ALL, although not statistically significant ($P = .22$, .31; [Table 1](#) and [Figs 1G-1I](#)).

t(10;11)(p12;q23)/*KMT2A::MLLT10*. All 14 t(10;11)-positive patients were age < 6 years, with 64.3% age < 2 years, and therefore, younger than patients with t(4;11)-positive B-ALL ($P < .001$; Data Supplement). Only 7.1% had leukocyte counts ≥ 100 × 10⁹/L, which was lower than that in patients with t(4;11)-positive B-ALL ($P < .001$; [Table 1](#)). Patients with t(10;11)-positive B-ALL had a 5y-pEFS of 77.9% ± 11.3%, a 5y-pOS of 92.9% ± 6.9%, and a 5y-pCIRR of 22.1% ± 11.8%, for which EFS and OS were not significantly different from those in patients with t(4;11)-positive B-ALL (EFS: $P = .14$; OS: $P = .083$; [Table 1](#) and [Figs 1D-1F](#)).

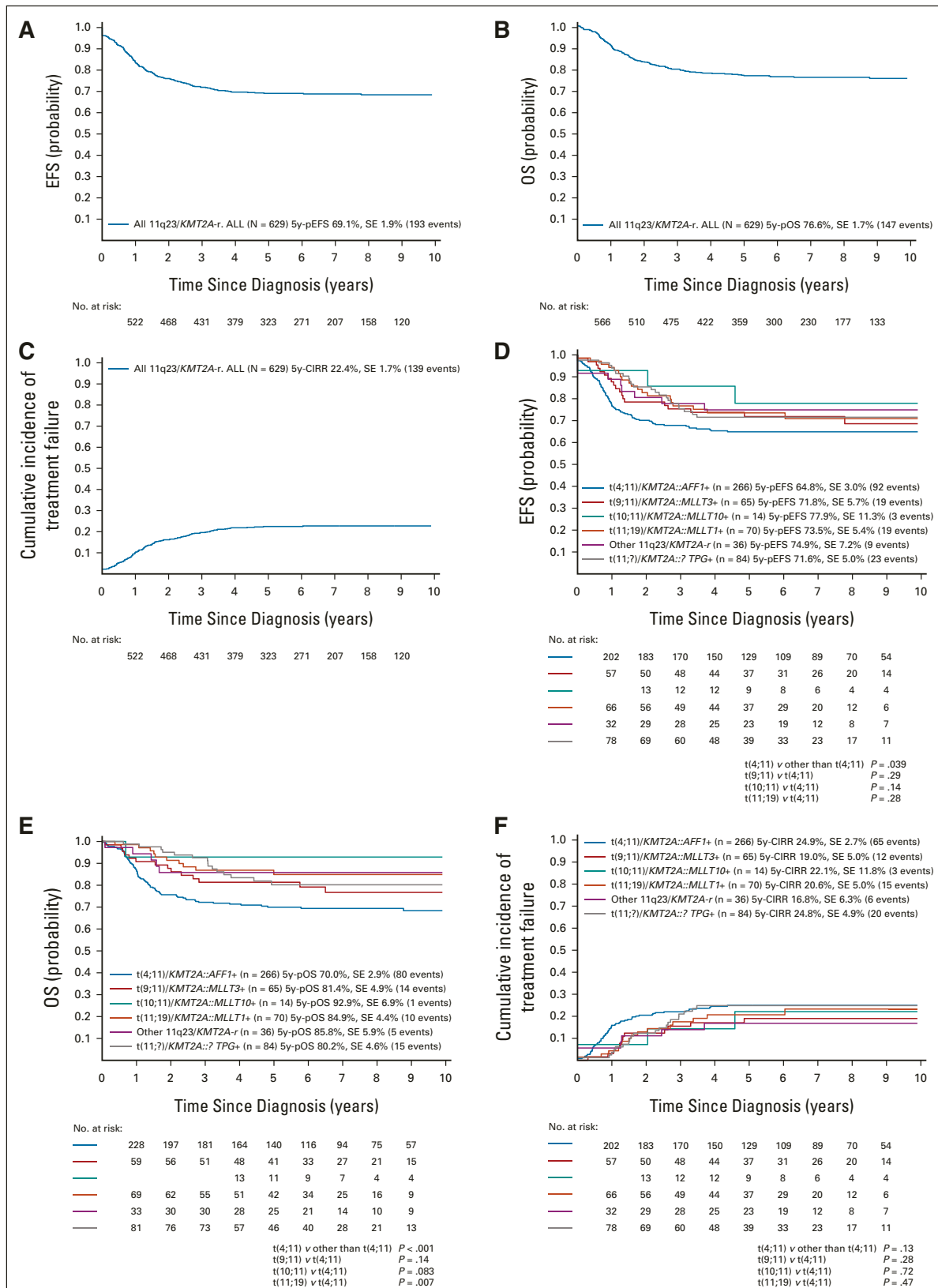


FIG 1. Outcomes of (A-C) all patients with 11q23/KMT2A-rearranged ALL and those with (D-F) B-ALL or (G-I) T-ALL according to the type of 11q23/KMT2A rearrangement: (A, D, and G) 5-year EFS; (B, E, and H) 5-year OS; and (C, F, and I) 5-year cumulative incidence of treatment failure. 5y-pEFS, probability of 5-year event-free survival; 5y-pOS, probability of 5-year overall survival; ALL, acute lymphoblastic leukemia; EFS, event-free survival; OS, overall survival; SE, standard error. (continued on following page)

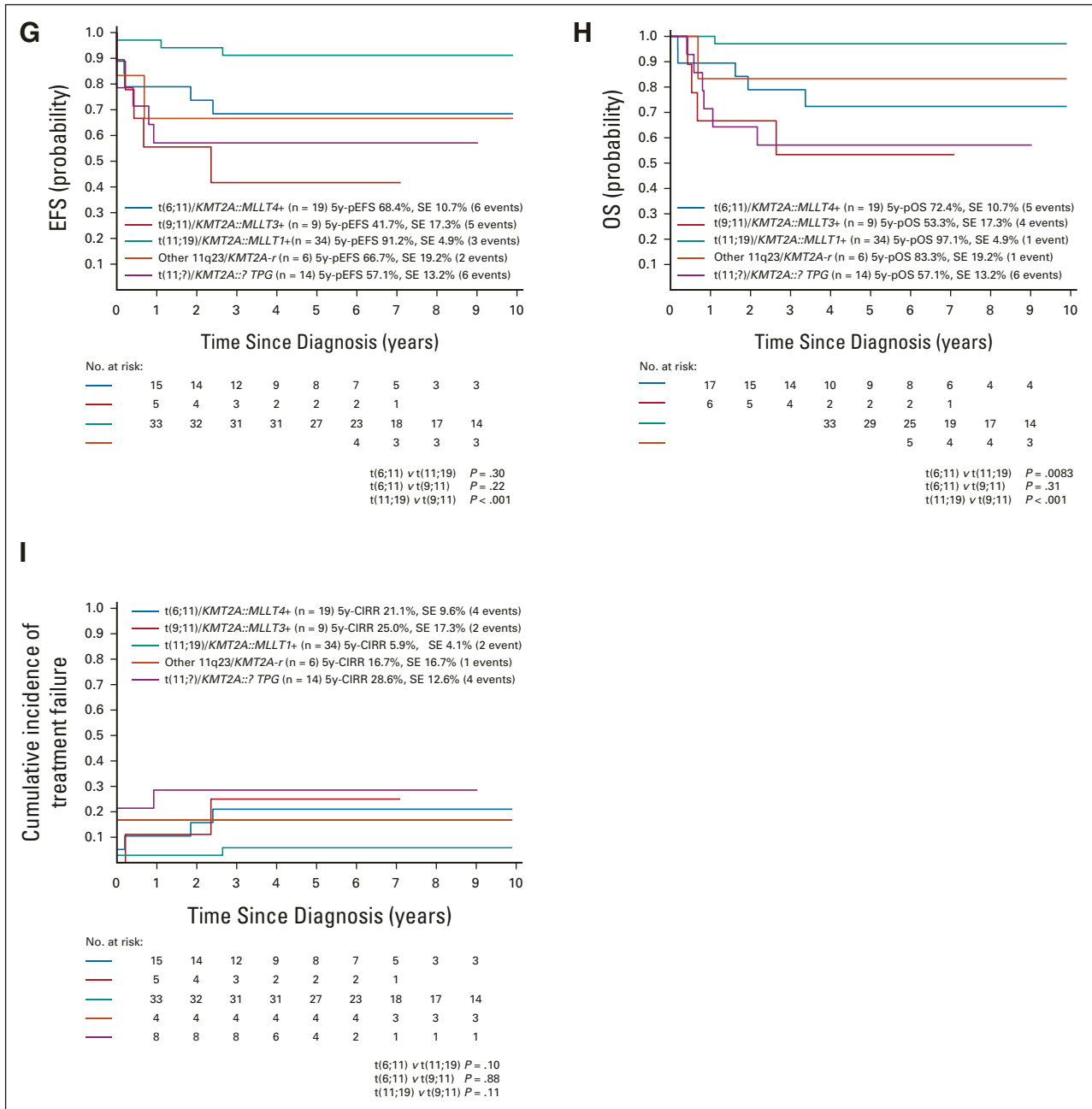


FIG 1. (Continued).

