original report

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

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abstract

PURPOSE Infant acute lymphoblastic leukemia (ALL) is characterized by *KMT2A* (*MLL*) gene rearrangements and coexpression of myeloid markers. The Interfant-06 study, comprising 18 national and international study groups, tested whether myeloid-style consolidation chemotherapy is superior to lymphoid style, the role of stem-cell transplantation (SCT), and which factors had independent prognostic value.

MATERIALS AND METHODS Three risk groups were defined: low risk (LR): *KMT2A* germline; high risk (HR): *KMT2A*-rearranged and older than 6 months with WBC count 300 $\times$ 10^9/L or more or a poor prednisone response; and medium risk (MR): all other *KMT2A*-rearranged cases. Patients in the MR and HR groups were randomly assigned to receive the lymphoid course low-dose cytosine arabinoside [araC], 6-mercaptopurine, cyclophosphamide (IB) or experimental myeloid courses, namely araC, daunorubicin, etoposide (ADE) and mitoxantrone, araC, etoposide (MAE).

RESULTS A total of 651 infants were included, with 6-year event-free survival (EFS) and overall survival of 46.1% (SE, 2.1) and 58.2% (SE, 2.0). In West European/North American groups, 6-year EFS and overall survival were 49.4% (SE, 2.5) and 62.1% (SE, 2.4), which were 10% to 12% higher than in other countries. The 6-year probability of disease-free survival was comparable for the randomized arms (ADE+MAE 39.3% [SE 4.0; n = 169] *v* IB 36.8% [SE, 3.9; n = 161]; log-rank $P = .47$). The 6-year EFS rate of patients in the HR group was 20.9% (SE, 3.4) with the intention to undergo SCT; only 46% of them received SCT, because many had early events. *KMT2A* rearrangement was the strongest prognostic factor for EFS, followed by age, WBC count, and prednisone response.

CONCLUSION Early intensification with postinduction myeloid-type chemotherapy courses did not significantly improve outcome for infant ALL compared with the lymphoid-type course IB. Outcome for infant ALL in Interfant-06 did not improve compared with that in Interfant-99.

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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

Infant acute lymphoblastic leukemia (ALL) is a rare aggressive type of leukemia. To address relevant treatment questions, large international collaborations are needed. The Interfant group was formed in 1999 and comprises 18 national and international study groups[1]. The *KMT2A* rearrangement is only present in 1% to 2% of older children with ALL but occurs in approximately 75% of infants with ALL. *KMT2A* is also rearranged in acute myeloid leukemia (AML) and is therefore also known as mixed-lineage leukemia (*MLL*).[2] Infant ALL occurs in an immature B-cell precursor with frequent coexpression of myeloid markers; is sensitive to cytosine arabinoside (araC),[3,4] a key drug for AML treatment; and can even switch to AML. Therefore, in this randomized Interfant-06 trial, we studied whether consolidation with myeloid-style chemotherapy is superior to lymphoid-style chemotherapy, on the backbone of Interfant chemotherapy. Additional aims were to determine the prognostic relevance of clinical and biologic parameters, establish the role of allogeneic stem-cell transplantation (SCT), and compare the outcome between Interfant-06 and Interfant-99. Because Interfant-99 showed outcome differences between the West European countries/North American institutes who initiated

Interfant (original groups) versus other countries mainly from South America, Eastern Europe, and Asia that joined later, analyses were also performed separately for these two groups. This is an unplanned post hoc comparison, which was decided after consulting the data monitoring committee.

MATERIALS AND METHODS

Patients and Eligibility Criteria

The Interfant-06 study was registered with the European Clinical Trials Database (EudraCT 2005-004599-19) and at (ClinicalTrials.gov identifier: NCT00550992). Patients were recruited from February 2006 to July 2016. Individual study groups obtained ethics approval and physicians obtained informed consent from parents. Eligibility criteria were a diagnosis of ALL (except those with a mature B phenotype), age 365 days or younger, and no prior antileukemic therapy other than emergency treatment.

