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Low rate of nonrelapse mortality in under-4-year-olds with ALL given chemotherapeutic conditioning for HSCT: a phase 3 FORUM study

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Key Points

- In the phase 3 FORUM trial, children aged <4 years with high-risk ALL had allogeneic HSCT after chemotherapeutic conditioning.
- Chemotherapeutic conditioning allowed for HSCT with a low complication and mortality rate in this vulnerable patient cohort.

Allogeneic hematopoietic stem cell transplantation (HSCT) is highly effective for treating pediatric high-risk or relapsed acute lymphoblastic leukemia (ALL). For young children, total body irradiation (TBI) is associated with severe late sequelae. In the FORUM study (NCT01949129), we assessed safety, event-free survival (EFS), and overall survival (OS) of 2 TBI-free conditioning regimens in children aged <4 years with ALL. Patients received fludarabine (Flu), thiotepa (Thio), and either busulfan (Bu) or treosulfan (Treo) before HSCT. From 2013 to 2021, 191 children received transplantation and were observed for ≥ 6 months (median follow-up: 3 years). The 3-year OS was 0.63 (95% confidence interval [95% CI], 0.52-0.72) and 0.76 (95% CI, 0.64-0.84) for Flu/Thio/Bu and Flu/Thio/Treo ($P = .075$), respectively. Three-year EFS was 0.52 (95% CI, 0.41-0.61) and 0.51 (95% CI, 0.39-0.62), respectively ($P = .794$). Cumulative incidence of nonrelapse mortality (NRM) and relapse at 3 years were 0.06 (95% CI, 0.02-0.12) vs 0.03 (95% CI, <0.01-0.09) ($P = .406$) and 0.42 (95% CI, 0.31-0.52) vs 0.45 (95% CI, 0.34-0.56) ($P = .920$), respectively. Grade >1 acute graft-versus-host disease (GVHD) occurred in 29% of patients receiving Flu/Thio/Bu and 17% of those receiving Flu/Thio/Treo ($P = .049$), whereas grade 3/4 occurred in 10% and 9%, respectively ($P = .813$). The 3-year incidence of chronic GVHD was 0.07 (95% CI, 0.03-0.13) vs 0.05 (95% CI, 0.02-0.11), respectively ($P = .518$). In conclusion, both chemotherapeutic conditioning regimens were well tolerated and NRM was low. However, relapse was the major cause of treatment failure. This trial was registered at www.clinicaltrials.gov as #NCT01949129.

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Data are available on request from the corresponding author, Peter Bader (p.bader@em.uni-frankfurt.de).

The full-text version of this article contains a data supplement.

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Introduction

Over recent decades, tremendous progress has been made in the treatment of children and adolescents with acute lymphoblastic leukemia (ALL). Rigorous studies to optimize treatment strategies, including allogeneic hematopoietic stem cell transplantation (HSCT), have driven this considerable success, with survival rates now approaching 90%.¹⁻⁴

Allogeneic HSCT is an important option for children with high-risk ALL, for whom conventional chemotherapy offers a dismal prognosis, and for infants with high-risk leukemia.^{5,6} Children with a slow response to initial treatment, as measured by minimal residual disease (MRD) monitoring, and children with genetic alterations associated with a poor prognosis such as hypodiploidy, *KMT2A* rearrangements, or *TP53* mutations are candidates for allogeneic HSCT.^{3,5,7-9} For patients who relapse after initial treatment, the site of relapse, time from initial diagnosis to relapse, immunophenotype, and response to remission induction are the major factors determining an indication for allogeneic HSCT.¹⁰⁻¹²

Allogeneic HSCT has proven immunological antileukemic efficacy in children with ALL through the so-called graft-versus-leukemia effect.¹³ Allogeneic HSCT was shown to contribute to a substantial improvement in the survival probability of patients with high-risk ALL in first or second complete remission (CR1 and CR2).^{4,9,14} Standardization of HSCT procedures was key to this progress. The ALL-SCT-BFM-2003 trial demonstrated that the outcomes for children with ALL who received a transplant from an unrelated donor matched for at least 9 of 10 HLA loci (matched unrelated donor [MUD]) were comparable with those of children who received a transplant from a matched sibling donor (MSD).¹⁵ In that study, HSCT in children aged >4 years was performed after conditioning with total body irradiation (TBI) and etoposide (Eto), resulting in excellent rates of leukemia-free survival and overall survival (OS).¹⁵

In the past, both relapse-related mortality and nonrelapse mortality (NRM) were major causes of treatment failure in infants and young children with high-risk ALL. Because TBI has lifelong adverse effects on growth, cognitive function, and fertility and promotes the occurrence of endocrinopathies and cataracts, it is not used for young children in most countries. However, the optimal chemotherapeutic approach (chemotherapeutic conditioning) to achieve high event-free survival (EFS) and reduce NRM has not yet been defined. Thus, in the nonrandomized part of the phase 3 “For Omitting Radiation Under Majority age” (FORUM) trial we set out to compare 2 established chemotherapeutic conditioning regimens for children younger than 4 years.

Methods

Study design

The FORUM study is a prospective, international, multicenter, randomized, open-label, active-comparator controlled, phase 3 trial (EudraCT 2012-003032-22; www.clinicaltrials.gov: NCT01949129). In the randomized portion, children aged ≥ 4 years with high-risk ALL were randomized to receive either TBI and Eto or chemotherapeutic conditioning alone before HSCT.¹⁶ In the nonrandomized part (reported here), children aged <4 years with high-risk ALL were

allocated to chemotherapeutic conditioning in 88 centers in 21 countries (supplemental Appendix 1).

Two widely established myeloablative chemotherapeutic conditioning regimens were used: fludarabine (Flu) and thiotepea (Thio) with either IV busulfan (Bu) or treosulfan (Treo). Participating countries decided before starting the trial whether patients would receive Bu- or Treo-based conditioning.