11q23/*KMT2A* rearrangements with other and unknown TPGs. Outcomes of 41 patients with other 11q23/*KMT2A* translocations and 99 without a known TPG are shown in the Data Supplement and Figures 1D-1I.

Prognostic Factors

11q23/*KMT2A*-rearranged B-ALL. The 5y-pOS of 76.6% ± 1.9% in 11q23/*KMT2A*-rearranged B-ALL was only slightly higher than the 5y-pEFS of 68.9 ± 2.0, because of not only high treatment-related mortality, accounting for 24% of the events, but also poor survival after relapse. The postrelapse 5y-pOS of the 114 patients with B-ALL who relapsed was

only 24.1% ± 4.5% (81 deaths, Data Supplement). Time to relapse was prognostically significant with a 5y-pOS of 14.1% ± 4.3% for relapses occurring within 18 months of initial diagnosis (n = 69, 60 deaths) versus 41.6% ± 9.6% for later relapses (n = 45, 21 deaths; Data Supplement). The effect of time to relapse was not apparent in t(4;11)-positive patients (5y-pOS after very early v later relapse: 12.8% ± 4.9% v 12.1% ± 10.3%; P = .22; Data Supplement) but was greater in other 11q23-rearranged patients (n = 16, 12.5% ± 8.3% v n = 16, 91.7% ± 8.0%; P = .0001; Data Supplement).

TABLE 2. Treatment Outcome of Patients With 11q23-Rearranged ALL According to Initial Characteristics, Response, and Therapy
11q23-Rearranged B-Lineage ALL

Parameter	No. ^a	5y-pEFS, % (SE)	P ^b	5y-pOS, % (SE)	P ^b	5y-CI Relapse, % (SE)	P ^b	5y-CI Resistance, % (SE)	P ^b	5y-CI Death in CR1, % (SE)	P ^b
ALL B-lineage patients	535	68.9 (2.0)		76.6 (1.9)		21.7 (1.8)		1.3 (0.5)		5.8 (1.0)	
Type of 11q23 rearrangement			.33		.006		.39		.082		.37
t(4;11)/KMT2A::AFF1	266	64.8 (3.0)		70.0 (2.9)		24.2 (2.7)		0.8 (0.5)		7.2 (1.6)	
t(11;19)/KMT2A::MLLT1	70	73.5 (5.4)		84.9 (4.4)		19.2 (4.8)		1.4 (1.4)		5.9 (2.9)	
t(9;11)/KMT2A::MLLT3	65	71.8 (5.7)		81.4 (4.9)		19.0 (5.0)		0.0 (0.0)		7.7 (3.3)	
t(10;11)/KMT2A::MLLT10	14	77.9 (11.3)		92.9 (6.9)		14.9 (10.2)		7.1 (7.1)		0.0 (0.0)	
t(v;11q23)/KMT2A::v. TPG ^c	36	74.9 (7.2)		85.8 (5.9)		11.2 (5.4)		5.6 (3.9)		5.6 (3.9)	
KMT2A + without known TPG	84	71.6 (5.0)		80.2 (4.6)		23.6 (4.8)		1.2 (1.2)		1.2 (1.2)	
Therapy era			.010		.025		.037		.75		.70
1995-1999	103	61.2 (4.8)		69.9 (4.5)		29.1 (4.5)		1.9 (1.4)		6.8 (2.5)	
2000-2004	133	63.8 (4.2)		71.1 (4.0)		24.2 (3.7)		1.5 (1.1)		6.8 (2.2)	
2005-2010	299	73.9 (2.6)		81.9 (2.3)		18.0 (2.3)		1.0 (0.6)		5.1 (1.3)	
Sex			.43		.61		.21		.72		.85
Female	268	71.0 (2.8)		77.2 (82.6)		19.2 (2.5)		1.5 (0.7)		5.7 (1.4)	
Male	267	66.8 (2.9)		76.1 (2.7)		24.1 (2.7)		1.1 (0.6)		6.0 (1.5)	
Age, years			.23		.003		.84		.20		.003
1-5	309	71.5 (2.6)		81.1 (2.3)		21.7 (2.4)		1.9 (0.8)		2.9 (1.0)	
6-9	62	67.6 (6.0)		76.8 (5.5)		19.5 (5.1)		1.6 (1.6)		8.1 (8.1)	
≥ 10	164	64.6 (3.8)		68.3 (3.7)		22.5 (3.3)		0.0 (0.0)		10.5 (2.4)	
Leukocyte count (× 10 ⁹ /L)			.018		.0018		.51		.35		.029
< 100.0	290	72.6 (2.7)		81.2 (2.4)		20.9 (2.4)		1.7 (0.8)		3.8 (1.1)	
≥ 100.0	245	64.5 (3.1)		71.2 (2.9)		22.7 (2.7)		0.8 (0.6)		8.3 (1.8)	
Initial CNS involvement			.063		.27		.11		.40		.98
No	489	69.7 (2.1)		76.9 (1.9)		21.2 (1.9)		1.2 (0.5)		6.0 (1.1)	
Yes	33	54.0 (8.8)		68.7 (8.2)		33.9 (8.6)		3.0 (3.0)		6.1 (4.2)	
NCI risk group ^d			.018		.0030		.26		.77		.16
SR	183	74.4 (3.3)		82.9 (2.9)		19.6 (3.0)		1.1 (0.8)		3.8 (1.4)	
HR	352	66.0 (2.6)		73.3 (2.4)		22.8 (2.3)		1.4 (0.6)		6.9 (1.4)	
Prednisone response			.46		.34		.71		.68		.97
GPR	182	67.9 (3.5)		75.4 (3.2)		21.7 (3.1)		0.5 (0.5)		7.7 (2.0)	
PPR	27	63.0 (9.3)		66.2 (9.2)		18.5 (7.7)		0.0 (0.0)		7.4 (5.2)	

(continued on following page)

TABLE 2. Treatment Outcome of Patients With 11q23-Rearranged ALL According to Initial Characteristics, Response, and Therapy (continued)