Risk Group Stratification and Treatment

On the basis of Interfant-99, three risk groups were defined: low risk (LR): *KMT2A* germline; high risk (HR): presence of a *KMT2A*-rearrangement and age < 6 months at diagnosis, with WBC count 300×10^9/L or more at diagnosis or a poor prednisone response; and medium risk (MR): comprising all other *KMT2A*-rearranged patients. Treatment details are shown in the Data Supplement. Chemotherapy was given for 2 years according to Interfant-99. The response to prednisone is defined as good if the leukemic blast cell count per microliter of blood is less than 1,000 and defined as poor if this is equal to or greater than 1,000. Complete remission (CR) was defined at the end of induction as bone marrow with less than 5% leukemic cells and regenerating hematopoiesis without evidence of leukemia elsewhere. Patients in the MR and HR groups in CR were eligible for randomized treatment with the standard lymphoid course IB in the control group (low-dose araC, 6-mercaptopurine, cyclophosphamide) versus two experimental myeloid courses, namely araC, daunorubicin, etoposide (ADE) and mitoxantrone, araC, etoposide (MAE). This was followed by mercaptopurine, Ara-C, methotrexate, and asparaginase, and oncovin, cyclofosfamide, thioguanine, AraC, dexamethasone, asparaginase, and (daunorubine; OCTADA[D]) and maintenance therapy. All patients in the HR group were eligible to receive SCT. Patients in the MR group with minimal residual disease (MRD) greater than or equal to 10^{-4} at the start of OCTADA(D) were recommended for SCT from June 2009, because the Interfant-99 update showed a dismal outcome for them.[5]

End Points, Randomization, and Statistics

The randomized study aimed at recruiting 320 patients to have 80% power to detect a disease-free survival (DFS) difference of 16% at 3 years (41% DFS in the control arm; $\alpha = 0.05$). Randomization was performed by each group, with a centralized Web-based system on the basis of random permuted blocks stratified by participating group and risk group.

DFS, the primary end point, was defined as time from random assignment to relapse, death in continuous complete remission from any cause, or second malignant neoplasm, whichever occurred first. The secondary end point was overall survival (OS), defined as the time from random assignment to death from any cause. Other secondary end points were event-free survival (EFS) and OS for the whole cohort; EFS was defined as time from diagnosis to first failure, including death in induction, resistance to induction therapy (ie, no CR at end of induction), relapse, death in CR from any cause, or second malignant neoplasm, and OS as death from any cause. Final follow-up was updated on December 31, 2017, and the median follow-up time was 5.3 years (range, 0.1 to 11.4 years). In estimating end points, time was censored at last follow-up if no events had been observed.

EFS, DFS, and OS curves were computed using the Kaplan-Meier estimator and the respective SEs according to the Greenwood formula and compared with the log-rank test. The association of patient characteristics and risk group was assessed with the χ^2 test. Cumulative incidence of relapse and death in remission was estimated accounting for competing risks and compared with the Gray test. The impact of prognostic factors on outcome was analyzed using the log-rank test for univariate comparisons, using the Cox model and the Wald test for multivariable analyses comparing the outcome of subgroups identified by each factor and using the Cox model for EFS (single step) and the Wald test for the joint analysis of sex, age at diagnosis, WBC count at diagnosis, CD10 expression, *KMT2A* status, and prednisone response. All analyses were according to intention to treat. All tests were two sided. All analyses were performed using SAS 9.2.

RESULTS

Patient Characteristics

There were 651 infants recruited onto the study: 167 LR (26%), 320 MR (49%), and 164 HR (25%). The CONSORT flow diagram is shown in Figure 1. Patient characteristics are reported in the Data Supplement. Forty-five percent of patients were male. Age distribution at diagnosis was 21% younger than 3 months, 29% 3 to 6 months, 27% 6 to 9 months, and 23% 9 to 12 months. WBC count at diagnosis was 100×10^9/L or greater in 53% of patients and 300×10^9/L or greater in 29%. There were 10 infants with T-cell ALL (1.5%) and 25 with biphenotypic leukemia (3.8%). Of the 568 B-lineage patients with a known CD10 status, 63% were CD10$^-$. There were 510 patients with evaluable CNS status, of whom 83 (16%) had CNS involvement. *KMT2A* status was known in 643 patients, of which 74% were *KMT2A* rearranged; 44% had t(4;11), 22% t(11;19), 11% t(9;11), and 23% had other *KMT2A* translocations.