The study was designed by members of several national pediatric transplantation groups, with the contribution of experts from the ALL-Frontline and Relapse study groups. The protocol and the statistical analysis plan were approved by the international steering committee, the national competent authorities for each country, and the local ethic committees for each participating center. The trial was performed according to the Declaration of Helsinki and was registered with international trial registries.

Between April 2013 and July 2021, 202 patients aged <4 years were registered for the trial and underwent HSCT before October 2021. The data cutoff was 1 February 2022, allowing a minimum observation period after HSCT of 6 months (and up to 7.2 years).

Patients

Patients eligible for the study had either relapsed or high-risk ALL as an indication for allogeneic HSCT according to frontline treatment protocols, were in morphological CR before HSCT, and had either an HLA-identical MSD or a donor matched after 4-digit high-resolution HLA typing in HLA-A, -B, -C, -DR, and -DQ in at least 9 of 10 evaluated loci (MUD). MSDs and MUDs fulfilling these criteria were defined as matched donors. The recommended stem cell source was bone marrow, peripheral blood, or cord blood from a matched donor. Written informed consent was provided by patients' parents or their legal guardians.

Procedures

Conditioning regimens consisted of Flu 30 mg/m² once a day over 5 days (total dose: 150 mg/m²), Thio 5 mg/kg twice a day for 1 day (total dose: 10 mg/kg), and either Treo 14 g/m² once a day for 3 consecutive days, or Bu 4 mg/kg over 4 consecutive days. Bu was given according to local guidelines, commonly with therapeutic drug monitoring (TDM) and dose adjustments. The recommended first dose of Bu was according to the European Medicines Agency dosing nomogram, with a TDM target of daily area under the curve of 14.8 to 21.6 mg/h per L (historical target).¹⁷

The decision to use either Bu- or Treo-based regimen was decided by the participating countries before the start of the trial.

Graft-versus-host disease (GVHD) prophylaxis was performed according to donor type. Patients who received a transplant from an MSD received cyclosporine only, whereas patients with MUDs received cyclosporine, methotrexate, and either antithymocyte globulin (thymoglobulin, 2.5 mg/kg for 3 days) or anti-T-cell globulin (grafalon, 15 mg/kg for 3 days), as detailed previously.¹⁰

CR was defined as <5% blasts in the bone marrow and no evidence of extramedullary disease. Relapse was defined as $\geq 5\%$ blasts and/or evidence of extramedullary disease. Adverse events (AEs), adverse reactions, serious AEs, and suspected or unexpected AEs were assessed by clinicians according to good clinical practice guidelines. Grading of AEs was performed according to

the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 4.03. Life-threatening, or other medically important serious events leading to intensive care unit admission were considered serious AEs. Acute and chronic GVHD was assessed according to the Glucksberg criteria.¹⁸

Outcomes

The primary end point was OS calculated from the date of transplantation to death from any cause, which was considered the event. Patients lost to follow-up without an event were censored at last follow-up. Secondary end points included EFS, cumulative incidence of relapse (CIR), NRM, and acute GVHD on day 100, cumulative incidence of chronic GVHD, GVHD-free and relapse-free survival (GRFS), and nonhematological AEs grade 3/4 on day 100.

EFS was calculated from the date of receiving transplantation to relapse, secondary malignancy, or death from any cause, whichever occurred first. Data of patients lost to follow-up without an event were censored on the date of their last follow-up evaluation. When calculating CIR, death without relapse/progression and secondary malignancy were considered competing events. Relapse and secondary malignancy were competing events for calculating the cumulative incidence of NRM; death without malignancy was a competing event for calculating the cumulative incidence of secondary malignancy. Relapse, progression of disease, death, and secondary malignancy were competing events for calculating GRFS. Acute GVHD (grade 3/4) was considered an event at day of onset. GRFS was calculated from date of transplantation to the first event.

Statistical analysis

The data analysis was conducted by U.P., and all authors had access to the primary clinical trial data. The significance level was set at .05 for all statistical analyses. OS, EFS, and GRFS were estimated using the Kaplan-Meier method, and the difference among groups was compared using the log-rank test. Three-year estimates and 95% confidence intervals (CIs) are reported in the manuscript.

Baseline characteristics evaluated were sex, age at HSCT and diagnosis, immunophenotype of ALL, MRD before HSCT, genetic aberrations, hypodiploidy or hyperdiploidy, donor type, stem cell source, remission status, and site and time of first relapse in CR2 patients. MRD was classified as low load ($<10^{-4}$) or high load ($\geq 10^{-4}$) detected via polymerase chain reaction or flow cytometry.

The proportion of patients with grade 3/4 acute GVHD and other AEs of grade 3/4 on day 100 as well as the distribution of baseline characteristics was compared using the χ^2 test. CIR, NRM, and secondary malignancy were estimated taking into account competing events and compared using the Gray test.

For multivariable analysis, Cox regression was used to explore the impact of baseline characteristics and conditioning regimen on OS and EFS. Factors evaluated were conditioning regimen, donor type, remission status, age at HSCT and diagnosis, presence of *KMT2A* rearrangements, and immunophenotype.

Median follow-up was estimated using the inverse Kaplan-Meier method.¹⁹

Results

Patient characteristics

Between April 2013 and July 2021, 202 patients aged <4 years from 21 countries underwent HSCT according to the FORUM protocol. Patient characteristics are shown in Table 1 for the 2 treatment arms. Eleven patients were excluded from this analysis: 5 received TBI-based conditioning, 3 had inconclusive documentation of the conditioning regimen, and 3 had no follow-up data reported. This led to 191 evaluable patients (Figure 1 [CONSORT diagram]).

Of the 191 evaluable patients, 107 (56%) were male and 84 (44%) were female. Median age at HSCT was 2.2 years (range, 0.5-4 years); 90 patients were aged <2 years (47%) and 101 were older (53%) at time of HSCT. At diagnosis, 92 patients (48%) were aged <1 year, and 99 patients (52%) were older. In total, 156 patients (82%) had B-cell precursor ALL, 28 patients (15%) had T-cell ALL, 6 patients (3%) had different phenotypes, and 1 patient (1%) had no differentiation reported. Genetic analysis at diagnosis revealed *BCR-ABL* in 13 patients (7%), *ETV6-RUNX1* in 6 patients (3%), and *KMT2A* rearrangements in 51 patients (29%).