11q23-Rearranged B-Lineage ALL											
Parameter	No. ^a	5y-pEFS, % (SE)	P ^b	5y-pOS, % (SE)	P ^b	5y-CI Relapse, % (SE)	P ^b	5y-CI Resistance, % (SE)	P ^b	5y-CI Death in CR1, % (SE)	P ^b
BM response on day 15			.076		.032		.59		< .001		.53
< 5% blasts	210	67.6 (3.3)		75.6 (3.0)		23.8 (3.0)		0.0 (0.0)		7.2 (1.8)	
5%-24% blasts	59	67.3 (6.2)		77.1 (5.6)		22.5 (5.6)		3.4 (2.4)		3.4 (2.4)	
≥ 25% blasts	26	47.2 (10.2)		59.4 (10.0)		33.5 (10.1)		11.5 (6.4)		3.8 (3.9)	
Remission status at EOI			< .001		< .001		.48		< .001		.80
CR	501	71.5 (2.0)		78.4 (1.9)		21.9 (1.9)		0.0 (0.0)		6.0 (1.1)	
Induction failure	23	33.2 (10.1)		50.1 (11.3)		13.8 (7.8)		26.1 (9.4)		4.7 (4.8)	
MRD at EOI (PCR + FCM)			.0020		.0045		.16		< .001		.49
< 0.5%	239	77.1 (2.8)		84.2 (2.4)		17.0 (2.5)		0.0 (0.0)		5.1 (1.4)	
≥ 0.5%	55	57.9 (6.9)		67.9 (6.7)		25.4 (6.2)		5.5 (3.1)		7.6 (3.7)	
MRD at EOI (PCR + FCM)			.0037		.0001		.12		.024		.15
< 0.05%	173	78.9 (3.2)		87.6 (2.5)		15.8 (2.9)		0.0 (0.0)		4.1 (1.5)	
≥ 0.05%	100	63.9 (4.9)		70.3 (4.7)		22.9 (4.3)		3.0 (1.7)		8.2 (2.8)	
allo-HSCT performed in CR1 ^e			.12		.25		.12		—		.94
Yes	83	69.6 (5.1)		72.9 (5.0)		18.4 (4.3)		—		10.9 (3.4)	
No	73	71.1 (5.3)		77.7 (4.9)		24.8 (5.1)		—		4.1 (2.4)	
11q23-Rearranged T-Lineage ALL											
Parameter	No. ^a	5y-pEFS, % (SE)	P ^b	5y-pOS, % (SE)	P ^b	5y-CI Relapse, % (SE)	P ^b	5y-CI Resistance, % (SE)	P ^b	5y-CI Death in CR1, % (SE)	P ^b
All T-lineage patients	82	73.1 (4.9)		79.1 (4.5)		8.6 (3.1)		7.3 (2.9)		8.5 (3.4)	
Type of 11q23 rearrangement			.001		.0058		.12		.17		.19
t(11;19)/KMT2A::MLL1	34	91.2 (4.9)		97.1 (2.9)		2.9 (2.9)		2.9 (2.9)		2.9 (2.9)	
t(6;11)/KMT2A::MLL4	19	68.4 (10.7)		72.4 (10.6)		15.8 (11.7)		5.3 (5.3)		5.3 (5.3)	
t(9;11)/KMT2A::MLL3	9	41.7 (17.3)		53.3 (17.3)		25.0 (17.3)		0.0 (0.0)		22.2 (15.1)	
t(v;11q23)/KMT2A::v. TPG ^c	6	66.7 (19.2)		83.3 (15.2)		0.0 (0.0)		16.7 (16.7)		16.7 (17.0)	
KMT2A + without known TPG	14	57.1 (13.2)		57.1 (13.2)		21.4 (11.4)		21.4 (11.4)		14.3 (9.8)	
Therapy era			.50		.33		.65		.084		.20
1995-1999	14	85.7 (9.4)		92.9 (6.9)		7.1 (7.3)		0.0 (0.0)		0.0 (0.0)	
2000-2004	34	73.5 (7.6)		79.3 (7.0)		5.9 (4.1)		14.7 (6.2)		5.9 (4.1)	
2005-2010	34	67.4 (8.1)		73.3 (7.6)		12.0 (5.6)		2.9 (2.9)		14.7 (6.2)	

(continued on following page)

TABLE 2. Treatment Outcome of Patients With 11q23-Rearranged ALL According to Initial Characteristics, Response, and Therapy (continued)**11q23-Rearranged T-Lineage ALL**

Parameter	No. ^a	5y-pEFS, % (SE)	P ^b	5y-pOS, % (SE)	P ^b	5y-CI Relapse, % (SE)	P ^b	5y-CI Resistance, % (SE)	P ^b	5y-CI Death in CR1, % (SE)	P ^b
Sex			.83		.29		.59		.12		.18
Female	39	71.5 (7.3)		73.8 (7.1)		10.5 (5.1)		2.6 (2.6)		12.8 (5.4)	
Male	43	74.4 (6.7)		83.7 (5.6)		7.0 (3.1)		11.6 (4.9)		4.7 (3.3)	
Age, years			.23		.20		.26		.34		.27
1-5	28	64.1 (9.1)		71.2 (8.6)		7.3 (5.1)		10.7 (6.0)		14.3 (6.8)	
6-9	17	88.2 (7.8)		94.1 (5.7)		5.9 (5.9)		11.8 (8.1)		0.0 (0.0)	
≥ 10	37	73.0 (7.3)		78.1 (6.9)		16.2 (6.2)		2.7 (2.7)		8.1 (8.1)	
Leukocyte count (× 10 ⁹ /L)			.58		.99		.68		.95		.22
< 100.0	53	75.3 (5.8)		78.9 (5.7)		7.7 (3.7)		7.5 (2.7)		5.7 (3.2)	
≥ 100.0	29	69.0 (8.6)		79.3 (7.5)		10.3 (5.8)		6.9 (4.8)		13.8 (6.5)	
CNS involvement			.88		.89		.26		.55		.56
No	76	73.6 (5.1)		80.1 (4.6)		8.0 (3.1)		7.9 (3.1)		7.9 (3.1)	
Yes	4	75.0 (21.7)		75.0 (21.7)		25.0 (25.0)		0.0 (0.0)		0.0 (0.0)	
NCI risk group ^d			.92		.74		.45		.74		.92
SR	22	72.4 (9.6)		77.0 (9.0)		10.0 (3.9)		9.1 (6.3)		9.1 (6.3)	
HR	60	73.3 (5.7)		79.9 (5.2)		8.8 (4.9)		6.7 (3.2)		8.3 (3.6)	
Prednisone response			.66		.85		.24		.17		.20
GPR	12	75.0 (12.5)		74.1 (12.9)		16.7 (11.3)		0.0 (0.0)		0.0 (0.0)	
PPR	23	69.6 (9.6)		78.3 (8.6)		4.8 (4.9)		13.0 (7.2)		13.0 (7.2)	
BM response on day 15			.26		.44		.17		.077		.28
< 5% blasts	18	88.9 (7.4)		88.9 (7.4)		11.1 (7.6)		0.0 (0.0)		0.0 (0.0)	
5%-24% blasts	6	66.7 (19.2)		66.7 (19.2)		16.7 (17.0)		0.0 (0.0)		16.7 (16.7)	
≥ 25% blasts	26	69.2 (9.1)		76.9 (8.3)		0.0 (0.0)		19.2 (7.9)		11.5 (6.4)	
Remission status at EO1			< .001		.021		.77		< .001		.19
CR	66	80.2 (4.9)		83.1 (4.7)		9.2 (3.6)		0.0 (0.0)		10.6 (3.8)	
Induction failure	14	35.7 (12.8)		57.1 (13.2)		7.1 (7.5)		42.9 (13.7)		0.0 (0.0)	
MRD at EO1 (PCR + FCM)			.009		.038		.73		.21		.024
< 0.5%	19	94.4 (5.4)		94.4 (5.4)		5.6 (5.6)		0.0 (0.0)		0.0 (0.0)	
≥ 0.5%	12	58.3 (14.2)		66.7 (13.6)		8.3 (8.4)		8.3 (8.3)		25.0 (13.3)	
MRD at EO1 (PCR + FCM)			.025		.039		.160		.44		.17
< 0.05%	12	100 (0.0)		100 (0.0)		0.0 (0.0)		0.0 (0.0)		0.0 (0.0)	
≥ 0.05%	20	64.6 (10.8)		69.3 (10.5)		15.4 (8.5)		5.0 (5.0)		15.0 (8.2)	

(continued on following page)

TABLE 2. Treatment Outcome of Patients With 11q23-Rearranged ALL According to Initial Characteristics, Response, and Therapy (continued)

11q23-Rearranged T-Lineage ALL											
Parameter	No.^a	5y-pEFS, % (SE)	<i>P</i>^b	5y-pOS, % (SE)	<i>P</i>^b	5y-CI Relapse, % (SE)	<i>P</i>^b	5y-CI Resistance, % (SE)	<i>P</i>^b	5y-CI Death in CR1, % (SE)	<i>P</i>^b
allo-HSCT performed in CR1 ^c			.69		.49		.89		—		.26
Yes	16	68.8 (11.6)		75.0 (10.8)		18.8 (10.2)		—		12.0 (8.5)	
No	10	100 (0.0)		100 (0.0)		0.0 (0.0)		—		0.0 (0.0)	

NOTE. Bold values indicate statistical significance at $P < .05$.

Abbreviations: 5y-CI, 5-year cumulative incidence; 5y-pEFS, probability of 5-year event-free survival; 5y-pOS, probability of 5-year overall survival; ALL, acute lymphoblastic leukemia; allo-HSCT, allogeneic hematopoietic stem-cell transplantation; BM, bone marrow; CNS, central nervous system; COG, Children's Oncology Group; CR, complete remission; CR1, first complete remission; EOI, end of induction; FCM, flow cytometry; GPR, good prednisone response; HR, high-risk; MRD, minimal residual disease; NCI, National Cancer Institute; PCR, polymerase chain reaction; PPR, poor prednisone response; SR, standard-risk; TPG, translocation partner gene; v, variant.