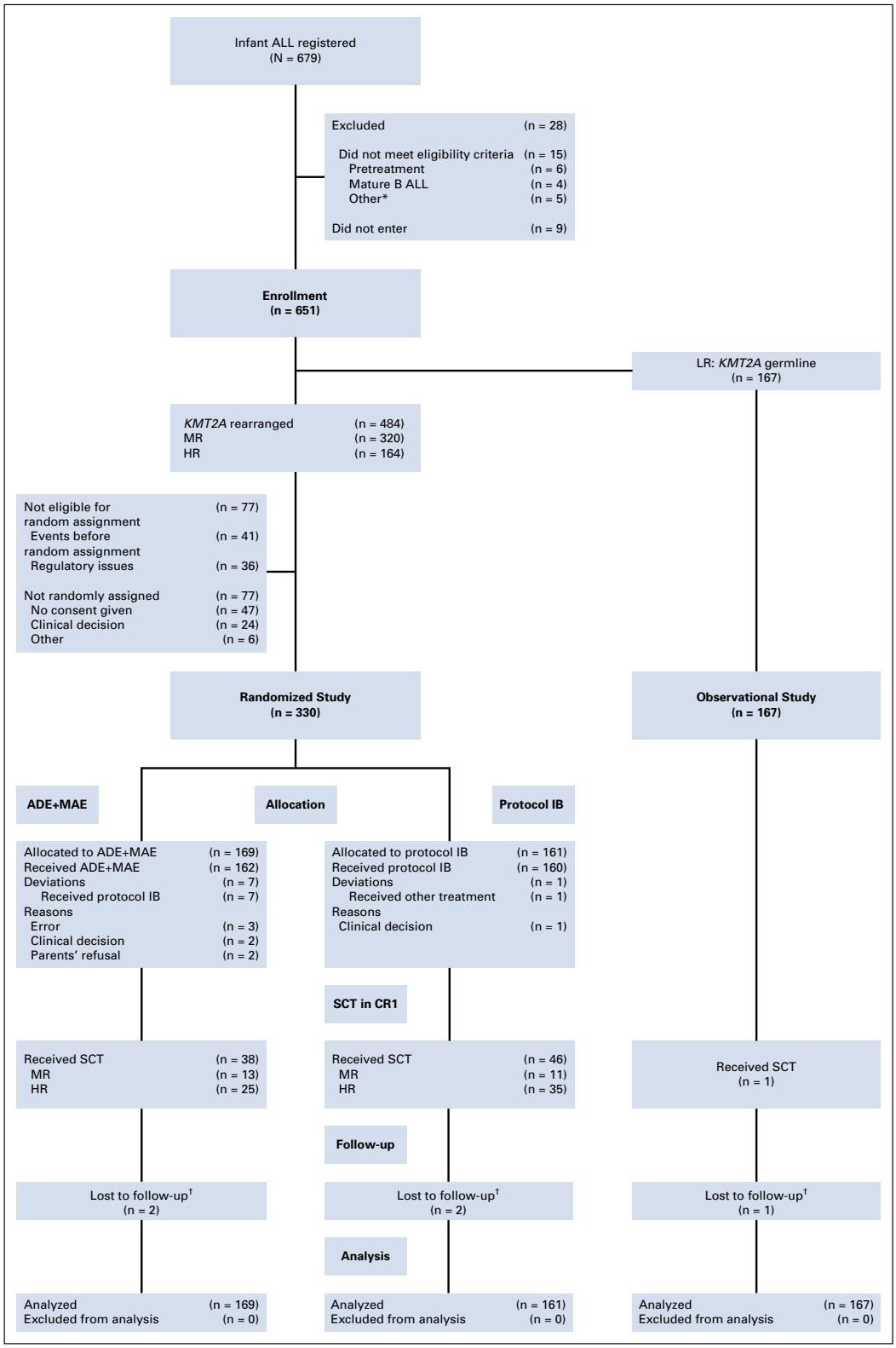
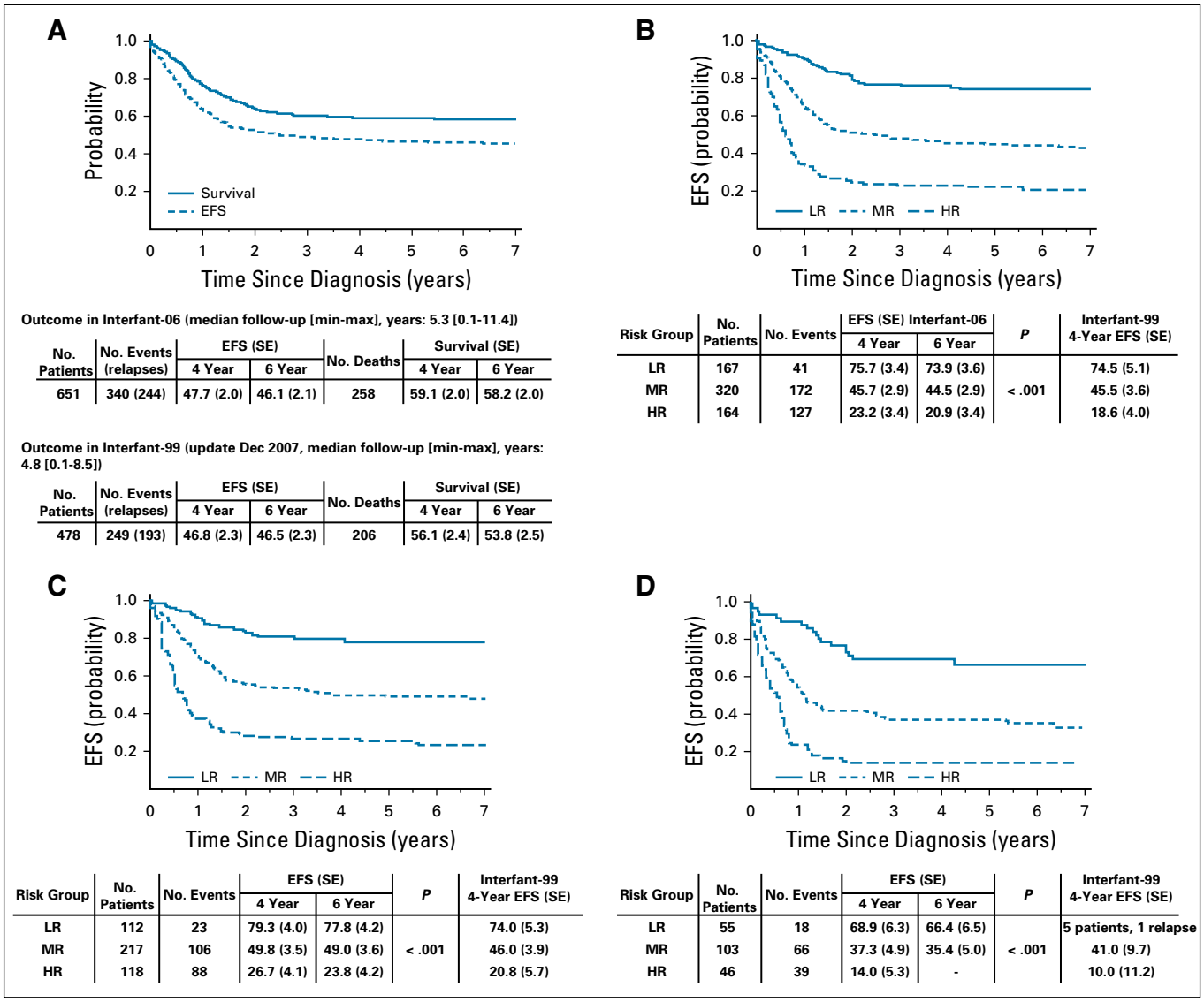