Overall, 139 patients (73%) received transplantation in CR1, and 52 patients (27%) were in \geq CR2. In 154 patients (81%), the donor was an MUD, whereas 37 (19%) patients had an MSD. The stem cell source was bone marrow for 131 (69%) patients, peripheral blood for 35 (18%) patients, and cord blood for 23 (12%) of patients; 1 patient ($\sim 0.5\%$) had a combination of bone marrow and cord blood, and 1 ($\sim 0.5\%$) patient had no available details on stem cell source.

Survival

For the whole study population, the 3-year probabilities of EFS and OS were .52 (95% CI, 0.44-0.59) and .69 (95% CI, 0.61-0.76), respectively. In the univariable analysis, there was no difference in probability of EFS or OS for patients aged <2 years vs those aged ≥ 2 but <4 years, according to the immunophenotype or genetic aberration (Table 2). The probability of EFS was .40 (95% CI, 0.29-0.50) in patients aged <1 year at diagnosis ($n = 92$) and .63 (95% CI, 0.52-0.72) for patients aged ≥ 1 year at diagnosis ($n = 99$; $P = .002$), whereas the probability of OS did not differ between these age groups (.64 [95% CI, 0.52-0.74] vs .73 [95% CI, 0.63-0.81], respectively; $P = .220$).

The 139 patients who received transplantation in CR1 had a significantly higher probability of EFS (.58 [95% CI, 0.49-0.66]) and OS (.74 [95% CI, 0.65-0.81]) compared with the 52 patients who received transplantation in \geq CR2 (.36 [95% CI, 0.23-0.50] and .57 [95% CI, 0.41-0.69], respectively; $P = .011$ and $P = .029$). These differences were due to a lower CIR among patients who received transplantation in CR1 vs patients who received transplantation in \geq CR2, whereas there was no difference in the NRM. Donor type, stem cell source, genetic alterations, immunophenotype, and hypodiploidy or hyperdiploidy did not significantly affect the probability of EFS or OS (Table 2).

When assessed based on the conditioning regimen, patients who received transplantation after conditioning with Flu/Thio/Bu and Flu/Thio/Treo had a comparable probability of EFS at 3 years (.52 [95% CI, 0.41-0.61] vs .51 [95% CI, 0.39-0.62], respectively;

Table 1. Basic characteristics according to chemotherapeutic conditioning regimen

Baseline characteristic	Total (N = 191)		Chemotherapeutic conditioning regimen				P
			Flu/Thio/Bu (n = 100)		Flu/Thio/Treo (n = 91)		
Sex, n (%)							.564
Male	107	56%	58	58%	49	54%	
Female	84	44%	42	42%	42	46%	
Age at HSCT, y, n (%)							
<2 y	90	47%	42	42%	48	53%	.137
≥2	101	53%	58	58%	43	47%	
Age at diagnosis, n (%)							
<6 mo	58	30%	27	27%	31	34%	.325
6 mo-1 y	34	18%	16	16%	18	19%	
≥1 y	99	52%	57	57%	42	46%	
Immunophenotype							
BCP	156	82%	86	86%	70	77%	.140
T-cell ALL	28	15%	13	13%	15	16%	
Other	6	3%	1	1%	5	5%	
Unknown	1	1%		0%	1	1%	
Donor, n (%)							
MSD	37	19%	23	23%	14	15%	.184
MUD	154	81%	77	77%	77	85%	
Remission status, n (%)							
CR1	139	73%	67	67%	72	79%	.098
CR2	50	26%	31	31%	19	21%	
CR3	2	1%	2	2%	0	0%	
Stem cell source, n (%)							
Bone marrow	131	69%	63	64%	68	75%	.041
Peripheral blood	35	18%	17	17%	18	20%	
Cord blood	23	12%	18	18%	5	5%	
Bone marrow + peripheral blood	1	1%	1	1%	0	0%	
Unknown*	1	1%	1	1%	0	0%	
MRD before HSCT, n (%)							
Low load (<10 ^{−4})	105	70%	62	77%	43	61%	.044
High load (≥10 ^{−4})	46	30%	19	23%	27	39%	
Genetic aberration, n (%)							
KMT2A-AFF1	51	29%	24	26%	27	32%	.465
ETV6-RUNX1	6	3%	4	4%	2	2%	
BCR-ABL†	13	7%	9	10%	4	5%	
None of the above	108	61%	56	60%	52	61%	
Unknown*	13	7%	7	7%	6	7%	
Hypodiploidy, n (%)							
No	169	99%	88	99%	81	99%	.954
Yes	2	1%	1	1%	1	1%	
Unknown*	20	10%	11	11%	9	10%	
Hyperdiploidy, n (%)							
No	149	87%	76	85%	73	88%	.622
Yes	23	13%	13	15%	10	12%	
Unknown*	19	10%	11	11%	8	9%	

Percentages were calculated using evaluable patients as the denominator, unless otherwise stated.

BCP, B-cell precursor; CNS, central nervous system.

*Percentage based on the total number of patients.

[†]Includes 1 patient with *BCR-ABL* and *KMT2a-AFF1* and 2 patients with *BCR-ABL* and *ETV6-RUNX1*.

Table 1 (continued)

Baseline characteristic	Total (N = 191)		Chemotherapeutic conditioning regimen				P
			Flu/Thio/Bu (n = 100)		Flu/Thio/Treo (n = 91)		
Time of relapse, mo, n (%)							
<18	32	67%	18	60%	14	78%	.390
18-30	15	31%	11	37%	4	22%	
>30	1	2%	1	3%	0	0%	
Unknown*	2	4%	1	3%	1	5%	
Type of relapse, n (%)							
Bone marrow	29	58%	19	61%	10	53%	.807
CNS	10	20%	6	19%	4	21%	
Other	11	22%	6	19%	5	26%	

Percentages were calculated using evaluable patients as the denominator, unless otherwise stated.