^aData refer to patients with available information on the respective criteria.

^bDistribution of survival functions and cumulative incidences was compared with the log-rank test or Gray's test, respectively, except for data on allo-HSCT, which were compared with the Mantel-Byar test.

^cThe t(v;11q23)/*KMT2A*-v. TPG groups include the patients with t(6;11)-positive B-ALL and t(4;11)-positive T-ALL.

^dNCI-SR, age ≥ 1 and < 10 years, and WBC $< 50 \times 10^9/L$; NCI-HR, age ≥ 10 years, or WBC $\geq 50 \times 10^9/L$.

^eAdjusted for waiting time to allo-HSCT and including only patients eligible for allo-HSCT; information on eligibility was not available for the following protocols: COG: AALL0232 and AALL0331; DFCl: 00001 and 05001; FRALLE: F2000; NOPHO: NOPHO 2000 and NOPHO 92; and SJCRH: Total XIIB/BH, Total XV, and Total XVI.

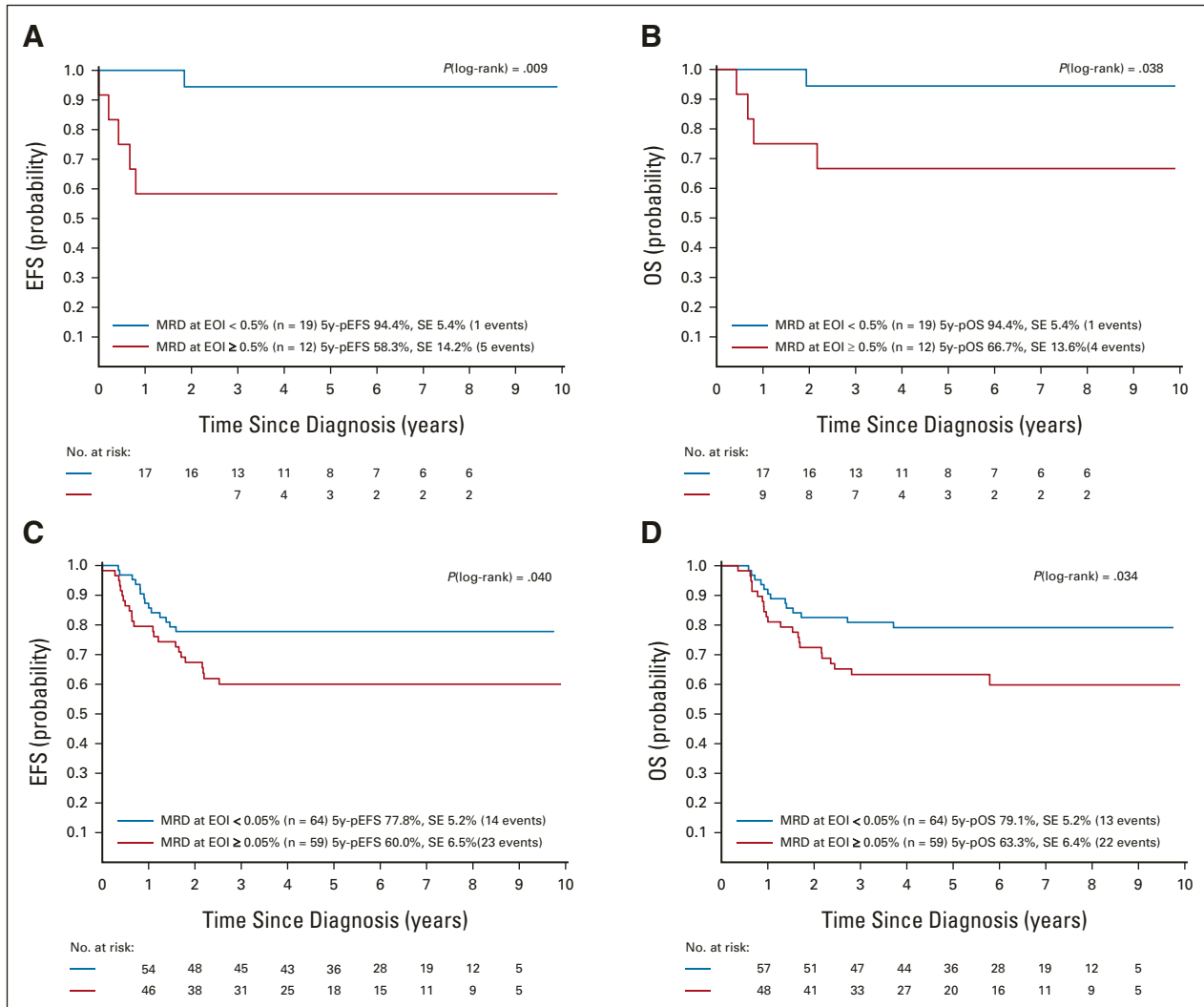


FIG 2. Outcomes of (A and B) patients with 11q23/*KMT2A*-rearranged T-ALL and (C and D) patients with t(4;11)/*KMT2A-AFF1*-rearranged B-ALL according to MRD levels at the EOI with a cutoff of 0.5% or 0.05% blasts, respectively. (A and C) 5-Year EFS; (B and D) 5-year OS. 5y-pEFS, probability of 5-year event-free survival; 5y-pOS, probability of 5-year overall survival; ALL, acute lymphoblastic leukemia; EFS, event-free survival; EOI, end of induction; MRD, minimal residual disease; OS, overall survival; SE, standard error.

Treatment during the later era (2005-2010 v 1995-2005) was associated with superior EFS and OS, mainly because of lower relapse events. Considering the different distribution of t(4;11)-positive patients in the later and earlier treatment periods (Table 1), multivariable analysis including t(4;11) status and treatment era showed independent significance for improved EFS and OS of the later era (data not shown).

Although older age did not significantly influence relapse or EFS in the whole group of 11q23-rearranged B-ALL, it was significantly associated with inferior OS. This was partly attributable to not only a significantly higher death in CR rate but also the exceptionally poor survival after relapse in patients age \geq 10 years (postrelapse 5y-pOS: age \geq 10 years: 9.4% \pm 5.1% [n = 36, 32 deaths], < 10 years: 31.7% \pm 5.8% [n = 78, 49 deaths]; $P < .001$; Data Supplement).

This was especially true for t(4;11)-positive patients (age \geq 10 years: postrelapse 5y-pOS: 3.3% \pm 3.3% [n = 30, 29 deaths]; Data Supplement) although the number of relapses in the corresponding group with other 11q23 rearrangements was too small for evaluation (Data Supplement). Multivariable analysis for risk of reduced postrelapse survival revealed independent significance of age \geq 10 years and a time to relapse of < 18 months with hazard ratios of 2.45 ($P < .001$) and 2.58 ($P = .0032$), respectively.

Poor response assessed morphologically on day 15, at EOI, and by MRD was predictive of resistant disease and related to poor EFS and OS (Table 2). The prognostic impact of response to induction was also evident in t(4;11)-rearranged B-ALL (Data Supplement and Figs 2C-2D) or other 11q23 rearrangements (Data Supplement) although statistical significance was not reached for all response parameters.

TABLE 3. Multivariable Cox Regression Analysis of the Patients With 11q23-Rearranged T-Lineage ALL for Event-Free Survival, Overall Survival, and Cumulative Incidence of Treatment Failure

Parameter (n = 66)	Event-Free Survival			Overall Survival			Treatment Failure ^a		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Type of <i>KMT2A</i> rearrangement									
t(11;19)/ <i>KMT2A</i> :: <i>MLLT1</i> -negative	1			1			1		
t(11;19)/ <i>KMT2A</i> :: <i>MLLT1</i> -positive	0.12	0.03 to 0.48	.003	0.08	0.01 to 0.63	.017	0.159	0.02 to 1.17	.071
Leukocyte count									
< 100.0 × 10 ⁹ /L	1			1			1		
≥ 100.0 × 10 ⁹ /L	2.77	0.89 to 8.62	.079	1.27	0.32 to 5.08	.74	3.67	0.72 to 18.68	.18
Remission status at EOI									
CR	1			1			1		
Induction failure	3.68	1.30 to 10.42	.014	1.58	0.41 to 6.13	.51	4.25	1.22 to 14.88	.023

NOTE. Bold values indicate statistical significance at $P < .05$. Because of the lack of events in the group of patients with low MRD levels ($< 0.5\%$ and $< 0.05\%$ blasts) at EOI, MRD could not be included in the multivariable Cox regression analysis.