FIG 1. CONSORT diagram. (*) *KMT2A* status not investigated (n = 2), diagnosis and start of treatment outside the Interfant network (n = 2), Philadelphia-positive acute lymphoblastic leukemia (ALL; n = 1). (†) Patients lost to follow-up had no follow-up update after December 2015 and less than 4 years of follow-up from diagnosis to last contact (in the analyses, these patients are censored at the date of last contact). araC, cytosine arabinoside; ADE, araC, daunorubicin, etoposide; CR1, first complete remission; HR, high risk; IB, low-dose araC, 6-mercaptopurine, cyclophosphamide; LR, low risk; MAE, mitoxantrone, araC, etoposide; MR, medium risk; SCT, stem-cell transplantation.

Outcome

The 6-year EFS and OS probabilities (SE) of all 651 patients were 46.1% (2.1) and 58.2% (2.0), respectively (Fig 2A). Out of 651 patients, 605 (92.9%) achieved CR, 24 (3.7%) died during induction, and 22 (3.4%) did not achieve CR after induction therapy, of whom 19 died (Data Supplement). There were 244 (37.5%) relapses, with 66.0% isolated bone marrow (BM) recurrences, 11.9% isolated CNS, 1.2% isolated testicular, 13.1% combined BM and CNS, 2.1% combined BM and testis, and 5.7% others. Death in remission occurred in 46 patients (7.1%); 52% were due to infection, and 35% were in patients who underwent SCT. Four patients experienced a second tumor; none of these patients died. Events stratified by risk groups are shown in the Data Supplement. The 6-year EFS for the LR group (*KMT2A* germline patients) was 73.9% (3.6) versus 44.5% (2.9) for the MR and 20.9% (3.4) for the HR group ($P < .001$; Fig 2B). The 6-year OS for the LR, MR,



Outcome in Interfant-06 (median follow-up [min-max], years: 5.3 [0.1-11.4])

No. Patients	No. Events (relapses)	EFS (SE) 4 Year	EFS (SE) 6 Year	No. Deaths	Survival (SE) 4 Year	Survival (SE) 6 Year
651	340 (244)	47.7 (2.0)	46.1 (2.1)	258	59.1 (2.0)	58.2 (2.0)

Outcome in Interfant-99 (update Dec 2007, median follow-up [min-max], years: 4.8 [0.1-8.5])

No. Patients	No. Events (relapses)	EFS (SE) 4 Year	EFS (SE) 6 Year	No. Deaths	Survival (SE) 4 Year	Survival (SE) 6 Year
478	249 (193)	46.8 (2.3)	46.5 (2.3)	206	56.1 (2.4)	53.8 (2.5)