BCP, B-cell precursor; CNS, central nervous system.

*Percentage based on the total number of patients.

†Includes 1 patient with *BCR-ABL* and *KMT2a-AFF1* and 2 patients with *BCR-ABL* and *ETV6-RUNX1*.

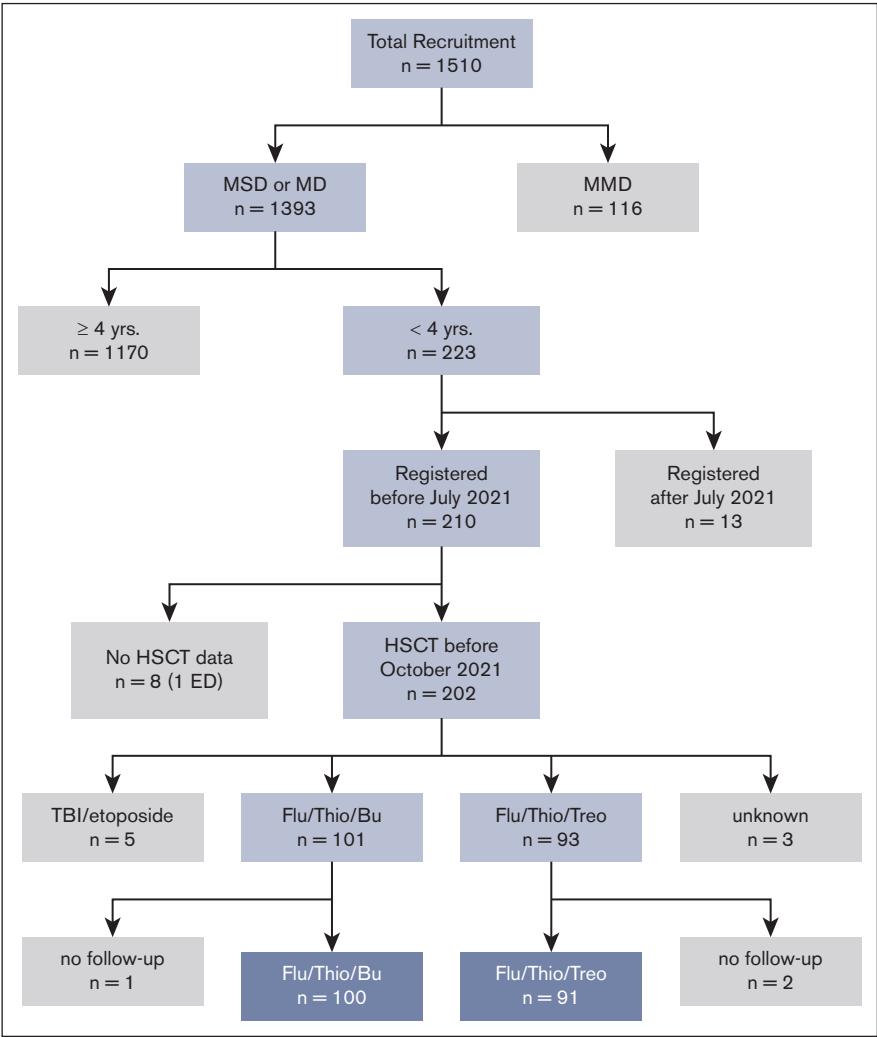


Figure 1. CONSORT diagram.

Table 2. Univariable analysis of the 3-year EFS and OS

	N	EFS			OS		
		Events	3-y EFS	P	Deaths	3-y OS	P
Total	191	87	0.52 (0.44-0.59)		56	0.69 (0.61-0.76)	
Sex							
Male	107	48	0.52 (0.41-0.61)	.989	31	0.69 (0.58-0.78)	.902
Female	84	39	0.52 (0.40-0.62)		25	0.69 (0.57-0.78)	
Age at HSCT, y							
<2	90	44	0.48 (0.37-0.59)	.328	26	0.71 (0.59-0.80)	.793
≥2	101	43	0.55 (0.44-0.64)		30	0.68 (0.57-0.76)	
Age at diagnosis, y							
<1	92	52	0.40 (0.29-0.50)	.002	30	0.64 (0.52-0.74)	.220
≥1	99	35	0.63 (0.52-0.72)		26	0.73 (0.63-0.81)	
Immunophenotype							
BCP	156	78	0.47 (0.38-0.55)	.038	50	0.66 (0.57-0.73)	.160
T-cell ALL	28	9	0.67 (0.46-0.81)		6	0.78 (0.57-0.89)	
Other	6	0	1.00 (1.00-1.00)		0	1.00 (1.00-1.00)	
MRD before HSCT							
Cutoff $\geq 10^{-4}$ vs $< 10^{-4}$							
Low	105	49	0.50 (0.40-0.60)	.172	32	0.68 (0.57-0.77)	.384
High	46	27	0.39 (0.24-0.53)		19	0.58 (0.42-0.71)	
Genetic aberration							
<i>KMT2A-AFF1</i>	51	28	0.41 (0.26-0.55)	.349	21	0.55 (0.39-0.68)	.164
<i>ETV6-RUNX1</i>	6	2	0.67 (0.19-0.90)		1	1.00 (1.00-1.00)	
<i>BCR-ABL*</i>	13	5	0.59 (0.28-0.81)		3	0.77 (0.44-0.92)	
None of the above	108	46	0.55 (0.45-0.64)		29	0.71 (0.60-0.79)	
Hypodiploidy							
No	169	78	0.51 (0.43-0.59)	.962	49	0.70 (0.61-0.77)	.761
Yes	2	1	0.50 (0.01-0.91)		1	0.50 (0.01-0.91)	
Hyperdiploidy							
No	149	71	0.50 (0.41-0.58)	.181	46	0.68 (0.59-0.75)	.195
Yes	23	8	0.65 (0.42-0.81)		4	0.81 (0.56-0.92)	
Donor							
MSD	37	14	0.58 (0.39-0.73)	.382	10	0.73 (0.54-0.85)	.883
MUD	154	73	0.50 (0.42-0.58)		46	0.68 (0.59-0.75)	
Remission status							
CR1	139	55	0.58 (0.49-0.66)	.035	34	0.74 (0.65-0.81)	.091
CR2	50	31	0.36 (0.22-0.49)		21	0.57 (0.41-0.70)	
CR3	2	1	0.50 (0.01-0.91)		1	0.50 (0.01-0.91)	
Remission status							.029
CR1	139	55	0.58 (0.49-0.66)	.011	34	0.74 (0.65-0.81)	
≥CR2	52	32	0.36 (0.23-0.50)		22	0.57 (0.41-0.69)	
Stem cell source							
Bone marrow	131	55	0.54 (0.45-0.63)	.264	37	0.70 (0.61-0.78)	.429
Peripheral blood	35	21	0.39 (0.23-0.55)		9	0.71 (0.52-0.84)	
Cord blood	23	11	0.52 (0.31-0.70)		10	0.58 (0.34-0.76)	
Bone marrow + peripheral blood	1	0	1.00 (1.00-1.00)		0	1.00 (1.00-1.00)	