Abbreviations: ALL, acute lymphoblastic leukemia; CR, complete remission; EOI, end of induction; HR, hazard ratio; MRD, minimal residual disease.

^aTreatment failure includes resistant disease (no achievement of CR according to the respective protocol criteria) and relapse.

The overall outcomes of the 535 patients with 11q23/*KMT2A*-rearranged B-ALL with regard to initial characteristics and response and by 11q23/*KMT2A* rearrangement status (t(4;11)-positive v others) are shown in the Data Supplement.

Multivariable analyses were performed with t(4;11) status, sex, age, leukocyte counts, and remission status at EOI as covariates, with and without MRD. In both models, IF remained an independent poor prognostic factor for EFS, OS, and treatment failure because of resistance/relapse, although only partly reaching statistical significance (Data Supplement, with additional analyses in the Data Supplement).

11q23/*KMT2A*-rearranged T-ALL. Analyses of the 82 patients with 11q23/*KMT2A*-rearranged T-ALL were limited by small numbers of patients and events (Table 2). Considering these limitations, no prognostic effect was evident, except for the presence of t(11;19) (Figs 1G-1I) and good morphologic and MRD response at EOI, which were associated with superior EFS and OS (Figs 2A and 2B). IF and EOI MRD $\geq 0.5\%$ indicated a higher cumulative risk of resistance and death in CR1, respectively (Table 2).

Because of the limited number of events in patients with available MRD data, multivariable analysis was performed in a model including t(11;19) status, leukocyte counts, and remission status at EOI without MRD (Table 3). The t(11;19) showed favorable independent significance for EFS and OS, with borderline significance for treatment failure because of resistance/relapse. In addition, IF was significantly associated with inferior EFS and treatment failure.

Allogeneic Hematopoietic Stem-Cell Transplantation

The role of allo-HSCT was evaluated in patients with t(4;11)-positive B-ALL and the entire T-ALL cohort, including only those patients who were eligible for allo-HSCT according to

the protocol (Data Supplement). There were no significant differences in EFS or OS between the 64 patients with t(4;11)-positive B-ALL who underwent allo-HSCT and the 51 patients who received chemotherapy alone (Figs 3A and 3B). When the analyses were stratified by EOI MRD ($< 0.05\%$ or $\geq 0.05\%$), there were also no differences between the groups (Data Supplement). Results were also not statistically different for the 16 and 10 patients with 11q23/*KMT2A*-rearranged T-ALL who received either allo-HSCT or chemotherapy only, respectively (Figs 3C and 3D). Cox regression analyses, including allo-HSCT as a time-dependent variable, did not show an advantage for allo-HSCT in t(4;11)-positive B-ALL, but rather indicated a disadvantage for 11q23/*KMT2A*-rearranged T-ALL (data not shown).

DISCUSSION

This study reports the largest cohort of children age ≥ 1 year with a wide variety of 11q23/*KMT2A*-rearranged ALL subgroups (Data Supplement). With a median presenting leukocyte count of $82.9 \times 10^9/L$, 11q23/*KMT2A*-positive patients had markedly higher leukocyte counts compared with the general ALL population. The 5-year EFS for the entire cohort was 69.1%, but differed according to TPGs and immunophenotype. Overall, the results were superior to the outcomes of not only noninfants in our previous study but also infant 11q23/*KMT2A*-rearranged B-ALL.^{10,13,14,16} For 11q23-rearranged B-ALL, the outcome was improved over the years, likely because of combinations of better chemotherapies (such as augmented Berlin-Frankfurt-Münster regimens, high-dose methotrexate at 5 g/m² given repeatedly over 24 hours as a continuous infusion, and use of dexamethasone), MRD- and immunophenotype-based stratifications, and advances in supportive care.^{64,65} Notably, deaths in CR1 accounted for 23% of postremission events,

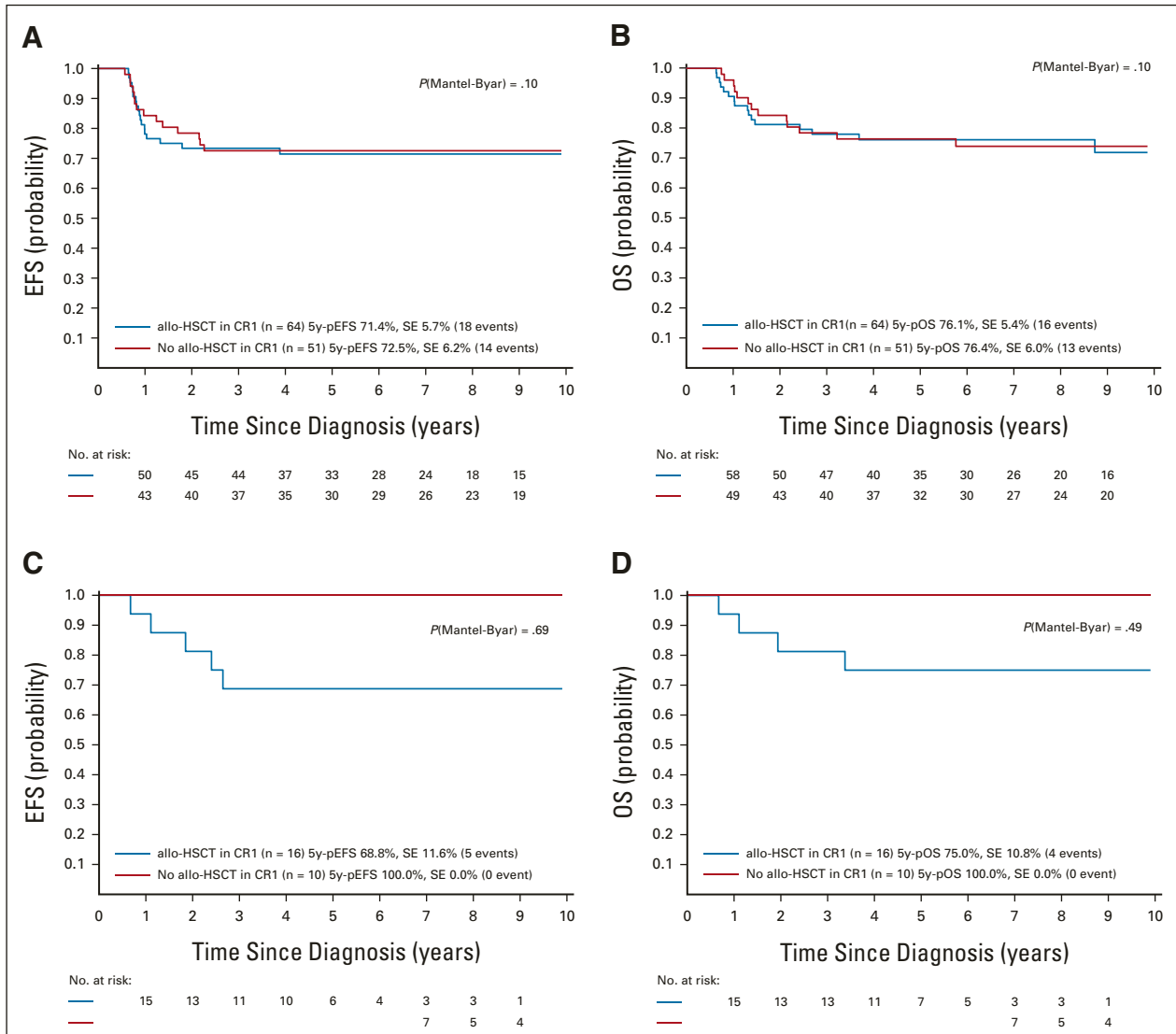


FIG 3. Outcomes of (A and B) patients with $t(4;11)/KMT2A-AFF1$ -rearranged B-ALL and (C and D) patients with $11q23/KMT2A$ -rearranged T-ALL according to therapy performed (allo-HSCT or chemotherapy only, adjusted by waiting time to allo-HSCT [landmark of 0.54 years]): (A and C) 5-year EFS and (B and D) 5-year OS. 5y-pEFS, probability of 5-year event-free survival; 5y-pOS, probability of 5-year overall survival; ALL, acute lymphoblastic leukemia; allo-HSCT, allogeneic hematopoietic stem-cell transplantation; CR1, first complete remission; EFS, event-free survival; OS, overall survival; SE, standard error.

similar to other high-risk ALL.^{65,66} For patients with B-ALL, survival was generally poor postrelapse, especially in adolescents, $t(4;11)$ -positive patients, and those experiencing very early relapses. Most deaths after relapse occurred within the first few months postrelapse, indicating that high mortality from relapse therapy and failure to achieve a second remission were crucial issues. Notable exceptions were those subgroups with rearrangements other than $t(4;11)$ and relapse ≥ 18 months after diagnosis. These 16 patients had a 5y-pOS of $91.7\% \pm 8.0\%$ postrelapse.