Risk Group	No. Patients	No. Events	EFS (SE) Interfant-06 4 Year	EFS (SE) Interfant-06 6 Year	*P*	Interfant-99 4-Year EFS (SE)
LR	167	41	75.7 (3.4)	73.9 (3.6)		74.5 (5.1)
MR	320	172	45.7 (2.9)	44.5 (2.9)	< .001	45.5 (3.6)
HR	164	127	23.2 (3.4)	20.9 (3.4)		18.6 (4.0)

Risk Group	No. Patients	No. Events	EFS (SE) 4 Year	EFS (SE) 6 Year	*P*	Interfant-99 4-Year EFS (SE)
LR	112	23	79.3 (4.0)	77.8 (4.2)		74.0 (5.3)
MR	217	106	49.8 (3.5)	49.0 (3.6)	< .001	46.0 (3.9)
HR	118	88	26.7 (4.1)	23.8 (4.2)		20.8 (5.7)

Risk Group	No. Patients	No. Events	EFS (SE) 4 Year	EFS (SE) 6 Year	*P*	Interfant-99 4-Year EFS (SE)
LR	55	18	68.9 (6.3)	66.4 (6.5)		5 patients, 1 relapse
MR	103	66	37.3 (4.9)	35.4 (5.0)	< .001	41.0 (9.7)
HR	46	39	14.0 (5.3)	-		10.0 (11.2)

FIG 2. (A) Event-free survival (EFS) and overall survival (OS) for all patients in Interfant-06. One second malignant neoplasm (acute myeloid leukemia) occurred at 9.6 years after diagnosis and is not depicted in the curve. (B) EFS by risk group in Interfant-06. (C) EFS by risk group in original study groups (Western European study groups and North American centers that founded Interfant) in Interfant-06. These groups represent the Dutch Childhood Oncology Group, United Kingdom Children Cancer Study Group, French Acute Lymphoblastic Leukemia Study Group, Associazione Italiana Ematologia Oncologia Pediatrica, German Cooperative Study Group for Childhood Acute Lymphoblastic Leukemia, European Organisation for Research and Treatment of Cancer Children Leukemia Group, Nordic Society of Pediatric Hematology/Oncology, Berlin-Frankfurt-Muenster Austria, St Jude Children's Research Hospital, Dana Farber Cancer Institute, Czech Working Group for Pediatric Hematology, and Berlin-Frankfurt-Muenster Group Germany. (D) EFS by risk group in other study groups (study groups that joined the Interfant group later) in Interfant-I06. These groups represent Argentina, Chilean National Pediatric Oncology Group, Australian and New Zealand Childrens Haematology/Oncology Group, The Chinese University of Hong Kong, Polish Pediatric Leukemia/Lymphoma Study Group, and Seattle Children's Hospital and Research Institute. HR, high risk; LR, low risk; MR, medium risk.

and HR groups was 87.2% (2.7), 58.1% (3.0), and 29.9% (3.7), respectively ($P < .001$).

Outcome by Randomized Arm

Of 484 patients in the MR and HR groups, 41 had an event before random assignment (22 deaths, 19 not in remission after induction), and 36 were recruited after random assignment was closed for regulatory reasons in two countries. Seventy-seven (19%) out of 407 eligible patients were not randomly assigned, mainly because of parental refusal (61%) or physician's choice (31%); 330 patients (81%) were randomly assigned, 169 to the experimental ADE+MAE arm and 161 to the control IB arm (Fig 1). The randomly assigned patients did not differ according to sex, age, WBC count, immunophenotype, *KMT2A* status, or response to prednisone (Data Supplement).

The 6-year cumulative incidence of relapse with ADE+MAE was 47.5% (4.0), which was not significantly lower than the 54.9% (4.1) with IB (log-rank $P = .11$; Fig 3A). The 6-year cumulative incidence of death in remission was 10.2% (2.4) with ADE+MAE versus 8.3% (2.2) with IB (log-rank $P = .51$; Fig 3A). This resulted in no significant difference in 6-year DFS rates when comparing ADE+MAE (39.3% [4.0]) to IB (36.8% [3.9]; log-rank $P = .47$; Fig 3B). The study was powered to detect a 16% difference in DFS at 3-year follow-up; this was not achieved with 3-year DFS rates of 45.3% (3.9) with ADE+MAE versus 38.6% (3.9) with IB. The 6-year OS for patients treated with ADE+MAE was 54.4% (4.0) versus 47.1% (4.2) for those treated with IB ($P = .27$; Fig 3C). DFS comparison, when adjusted for participating group in a stratified Cox model, confirmed a nonsignificant effect of treatment (hazard ratio, 0.88; 95% CI, 0.66 to 1.17; $P = .39$). A separate Cox model, including a covariate for original versus other countries, showed that the treatment effect was not different in these two groups.