Data presented are probabilities and 95% CIs. BCP, B-cell precursor; CNS, central nervous system.
 *Includes 1 patient with *BCR-ABL* and *KMT2A-AFF1* and 2 patients with *BCR-ABL* and *ETV6-RUNX1*.

Table 2 (continued)

	N	EFS			OS		
		Events	3-y EFS	P	Deaths	3-y OS	P
Time of relapse, mo							
<18	32	21	0.30 (0.14-0.47)	.577	13	0.60 (0.40-0.75)	.569
18-30	15	9	0.40 (0.16-0.63)		8	0.42 (0.16-0.66)	
>30	1	0	1.00 (1.00-1.00)		0	1.00 (1.00-1.00)	
Type of relapse							
Bone marrow	29	15	0.45 (0.26-0.63)	.017	9	0.66 (0.44-0.81)	.080
CNS	10	7	0.27 (0.05-0.56)		4	0.53 (0.17-0.80)	
Other	11	9	0.18 (0.03-0.44)		8	0.36 (0.11-0.63)	

Data presented are probabilities and 95% CIs. BCP, B-cell precursor; CNS, central nervous system.

*Includes 1 patient with *BCR-ABL* and *KMT2A-AFF1* and 2 patients with *BCR-ABL* and *ETV6-RUNX1*.

$P = .794$; Table 3; Figure 2). Probability of OS at 3 years was numerically lower for patients receiving Flu/Thio/Bu compared with patients receiving Flu/Thio/Treo (.63 [95% CI, 0.52-0.72] vs .76 [95% CI, 0.64-0.84], respectively; $P = .075$; Table 3; Figure 2).

Relapse

No difference was observed in the CIR or NRM between treatment arms. Importantly, of those patients who relapsed after HSCT ($n = 78$), those receiving Flu/Thio/Treo ($n = 37$) had a better OS at 3 years after relapse compared with those receiving Flu/Thio/Bu ($n = 41$; 0.38 [95% CI, 0.18-0.58] vs 0.16 [95% CI, 0.05-0.32], respectively; $P = .012$; Figure 2).

GVHD

The percentage of patients with severe acute GVHD was low, and there was no significant difference between the 2 treatment arms through day 100. Of the patients evaluable on day 100, 29 of 100 (29%) receiving Flu/Thio/Bu developed grade 2 to 4 acute GVHD and 10 of 100 (10%) developed grade 3/4 acute GVHD, whereas 15 of 89 (17%) receiving Flu/Thio/Treo developed grade 2 to 4 acute GVHD and 8 of 89 (9%) experienced grade 3/4 acute GVHD (Table 3).

At 3 years, the cumulative incidence of chronic GVHD among patients receiving Flu/Thio/Bu and Flu/Thio/Treo was 0.07 (95% CI, 0.03-0.13) and 0.05 (95% CI, 0.02-0.11), respectively ($P = .518$; Table 3). GRFS at 3 years was 0.41 (95% CI, 0.31-0.51) in the Flu/Thio/Bu group compared with 0.41 (95% CI, 0.29-0.52) in the Flu/Thio/Treo group ($P = .663$; Figure 2).

Multivariable analysis

In the multivariable analysis of EFS (which considered conditioning regimen, donor source, remission status, immunophenotype, age at HSCT, and *KMT2A* gene rearrangement), we found only age < 1 year at diagnosis to be significantly associated with a reduced outcome (hazard ratio [HR], 0.49 for age ≥ 1 year). For OS, only the presence of *KMT2A* gene rearrangement was found to be negatively associated with outcome, with an HR of 1.96 (Table 4).

Toxicity and safety

Both regimens were well tolerated, with very favorable toxicity and safety. In supplemental Table 1 (supplemental Appendix 2) all AEs

are listed. When comparing the Flu/Thio/Bu and Flu/Thio/Treo groups, the most frequently reported nonhematological toxicities were stomatitis (grade 3/4: 33% and 41%, respectively), infection (grade 3/4: 42% and 44%, respectively), and nausea (grade 3/4: 31% and 26%, respectively). Grade 3/4 veno-occlusive disease (VOD) of the liver occurred in 12% of patients in the Flu/Thio/Bu group compared with 0% in the Flu/Thio/Treo group. Secondary malignancies were not observed (supplemental Table 1).