Our data highlight the heterogeneity among childhood noninfant ALL with $11q23/KMT2A$ rearrangements, which has not been hitherto clearly documented.^{12-14,18,67-73} The

heterogeneity is also reflected in the different age distributions depending on the TPG. The peak incidence in early childhood observed in all B-ALL subgroups indicates a bridge to infant ALL, in which most patients have $11q23/KMT2A$ rearrangements. The second peak observed in adolescence for $t(4;11)$ - and $t(11;19)$ -positive B-ALL is likely related to different disease biology, which is, at least in $t(4;11)$ -positive patients, also indicated by different age-dependent patient characteristics (sex distribution and leukocyte count). Unsurprisingly, among the B-ALL cohort, $t(4;11)$ -positive patients had the highest proportion of high EOI MRD, the lowest EFS, and highest risk of resistance and relapse. The most frequent $11q23$ translocations in T-ALLs were $t(11;19)$, $t(6;11)$, and $t(9;11)$. Age distribution significantly differed

from that of B-ALL without an evident peak incidence in early childhood. Notably, t(11;19)-positive T-ALLs differed from their B-ALL counterpart with respect to clinical characteristics, including age and sex. As t(6;11)- and t(9;11)-positive T-ALL subgroups, response to induction therapy was particularly poor in patients with t(11;19)-positive T-ALL. However, in contrast to the t(6;11)- or t(9;11)-positive T-ALLs, t(11;19)-positive T-ALL had excellent outcomes (5y-pEFS 91.2% and 5y-pOS 97.1%). These data confirm the results of our previous study and others suggesting a good outcome for t(11;19)-positive T-ALL.¹⁶ Comparison of our cohort with published infant 11q23/*KMT2A*-rearranged ALL suggested that the differences and similarities between cohorts partly reflect the age-dependent incidences of the different 11q23/*KMT2A* rearrangements.^{10,11,16} Interestingly, young children age 1-2 years showed some similarities with infants, which also distinguished them from older patients, such as the well-known female predominance and the small proportion of T-ALL (2.2%). Regarding other features, however, this young age group differed from infants, showing a divergent relative distribution of various 11q23 translocations (lower proportion of t(4;11) and t(11;19) and higher proportion of t(9;11)), less frequent hyperleukocytosis, and better outcomes than those of their Interfant-06 counterparts.¹³ In the Interfant-99 and Interfant-06 studies, age-related prognostic differences were also observed, with increasing age being associated with improved outcomes.^{13,14} This effect seemed to continue beyond the first birthday. Conceivably, in 11q23/*KMT2A*-rearranged childhood ALL, patient age at diagnosis may reflect time from the prenatal evolution until clinical manifestation of the leukemia, therefore reflecting the aggressiveness of disease. The underlying biology of these different progressions, however, is unclear.

Our study showed no benefit of allo-HSCT in the two large subgroups of t(4;11)-positive B-ALL and 11q23/*KMT2A*-rearranged T-ALL. These data, however, have limitations because of presumed heterogeneity in selection of patients on the basis of different allo-HSCT eligibility criteria. In addition, analyses stratified by MRD at EO1 to control for a potential MRD-related bias between patients treated with

allo-HSCT or chemotherapy resulted in very small subgroups. Nevertheless, these data show that routine allo-HSCT in CR1 is not indicated for patients with 11q23/*KMT2A*-positive ALL. Whether pretransplant consolidation with novel immunotherapeutics can induce a deeper MRD remission for and less toxicity of a subsequent successful allo-HSCT remains to be determined.

Apart from the genetic- and phenotype-based subgroup analyses, which limited the power of the results within the minor genetic subgroups, further limitations of our study include the retrospective collection of data over a 15-year period. An unknown number of patients with 11q23/*KMT2A*-rearranged ALL might have been missed by the participating groups because of different screening methods. Moreover, chemotherapies, risk stratification, and allo-HSCT conduction were heterogeneous, and comparison of allo-HSCT and chemotherapy only was not based on a randomized study.

In conclusion, results from noninfants with 11q23/*KMT2A*-rearranged ALL in our study were superior to those of corresponding patients with infant ALL and had improved in comparison with our historical cohort.^{16,17} Nevertheless, outcomes remain clearly inferior to those of childhood ALL overall, and for most relapsed patients, their chances of rescue were extremely low. Despite the heterogeneity, no genetic subgroup could be identified with an excellent prognosis, with the exception of t(11;19)-positive T-ALL. Although early therapy response was shown to be prognostically important, the superior outcome of 11q23/*KMT2A*-rearranged patients with favorable EO1 status appeared to remain below the 90%-95% level expected from other MRD-defined low-risk ALL subgroups.⁴⁷ Moreover, as no benefit was shown from allo-HSCT in both t(4;11)-positive B-ALL and 11q23/*KMT2A*-rearranged T-ALL, alternatives to conventional treatments are required for improved outcomes.⁷⁴⁻⁸⁰ As our cohort of patients stems from a preimmunotherapy era, this may be eventually achieved through novel immunotherapeutic approaches including blinatumomab or inotuzumab ozogamicin, as well as chimeric antigen-receptor T cells and improved procedures of allo-HSCT.

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REFERENCES

- Mullighan CG: New strategies in acute lymphoblastic leukemia: Translating advances in genomics into clinical practice. *Clin Cancer Res* 17:396-400, 2011
- Pui CH, Carroll WL, Meshinchi S, et al: Biology, risk stratification, and therapy of pediatric acute leukemias: An update. *J Clin Oncol* 29:551-565, 2011
- Enshaei A, O'Connor D, Bartram J, et al: A validated novel continuous prognostic index to deliver stratified medicine in pediatric acute lymphoblastic leukemia. *Blood* 135:1438-1446, 2020
- Meyer C, Burmeister T, Groger D, et al: The MLL recombinome of acute leukemias in 2017. *Leukemia* 32:273-284, 2018
- Meyer C, Hofmann J, Burmeister T, et al: The MLL recombinome of acute leukemias in 2013. *Leukemia* 27:2165-2176, 2013
- Meyer C, Kowarz E, Hofmann J, et al: New insights to the MLL recombinome of acute leukemias. *Leukemia* 23:1490-1499, 2009
- Schieck M, Lentjes J, Thomay K, et al: Implementation of RNA sequencing and array CGH in the diagnostic workflow of the AIEOP-BFM ALL 2017 trial on acute lymphoblastic leukemia. *Ann Hematol* 99:809-818, 2020
- Harrison CJ, Haas O, Harbott J, et al: Detection of prognostically relevant genetic abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: Recommendations from the Biology and Diagnosis Committee of the International Berlin-Frankfurt-Munster Study Group. *Br J Haematol* 151:132-142, 2010
- Forgione MO, McClure BJ, Eadie LN, et al: KMT2A rearranged acute lymphoblastic leukaemia: Unravelling the genomic complexity and heterogeneity of this high-risk disease. *Cancer Lett* 469:410-418, 2020
- Pieters R, De Lorenzo P, Ancliffe P, et al: Outcome of infants younger than 1 year with acute lymphoblastic leukemia treated with the Interfant-06 protocol: Results from an international phase III randomized study. *J Clin Oncol* 37:2246-2256, 2019
- Pieters R, Schrappe M, De Lorenzo P, et al: A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): An observational study and a multicentre randomised trial. *Lancet* 370:240-250, 2007
- Pui CH: Acute leukemias with the t(4;11)(q21;q23). *Leuk Lymphoma* 7:173-179, 1992
- Pui CH, Chessells JM, Camitta B, et al: Clinical heterogeneity in childhood acute lymphoblastic leukemia with 11q23 rearrangements. *Leukemia* 17:700-706, 2003
- Pui CH, Gaynon PS, Boyett JM, et al: Outcome of treatment in childhood acute lymphoblastic leukaemia with rearrangements of the 11q23 chromosomal region. *Lancet* 359:1909-1915, 2002
- Mann G, Attarbaschi A, Schrappe M, et al: Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with mixed-lineage-leukemia (MLL)-rearranged acute lymphoblastic leukemia: Results from the Interfant-99 study. *Blood* 116:2644-2650, 2010
- Brown PA, Kairalla JA, Hilden JM, et al: FLT3 inhibitor lestaurtinib plus chemotherapy for newly diagnosed KMT2A-rearranged infant acute lymphoblastic leukemia: Children's Oncology Group trial AALL0631. *Leukemia* 35:1279-1290, 2021