The 6-year DFS was not significantly different between the ADE+MAE arm (49.8% [5.0]) and IB arm (42.6% [5.1]; $P = .31$) within the MR group (Fig 3D), nor did the 4-year DFS differ within the HR group (25.5% [5.8] and 26.3% [5.8], respectively; $P = .80$; Fig 3E). Details of the events in the randomized arms are shown in the Data Supplement. Censoring patients who received SCT or analysis by performed treatment instead of intention to treat (seven patients shifted from the experimental arm to the control arm) gave comparable results.

Outcome by Patient Characteristics

The 6-year EFS (SE) for *KMT2A* germline patients was 73.9% (3.4) versus 36.4% (2.3) for *KMT2A*-rearranged patients ($P < .001$; Data Supplement). t(4;11)- and t(11;19)-rearranged cases seemed to have a lower 6-year EFS than patients with a t(9;11) or other *KMT2A* translocations ($P = .0052$; Data Supplement), but this finding was not confirmed by multivariate analysis (Tables 1 and 2). Younger age at diagnosis correlated with inferior outcome, with 6-year EFS of 25.1% (3.9), 41.5% (3.8), 49.0% (4.0), and 68.1% (4.0) for patients age 0 to 3, 3 to 6, 6 to 9, and 9 to 12 months, respectively ($P < .001$), mainly because of differences in relapse rate (Data Supplement).

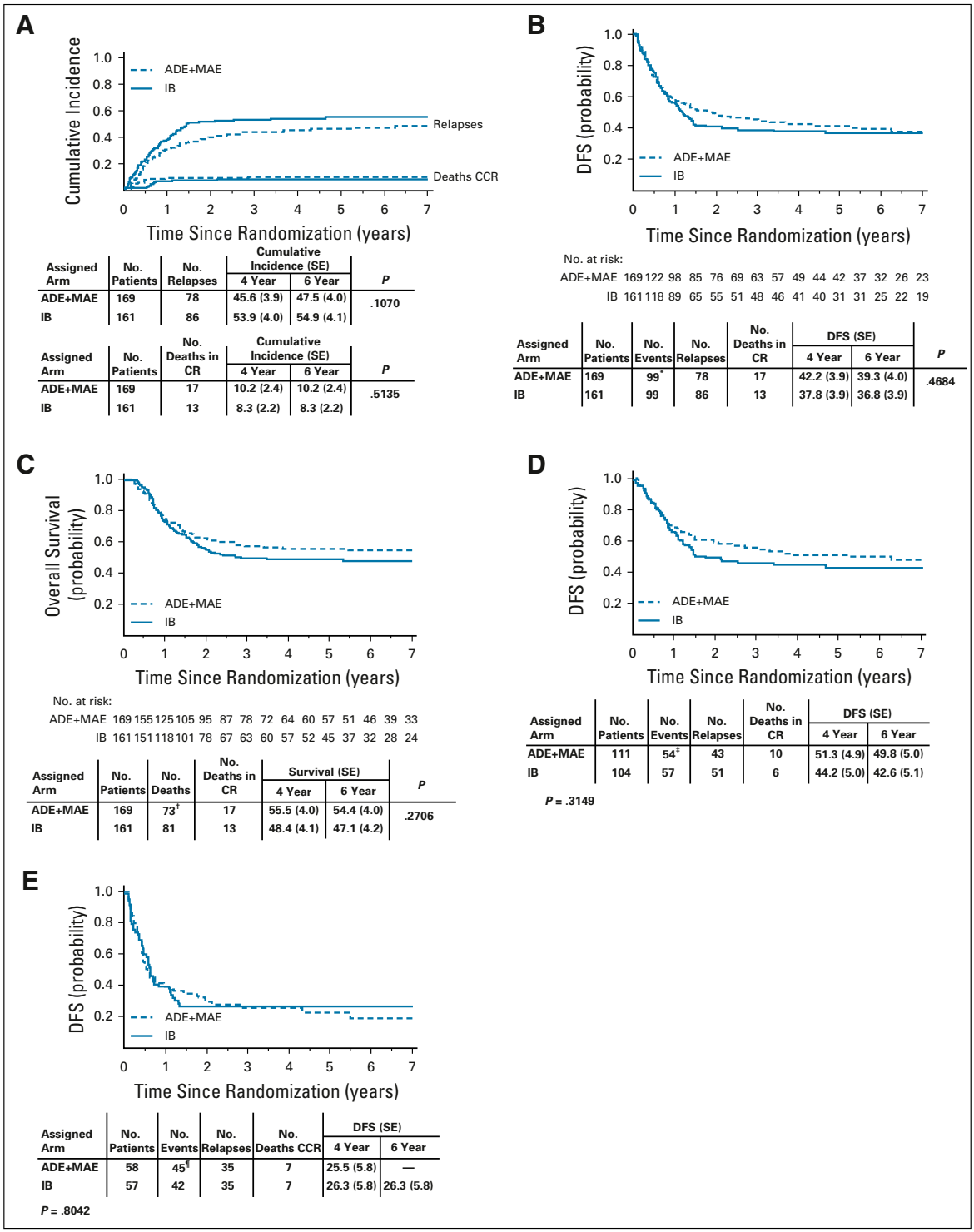
Patients with a WBC count of 300×10^9/L or greater had a 6-year EFS of 24.5% (3.3) versus 41.0% (4.1) for those with WBC count of 100 to 300×10^9/L and 62.4% (2.9) for those with WBC less than 100×10^9/L at diagnosis ($P < .001$; Data Supplement). $CD10^-$ B-lineage ALL had a lower 6-year EFS of 38.5% (2.6) than $CD10^+$ B-lineage ALL (57.7% [3.6]; $P < .001$; Data Supplement). The 4-year EFS for biphenotypic ALL was 36.0% (9.6), whereas it was 45.7% (16.6) for T-cell ALL. Males had a slightly higher 6-year EFS (49.8% [3.0]) than females (43.2% [2.8]; $P = .032$; Data Supplement). Patients with a good response to prednisone had a better 6-year EFS (49.6% [2.4]) than those with a poor response (31.9% [4.1]; $P < .001$; Data Supplement).