Historical comparison

In the previously reported studies ALL-SCT BFM 2003 (NCT01423747)¹⁵ and ALL-SCT BFM International (NCT01423500),²⁰ 35 and 16 children, respectively, aged 2 to 4 years received TBI/Eto conditioning. We performed a retrospective analysis to compare these 2 cohorts with the 101 children aged 2 to 4 years in this FORUM trial. In the ALL-SCT BFM 2003 trial, 3-year probability of EFS and OS was 0.83 (95% CI, 0.66-0.92) and 0.91 (95% CI, 0.76-0.97), respectively, for children aged 2 to 4 years,¹⁵ whereas in the ALL-SCT BFM International trial, the 3-year probabilities of EFS and OS were .87 (95% CI, 0.57-0.97) and .93 (95% CI, 0.61-0.99), respectively.²⁰ In comparison, in this FORUM trial, 3-year probabilities of EFS and OS for children aged 2 to 4 years receiving either chemotherapeutic conditioning regimen were .55 (95% CI, 0.44-0.64) and .68 (95% CI, 0.57-0.76), respectively (Figure 3).

Discussion

Allogeneic HSCT is an important treatment option for pediatric ALL. When initiating the FORUM trial, international experts had reached consensus to raise the age at which children with ALL could receive TBI from 2 to 4 years. The aim was to prevent the severe late effects of radiation therapy in younger children.^{6,21} As a consequence, 2 chemotherapeutic conditioning regimens were used for children aged <4 years in the trial. Morbidity was generally low, and the NRM rates at 3 years were 6% with Flu/Thio/Bu and 3% with Flu/Thio/Treo. This is a remarkably low NRM rate for such a high-risk group, considering that it was obtained in a multicenter, international trial in which 81% of patients received a transplant from an MUD.

We did not find statistically significant differences in the NRM rates between patients who received transplantation with low MRD and those with high MRD; however, that might be because of small

Table 3. Outcome according to conditioning regimen

	Flu/Thio/Bu	Flu/Thio/Treo	P
Evaluable patients, n	100	91	
Primary end point			
Death			
Death, n	36	20	
3-y OS (95% CI)	0.63 (0.52-0.72)	0.76 (0.64-0.84)	.075
Secondary end points			
Any failure			
Relapse, secondary malignancy, or death, n	47	40	
3-y EFS (95% CI)	0.52 (0.41-0.61)	0.51 (0.39-0.62)	.794
Relapse			
Relapse, n	41	37	
3-y CIR (95% CI)	0.42 (0.31-0.52)	0.45 (0.34-0.56)	.920
NRM			
Death in CR, n	6	3	
3-y NRM (95% CI)	0.06 (0.02-0.12)	0.03 (<0.01-0.09)	.406
Acute GVHD by day 100			
Evaluable, n	100	89	
Grade 0/1, n (%)	71 (71%)	74 (83%)	
Grade 2, n (%)	19 (19%)	7 (8%)	.049*
Grade 3/4, n (%)	10 (10%)	8 (9%)	.813†
cGVHD by 3 y			
cGVHD/events without cGVHD/patients, n	7/45/100	4/39/90	
3-y cumulative incidence of cGVHD (95% CI)	0.07 (0.03-0.13)	0.05 (0.02-0.11)	.518
3-y cumulative incidence of event without cGVHD (95% CI)	0.46 (0.36-0.56)	0.48 (0.36-0.59)	.902
GVHD and relapse			
Events/patients, n	57/99	47/88	
3-y GRFS (95% CI)	0.41 (0.31-0.51)	0.41 (0.29-0.52)	.663
Nonhematologic AEs of grade 3/4 at day 100			
Evaluable, n	98	91	
Grade 3/4, n (%)	76 (78%)	63 (69%)	.195

cGVHD, chronic GVHD.

*Grade 1 to 4 acute GVHD.

†Grade 3 to 4 acute GVHD.

patient numbers. Patients with aberrations in the *KMT2A-AFF1* gene had a nearly twofold higher HR for death than patients without this aberration. Children who were diagnosed with ALL at an age <1 year had poorer EFS than those diagnosed when older. However, allogeneic HSCT could rescue them if they received transplantation in CR1.

One of the most important findings of this part of the FORUM trial is that remission status at the time of HSCT affects the prognosis of children with ALL aged <4 years. Children aged <4 years who underwent HSCT in CR1 achieved higher EFS and OS than those who received transplantation in CR2 or CR3, comparable with children aged >4 years who underwent chemotherapeutic conditioning in the randomized part of FORUM.¹⁶

We found similar outcomes for patients who received transplantation from either an MUD or an MSD. As demonstrated in our

previous studies, this outcome for MUD HSCT is achieved using a stringent transplant protocol with in vivo T-cell depletion/modulation using antithymocyte globulin or anti-T-cell globulin.^{15,16} The use of serotherapy most likely also contributed to the very low incidence of severe acute GVHD and chronic GVHD.

In this vulnerable age group of patients with ALL, the composition of the conditioning regimen plays an important role with regard to toxicity and mortality. We observed a very low rate of NRM of only 0.06 (95% CI, 0.02-0.12) in the Flu/Thio/Bu cohort and 0.03 (95% CI, <0.01-0.09) in the Flu/Thio/Treo cohort. VOD occurred in only 12% of patients receiving Bu. Our results are superior to those observed in other trials, such as the Japanese Pediatric Leukemia/Lymphoma Study Group MLL-10 trial, which used conditioning with Bu, cyclophosphamide, and Eto, and reported VOD and pulmonary toxicities in 21.9% and 28.1% of patients, respectively.⁵