17. Bai L, Cheng YF, Lu AD, et al: Prognosis of haploidentical hematopoietic stem cell transplantation in non-infant children with t(v;11q23)/MLL-rearranged B-cell acute lymphoblastic leukemia. *Leuk Res* 91:106333, 2020
18. Mann G, Cazzaniga G, van der Velden VH, et al: Acute lymphoblastic leukemia with t(4;11) in children 1 year and older: The 'big sister' of the infant disease? *Leukemia* 21:642-646, 2007
19. Peterson JF, Baughn LB, Pearce KE, et al: *KMT2A* (MLL) rearrangements observed in pediatric/young adult T-lymphoblastic leukemia/lymphoma: A 10-year review from a single cytogenetic laboratory. *Genes Chromosomes Cancer* 57:541-546, 2018
20. Tomizawa D, Kato M, Takahashi H, et al: Favorable outcome in non-infant children with MLL-AF4-positive acute lymphoblastic leukemia: A report from the Tokyo Children's Cancer Study Group. *Int J Hematol* 102:602-610, 2015
21. van der Burg M, Beverloo HB, Langerak AW, et al: Rapid and sensitive detection of all types of MLL gene translocations with a single FISH probe set. *Leukemia* 13:2107-2113, 1999
22. Moorman AV, Ensor HM, Richards SM, et al: Prognostic effect of chromosomal abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: Results from the UK Medical Research Council ALL97/99 randomised trial. *Lancet Oncol* 11:429-438, 2010
23. Reichel M, Gillert E, Angermuller S, et al: Biased distribution of chromosomal breakpoints involving the MLL gene in infants versus children and adults with t(4;11) ALL. *Oncogene* 20:2900-2907, 2001
24. Attarbaschi A, Mann G, Strehl S, et al: Deletion of 11q23 is a highly specific nonrandom secondary genetic abnormality of ETV6/RUNX1-rearranged childhood acute lymphoblastic leukemia. *Leukemia* 21:584-586, 2007
25. Raimondi SC, Frestedt JL, Pui CH, et al: Acute lymphoblastic leukemias with deletion of 11q23 or a novel inversion (11)(p13q23) lack MLL gene rearrangements and have favorable clinical features. *Blood* 86:1881-1886, 1995
26. Harbott J, Mancini M, Verellen-Dumoulin C, et al: Hematological malignancies with a deletion of 11q23: Cytogenetic and clinical aspects. European 11q23 Workshop participants. *Leukemia* 12:823-827, 1998
27. Bene MC, Castoldi G, Knapp W, et al: Proposals for the immunological classification of acute leukemias. European Group for the Immunological Characterization of Leukemias (EGIL). *Leukemia* 9:1783-1786, 1995
28. Borowitz MJ, Wood BL, Devidas M, et al: Prognostic significance of minimal residual disease in high risk B-ALL: A report from Children's Oncology Group study AALL0232. *Blood* 126:964-971, 2015
29. Maurer-Granofszky M, Schumich A, Buldini B, et al: An extensive quality control and quality assurance (QC/QA) program significantly improves inter-laboratory concordance rates of flow-cytometric minimal residual disease assessment in acute lymphoblastic leukemia: An I-BFM-FLOW-Network report. *Cancers (Basel)* 13:6148-6163, 2021
30. van der Velden VH, Panzer-Grumayer ER, Cazzaniga G, et al: Optimization of PCR-based minimal residual disease diagnostics for childhood acute lymphoblastic leukemia in a multi-center setting. *Leukemia* 21:706-713, 2007
31. Arico M, Valsecchi MG, Rizzari C, et al: Long-term results of the AIEOP-ALL-95 Trial for Childhood Acute Lymphoblastic Leukemia: Insight on the prognostic value of DNA index in the framework of Berlin-Frankfurt-Muenster based chemotherapy. *J Clin Oncol* 26:283-289, 2008
32. Bartram J, Wade R, Vora A, et al: Excellent outcome of minimal residual disease-defined low-risk patients is sustained with more than 10 years follow-up: Results of UK paediatric acute lymphoblastic leukaemia trials 1997-2003. *Arch Dis Child* 101:449-454, 2016
33. Conter V, Bartram CR, Valsecchi MG, et al: Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: Results in 3184 patients of the AIEOP-BFM ALL 2000 study. *Blood* 115:3206-3214, 2010
34. De Moerloose B, Suci S, Bertrand Y, et al: Improved outcome with pulses of vincristine and corticosteroids in continuation therapy of children with average risk acute lymphoblastic leukemia (ALL) and lymphoblastic non-Hodgkin lymphoma (NHL): Report of the EORTC randomized phase 3 trial 58951. *Blood* 116:36-44, 2010
35. Escherich G, Troger A, Gobel U, et al: The long-term impact of in vitro drug sensitivity on risk stratification and treatment outcome in acute lymphoblastic leukemia of childhood (CoALL 06-97). *Haematologica* 96:854-862, 2011
36. Escherich G, Zur Stadt U, Zimmermann M, et al: Clofarabine in combination with pegylated asparaginase in the frontline treatment of childhood acute lymphoblastic leukaemia: A feasibility report from the CoALL 08-09 trial. *Br J Haematol* 163:240-247, 2013
37. Gandemer V, Auclerc MF, Perel Y, et al: Impact of age, leukocyte count and day 21-bone marrow response to chemotherapy on the long-term outcome of children with Philadelphia chromosome-positive acute lymphoblastic leukemia in the pre-imatinib era: Results of the FRALLE 93 study. *BMC Cancer* 9:14, 2009
38. Hasegawa D, Imamura T, Yumura-Yagi K, et al: Risk-adjusted therapy for pediatric non-T cell ALL improves outcomes for standard risk patients: Results of JACLS ALL-02. *Blood Cancer J* 10:23, 2020
39. Horibe K, Yumura-Yagi K, Kudoh T, et al: Long-term results of the risk-adapted treatment for childhood B-cell acute lymphoblastic leukemia: Report from the Japan Association of Childhood Leukemia Study ALL-97 trial. *J Pediatr Hematol Oncol* 39:81-89, 2017
40. Igarashi S, Manabe A, Ohara A, et al: No advantage of dexamethasone over prednisolone for the outcome of standard- and intermediate-risk childhood acute lymphoblastic leukemia in the Tokyo Children's Cancer Study Group L95-14 protocol. *J Clin Oncol* 23:6489-6498, 2005
41. Jeha S, Pei D, Choi J, et al: Improved CNS control of childhood acute lymphoblastic leukemia without cranial irradiation: St Jude Total Therapy Study 16. *J Clin Oncol* 37:3377-3391, 2019
42. Kamps WA, Bokkerink JP, Hakvoort-Cammel FG, et al: BFM-oriented treatment for children with acute lymphoblastic leukemia without cranial irradiation and treatment reduction for standard risk patients: Results of DCLSG protocol ALL-8 (1991-1996). *Leukemia* 16:1099-1111, 2002
43. Larsen EC, Devidas M, Chen S, et al: Dexamethasone and high-dose methotrexate improve outcome for children and young adults with high-risk B-acute lymphoblastic leukemia: A report from Children's Oncology Group study AALL0232. *J Clin Oncol* 34:2380-2388, 2016
44. Maloney KW, Devidas M, Wang C, et al: Outcome in children with standard-risk B-cell acute lymphoblastic leukemia: Results of Children's Oncology Group trial AALL0331. *J Clin Oncol* 38:602-612, 2020
45. Manabe A, Ohara A, Hasegawa D, et al: Significance of the complete clearance of peripheral blasts after 7 days of prednisolone treatment in children with acute lymphoblastic leukemia: The Tokyo Children's Cancer Study Group study L99-15. *Haematologica* 93:1155-1160, 2008
46. Moricke A, Reiter A, Zimmermann M, et al: Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: Treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. *Blood* 111:4477-4489, 2008
47. Pieters R, de Groot-Kruseman H, Van der Velden V, et al: Successful therapy reduction and intensification for childhood acute lymphoblastic leukemia based on minimal residual disease monitoring: Study ALL10 from the Dutch Childhood Oncology Group. *J Clin Oncol* 34:2591-2601, 2016
48. Place AE, Stevenson KE, Vrooman LM, et al: Intravenous pegylated asparaginase versus intramuscular native *Escherichia coli* L-asparaginase in newly diagnosed childhood acute lymphoblastic leukaemia (DFCI 05-001): A randomised, open-label phase 3 trial. *Lancet Oncol* 16:1677-1690, 2015
49. Pui CH, Pei D, Sandlund JT, et al: Long-term results of St Jude Total Therapy studies 11, 12, 13A, 13B, and 14 for childhood acute lymphoblastic leukemia. *Leukemia* 24:371-382, 2010