On multivariate analysis, *KMT2A* status had the strongest prognostic value for EFS. Age and WBC at diagnosis and prednisone response remained of independent prognostic value, but CD10 status and sex did not (Table 1). Performing the multivariate analysis within the *KMT2a*-rearranged population resulted in the same conclusions (Table 2). An exploratory analysis looking for a more favorable subgroup of *KMT2A*-rearranged patients showed that infants age 9 months or older at diagnosis (n = 55) had a 6-year EFS of 61.9% (SE, 6.8).

Outcome by Country and Comparison of Interfant-06 Versus Interfant-99

Outcome was better for patients treated in the original groups (n = 447) than in the other countries (n = 204): 6-year EFS probabilities were 49.4% (2.5) versus 39.0% (3.6; $P = .0018$), and 6-year OS probabilities were 62.1% (2.4) versus 49.7% (3.7), respectively ($P < .001$; Fig 4A). This was due to differences in induction death (2.2% *v* 6.9%), resistance to induction (2.9% *v* 4.4%), and death in remission (5.4% *v* 10.8%); the relapse rate was comparable (37.6% *v* 37.3%). Outcome for the original groups was also more favorable within risk groups: 6-year EFS for LR, MR, and HR was 77.8% (4.2), 49.0% (3.6), and 23.8% (4.2; Fig 2C), respectively, versus 66.4% (6.5), 35.4% (5.0), and 14.0% (5.3) for the other countries (Fig 2D). Analogous findings were observed for survival, with respective 6-year OS 91.2% (2.8), 62.5% (3.5), and 33.9% (4.7) versus 79.5% (5.5), 51.0% (5.1), and 14.9% (5.6).

For the original groups there was no significant difference in 6-year EFS, (49.4% [2.5] *v* 48.0% [2.6]; $P = .73$) or 6-year OS (62.1% [2.4] *v* 55.5% [2.6]; $P = .20$) when comparing Interfant-06 to Interfant-99 (Fig 4B). There was also no significant difference in outcome for the other countries (6-year EFS, 39.0% [3.6] *v* 40.0% [5.3]; 6-year OS, 49.7% [3.7] *v* 46.1% [5.4]) when comparing Interfant-06 to Interfant-99.



Assigned Arm	No. Patients	No. Relapses	Cumulative Incidence (SE) 4 Year	Cumulative Incidence (SE) 6 Year	P
ADE+MAE	169	78	45.6 (3.9)	47.5 (4.0)	.1070
IB	161	86	53.9 (4.0)	54.9 (4.1)	

Assigned Arm	No. Patients	No. Deaths in CR	Cumulative Incidence (SE) 4 Year	Cumulative Incidence (SE) 6 Year	P
ADE+MAE	169	17	10.2 (2.4)	10.2 (2.4)	.5135
IB	161	13	8.3 (2.2)	8.3 (2.2)	

No. at risk:

ADE+MAE	169	122	98	85	76	69	63	57	49	44	42	37	32	26	23
IB	161	118	89	65	55	51	48	46	41	40	31	31	25	22	19

Assigned Arm	No. Patients	No. Events	No. Relapses	No. Deaths in CR	DFS (SE) 4 Year	DFS (SE) 6 Year	P
ADE+MAE	169	99*	78	17	42.2 (3.9)	39.3 (4.0)	.4684
IB	161	99	86	13	37.8 (3.9)	36.8 (3.9)	