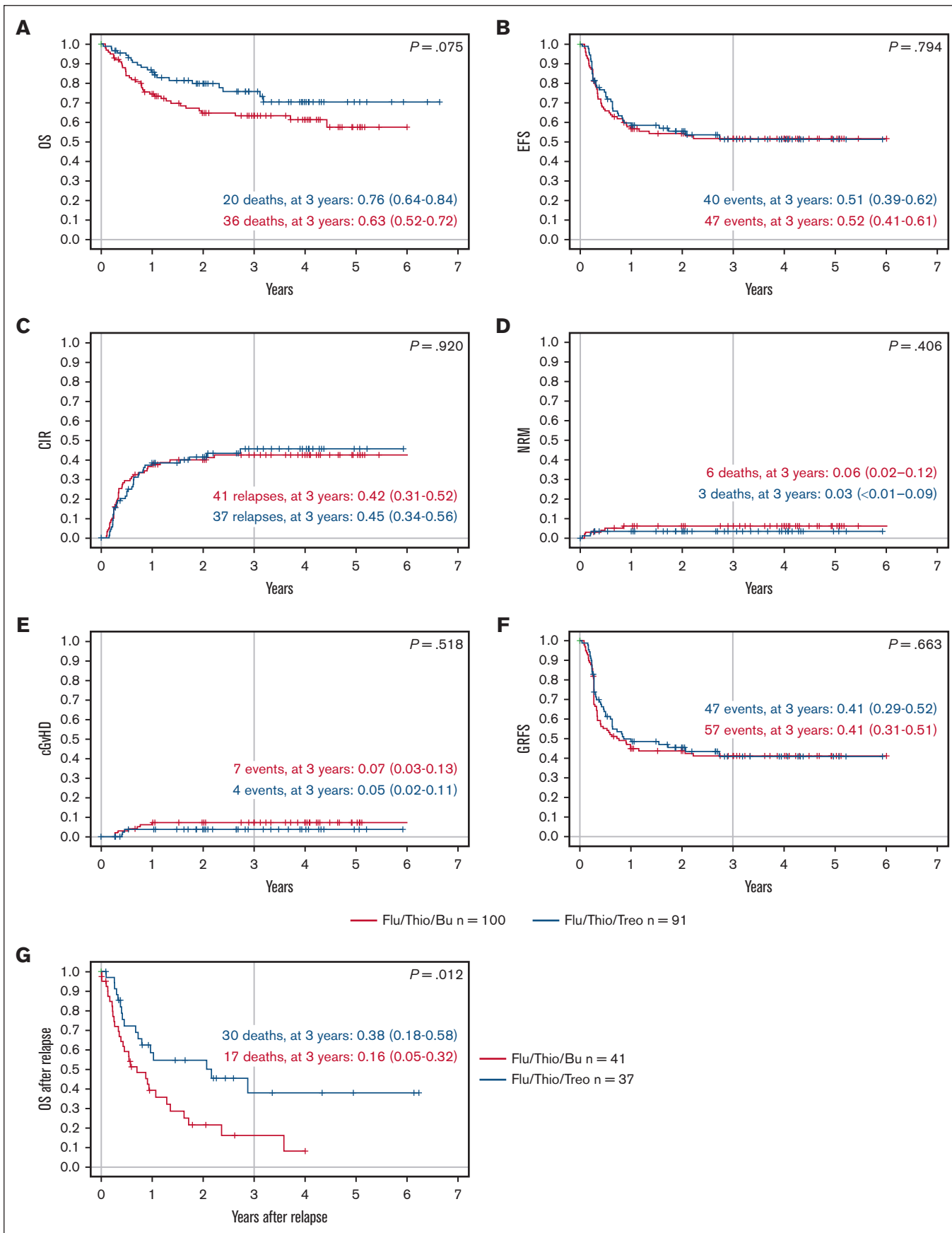


Figure 2.

Table 4. Multivariable analysis of OS and EFS

		EFS		OS	
		HR (95% CI)	P	HR (95% CI)	P
Conditioning regimen	Flu/Thio/Bu	1		1	
	Flu/Thio/Treo	0.94 (0.60-1.46)	.769	0.64 (0.37-1.13)	.124
Donor	MSD	1		1	
	MUD	1.31 (0.71-2.42)	.388	3 (0.51-2.10)	.928
Remission status	CR1	1		1	
	≥CR2	1.49 (0.88-2.52)	.136	1.44 (0.75-2.76)	.271
Immunophenotype	BCP	1		1	
	T-cell ALL	0.81 (0.37-1.78)	.603	0.98 (0.38-2.49)	.964
	Other	NA*	NA*	NA*	NA*
Age at HSCT, y	<2	1		1	
	>2 to ≥4	1.23 (0.74-2.08)	.403	1.42 (0.62-3.22)	.405
<i>KMT2A-AFF1</i>	No	1		1	
	Yes	1.25 (0.74-2.08)	.403	1.96 (1.05-3.68)	.036
Age at diagnosis, y	<1	1		1	
	≥1	0.49 (0.25-0.99)	.046	0.70 (0.31-1.59)	.397

*No estimates or *P* values are given because of limited sample size in this subgroup (6 patients and 0 events).

Although TDM was used in that trial to guide Bu concentration, these complication rates were high. In the Interfant-06 trial, the conditioning regimen was Bu, cyclophosphamide, and melphalan between 2006 and 2011: 13 of 50 children (26%) died because of HSCT-related complications. Thereafter, the conditioning regimen was changed to Flu/Thio/Bu, and between 2012 and 2016 only 3 of 61 patients (5%) died in remission after HSCT.²²

No difference was observed with regard to the probability of EFS, CIR, or NRM between the 2 regimens used in the FORUM trial. It is to be acknowledged, however, that in the Treo group, slightly more patients were treated in CR1 and fewer patients received cord blood grafts than in the Bu group.

Interestingly, patients conditioned with Flu/Thio/Treo with subsequent relapse had a better probability of OS than patients receiving Flu/Thio/Bu. Because data on posttransplant treatment of relapse were not available, one can only speculate on the reason for this finding. It might be that patients relapsing after HSCT conditioned with Treo-based regimens have another chance of rescue with either a second allograft or chimeric antigen receptor (CAR) T-cell therapy.²³⁻²⁵ In fact, in a recent retrospective study of European real-world data of patients with ALL who relapsed after HSCT and were treated with the anti-CD19 CAR T-cell therapy tisagenlecleucel, patients had superior EFS and OS when the conditioning for HSCT was based on Treo not Bu.²⁶ Importantly, in our study, Bu-based conditioning was chosen and administered in countries with access to anti-CD19 CAR T-cell therapies.