50. Pui CH, Relling MV, Sandlund JT, et al: Rationale and design of Total Therapy Study XV for newly diagnosed childhood acute lymphoblastic leukemia. *Ann Hematol* 83:S124-S126, 2004 (suppl 1)
51. Sakamoto K, Imamura T, Kihira K, et al: Low incidence of osteonecrosis in childhood acute lymphoblastic leukemia treated with ALL-97 and ALL-02 study of Japan Association of Childhood Leukemia Study group. *J Clin Oncol* 36:900-907, 2018
52. Schmiegelow K, Forestier E, Hellebostad M, et al: Long-term results of NOPHO ALL-92 and ALL-2000 studies of childhood acute lymphoblastic leukemia. *Leukemia* 24:345-354, 2010
53. Schramm F, Zimmermann M, Jorch N, et al: Daunorubicin during delayed intensification decreases the incidence of infectious complications—A randomized comparison in trial CoALL 08-09. *Leuk Lymphoma* 60:60-68, 2019
54. Schramm F, Zur Stadt U, Zimmermann M, et al: Results of CoALL 07-03 study childhood ALL based on combined risk assessment by in vivo and in vitro pharmacosensitivity. *Blood Adv* 3:3688-3699, 2019
55. Schrappe M, Valsecchi MG, Bartram CR, et al: Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: Results of the AIEOP-BFM-ALL 2000 study. *Blood* 118:2077-2084, 2011
56. Stary J, Zimmermann M, Campbell M, et al: Intensive chemotherapy for childhood acute lymphoblastic leukemia: Results of the randomized intercontinental trial ALL IC-BFM 2002. *J Clin Oncol* 32:174-184, 2014
57. Steinherz PG, Seibel NL, Sather H, et al: Treatment of higher risk acute lymphoblastic leukemia in young people (CCG-1961), long-term follow-up: A report from the Children's Oncology Group. *Leukemia* 33:2144-2154, 2019
58. Takahashi H, Kajiwara R, Kato M, et al: Treatment outcome of children with acute lymphoblastic leukemia: The Tokyo Children's Cancer Study Group (TCCSG) study L04-16. *Int J Hematol* 108:98-108, 2018
59. Toft N, Birgens H, Abrahamsson J, et al: Results of NOPHO ALL2008 treatment for patients aged 1-45 years with acute lymphoblastic leukemia. *Leukemia* 32:606-615, 2018
60. Veerman AJ, Kamps WA, van den Berg H, et al: Dexamethasone-based therapy for childhood acute lymphoblastic leukaemia: Results of the prospective Dutch Childhood Oncology Group (DCOG) protocol ALL-9 (1997-2004). *Lancet Oncol* 10:957-966, 2009
61. Vilmer E, Suciou S, Ferster A, et al: Long-term results of three randomized trials (58831, 58832, 58881) in childhood acute lymphoblastic leukemia: A CLCG-EORTC report. *Children Leukemia Cooperative Group. Leukemia* 14:2257-2266, 2000
62. Vrooman LM, Blonquist TM, Harris MH, et al: Refining risk classification in childhood B acute lymphoblastic leukemia: Results of DFCI ALL Consortium Protocol 05-001. *Blood Adv* 2:1449-1458, 2018
63. Vrooman LM, Stevenson KE, Supko JG, et al: Postinduction dexamethasone and individualized dosing of *Escherichia coli* L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: Results from a randomized study—Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. *J Clin Oncol* 31:1202-1210, 2013
64. Pui CH, Rebora P, Schrappe M, et al: Outcome of children with hypodiploid acute lymphoblastic leukemia: A retrospective multinational study. *J Clin Oncol* 37:770-779, 2019
65. Attarbaschi A, Mann G, Zimmermann M, et al: Randomized post-induction and delayed intensification therapy in high-risk pediatric acute lymphoblastic leukemia: Long-term results of the international AIEOP-BFM ALL 2000 trial. *Leukemia* 34:1694-1700, 2020
66. Testi AM, Attarbaschi A, Valsecchi MG, et al: Outcome of adolescent patients with acute lymphoblastic leukaemia aged 10-14 years as compared with those aged 15-17 years: Long-term results of 1094 patients of the AIEOP-BFM ALL 2000 study. *Eur J Cancer* 122:61-71, 2019
67. Behm FG, Raimondi SC, Frestedt JL, et al: Rearrangement of the MLL gene confers a poor prognosis in childhood acute lymphoblastic leukemia, regardless of presenting age. *Blood* 87:2870-2877, 1996
68. Huret JL, Brizard A, Slater R, et al: Cytogenetic heterogeneity in t(11;19) acute leukemia: Clinical, hematological and cytogenetic analyses of 48 patients—Updated published cases and 16 new observations. *Leukemia* 7:152-160, 1993
69. Moorman AV, Hagemeyer A, Charrin C, et al: The translocations, t(11;19)(q23;p13.1) and t(11;19)(q23;p13.3): A cytogenetic and clinical profile of 53 patients. *European 11q23 Workshop participants. Leukemia* 12:805-810, 1998
70. Pui CH, Campana D: Age-related differences in leukemia biology and prognosis: The paradigm of MLL-AF4-positive acute lymphoblastic leukemia. *Leukemia* 21:593-594, 2007
71. Pui CH, Frankel LS, Carroll AJ, et al: Clinical characteristics and treatment outcome of childhood acute lymphoblastic leukemia with the t(4;11)(q21;q23): A collaborative study of 40 cases. *Blood* 77:440-447, 1991
72. Rubnitz JE, Camitta BM, Mahmoud H, et al: Childhood acute lymphoblastic leukemia with the MLL-ENL fusion and t(11;19)(q23;p13.3) translocation. *J Clin Oncol* 17:191-196, 1999
73. Swansbury GJ, Slater R, Bain BJ, et al: Hematological malignancies with t(9;11)(p21-22;q23)—A laboratory and clinical study of 125 cases. *European 11q23 Workshop participants. Leukemia* 12:792-800, 1998
74. Bhojwani D, Sposto R, Shah NN, et al: Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *Leukemia* 33:884-892, 2019
75. Gore L, Locatelli F, Zugmaier G, et al: Survival after blinatumomab treatment in pediatric patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia. *Blood Cancer J* 8:80, 2018
76. Locatelli F, Whitlock JA, Peters C, et al: Blinatumomab versus historical standard therapy in pediatric patients with relapsed/refractory Ph-negative B-cell precursor acute lymphoblastic leukemia. *Leukemia* 34:2473-2478, 2020
77. Maude SL, Frey N, Shaw PA, et al: Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med* 371:1507-1517, 2014
78. Maude SL, Shpall EJ, Grupp SA: Chimeric antigen receptor T-cell therapy for ALL. *Hematology Am Soc Hematol Educ Program* 2014:559-564, 2014
79. von Stackelberg A, Locatelli F, Zugmaier G, et al: Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *J Clin Oncol* 34:4381-4389, 2016
80. Kuhn MW, Armstrong SA: Designed to kill: Novel menin-MLL inhibitors target MLL-rearranged leukemia. *Cancer Cell* 27:431-433, 2015



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Outcomes of Childhood Noninfant Acute Lymphoblastic Leukemia With 11q23/*KMT2A* Rearrangements in a Modern Therapy Era: A Retrospective International Study**

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