Although our study protocol provided a robust platform for safe allogeneic HSCT in young children with high-risk ALL and achieved

low NRM rates, the 3-year EFS and OS rates were low vs historical cohorts of patients aged 2 to 4 years receiving TBI/Eto (from the ALL-SCT BFM 2003 trial and the ALL-SCT BFM International trial).

Because no observed increase in fatal complication rates has been observed in trials comparing TBI with chemotherapy in childhood ALL, the ideal age threshold below which non-TBI-containing regimens should be used is yet to be determined.^{16,27,28} Previous long-term studies have demonstrated that younger age at HSCT is a risk factor for compromised cognitive development in a dose-dependent manner, particularly when conditioning regimens involve myeloablative doses of TBI.^{27,29} Furthermore, younger children who undergo TBI are susceptible to enduring long-term toxicities such as gonadal and thyroid dysfunction, growth impairment, and secondary malignancies, but this does happen with Bu-based regimens as well.

In the ALL-SCT BFM 2003 trial, 4 of 55 children aged 2 to 4 years developed a secondary malignancy within 10 years after transplantation, all of whom were treated with TBI.³⁰ Secondary malignancies have been reported with Bu-containing regimens too and other long-term toxicities are reported as well,^{31,32} whereas data on the long-term effects of Treo-containing regimens are currently lacking.

Further prospective studies are required to determine the optimal age for TBI conditioning in pediatric patients with ALL. In light of this, the planned FORUM-2 trial will assign children aged >2 years to TBI/Eto conditioning before HSCT. In children aged <2 years, upfront treatment with immunotherapy using blinatumomab or inotuzumab could be helpful in reducing disease recurrence.³³

Figure 2. Key outcomes according to conditioning regimen. (A) Probability of OS; (B) probability of EFS over time; (C) CIR; (D) NRM; (E) probability of cGVHD; (F) probability of GRFS over time; and (G) probability of OS after relapse. Flu/Thio/Bu is shown in red and Flu/Thio/Treo in blue. *n* = 100 for Flu/Thio/Bu, and *n* = 91 for Flu/Thio/Treo for panels A to F; *n* = 41 for Flu/Thio/Bu, and *n* = 37 for Flu/Thio/Treo for panel G; 95% CIs are shown in parentheses. cGVHD, chronic GVHD.

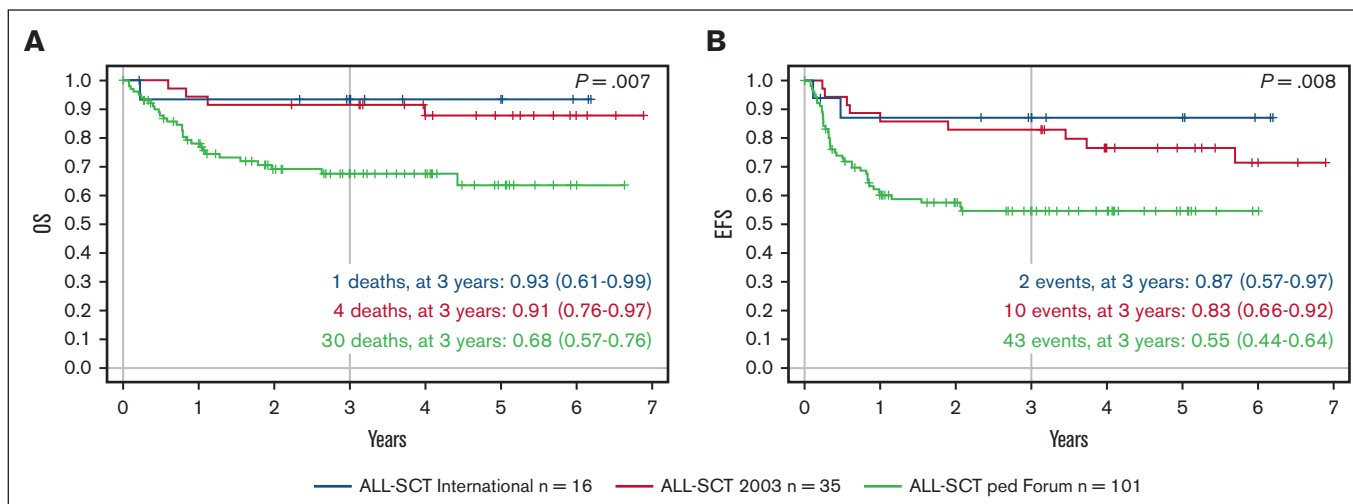


Figure 3. Outcomes in comparison with those of historical cohorts of children aged ≥ 2 but < 4 years with high-risk ALL undergoing HSCT. (A) Probability of OS over time and (B) probability of EFS over time, showing the ALL-SCT BFM International trial of TBI/Eto (blue; $n = 16$), the ALL-SCT BFM 2003 trial of TBI/Eto (red; $n = 35$), and children aged > 2 but ≤ 4 years in the FORUM study of chemotherapeutic conditioning (green; $n = 101$).

Deciding upon the best choice of conditioning, and weighing the possible lifelong consequences of sequelae against the risk of relapse is a very challenging decision. Addressing and acknowledging the individual risks and fears of each child and their family should remain an important part of the shared decision process.

In conclusion, this nonrandomized part of the international, multicenter FORUM trial showed that chemotherapeutic conditioning with either Flu/Thio/Bu or Flu/Thio/Treo allows for HSCT for children with high-risk ALL aged < 4 years with a low complication rate. Further prospective trials are required and planned to reduce the risk of leukemia recurrence and to improve survival in this vulnerable young population.

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Authorship

Contribution: All authors contributed to study conception and design, the collection and assembly of data, data analysis, manuscript writing, and final approval of the manuscript, and are

accountable for all aspects of the work; and all authors other than U.P. provided study materials or recruited patients.

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