No. at risk:

ADE+MAE	169	155	125	105	95	87	78	72	64	60	57	51	46	39	33
IB	161	151	118	101	78	67	63	60	57	52	45	37	32	28	24

Assigned Arm	No. Patients	No. Deaths	No. Deaths in CR	Survival (SE) 4 Year	Survival (SE) 6 Year	P
ADE+MAE	169	73†	17	55.5 (4.0)	54.4 (4.0)	.2706
IB	161	81	13	48.4 (4.1)	47.1 (4.2)	

Assigned Arm	No. Patients	No. Events	No. Relapses	No. Deaths in CR	DFS (SE) 4 Year	DFS (SE) 6 Year
ADE+MAE	111	54‡	43	10	51.3 (4.9)	49.8 (5.0)
IB	104	57	51	6	44.2 (5.0)	42.6 (5.1)

P = .3149

Assigned Arm	No. Patients	No. Events	No. Relapses	No. Deaths CCR	DFS (SE) 4 Year	DFS (SE) 6 Year
ADE+MAE	58	45¶	35	7	25.5 (5.8)	—
IB	57	42	35	7	26.3 (5.8)	26.3 (5.8)

P = .8042

FIG 3. Outcome in Interfant-06 by randomized arm; low-dose cytosine arabinoside (araC), 6-mercaptopurine, cyclophosphamide (IB) versus araC, daunorubicin, etoposide (ADE) plus mitoxantrone, araC, etoposide (MAE). (A) Cumulative incidence of relapse and death in complete remission (CR) in Interfant-06 by randomized arm: IB versus ADE+MAE. (B) Disease-free survival (DFS) in Interfant-06 by randomized arm: IB versus ADE+MAE. (*) Includes one death in induction and three second malignant neoplasms. (C) Overall survival in Interfant-06 by randomized arm: IB versus ADE+MAE. (†) Includes one death in induction. (D) DFS in Interfant-06 patients in medium-risk group by randomized arm: IB versus ADE+MAE. (‡) Includes one second malignant neoplasm (post-transplantation lymphoproliferative disorder after heart transplantation). (E) DFS in Interfant-06 patients in high-risk group by randomized arm: IB versus ADE+MAE. (¶) Includes one death in induction and two second malignant neoplasms (non-Hodgkin lymphoma and myelodysplastic syndrome). CCR, continuous complete remission.

TABLE 1. Multivariate Analysis of Prognostic Factors in All Interfant-06 Cases

Variable	HR	95% CI	P
KMT2A status			
Germline	1		
t(4;11) + t(11;19)	2.73	1.79 to 4.17	< .001
t(9;11) + other rearranged	2.41	1.57 to 3.70	< .001
Age at diagnosis, months			
≥ 6	1		
< 6	1.57	1.23 to 2.00	< .001
WBC count at diagnosis, $\times 10^9$/L			
< 300	1		
≥ 300	1.69	1.32 to 2.16	< .001
Prednisone response			
PGR	1		
PPR	1.53	1.18 to 1.99	.0014
Immunophenotype			
B-lineage: $CD10^+$	1		
B-lineage: $CD10^-$	1.18	0.90 to 1.54	.2254
Sex			
Male	1		
Female	1.05	0.83 to 1.33	.6702

NOTE. Analysis was done on 576 patients with available data.

Abbreviations: HR, hazard risk; PGR, prednisone good response; PPR, prednisone poor response.

TABLE 2. Multivariate Analysis of Prognostic Factors in *KMT2A*-Rearranged Infant ALL Cases

Variable	HR	95% CI	P
KMT2A status			
t(9;11) + other rearranged	1		
t(4;11) + t(11;19)	1.21	0.86 to 1.47	< .4083
Age at diagnosis, months			
≥ 6	1		
< 6	1.75	1.34 to 2.28	< .001
WBC count at diagnosis, $\times 10^9$/L			
< 300	1		
≥ 300	1.63	1.26 to 2.10	< .002
Prednisone response			
PGR	1		
PPR	1.70	1.30 to 2.23	< .001
Immunophenotype			
B-lineage: $CD10^+$	1		
B-lineage: $CD10^-$	1.26	0.94 to 1.68	.1166
Sex			
Male	1		
Female	1.05	0.82 to 1.34	.6997

NOTE. Analysis was done on 427 *KMT2A*-rearranged patients with available data.

Abbreviations: ALL, acute lymphoblastic leukemia; HR, hazard risk; PGR, prednisone good response; PPR, prednisone poor response.

SCT

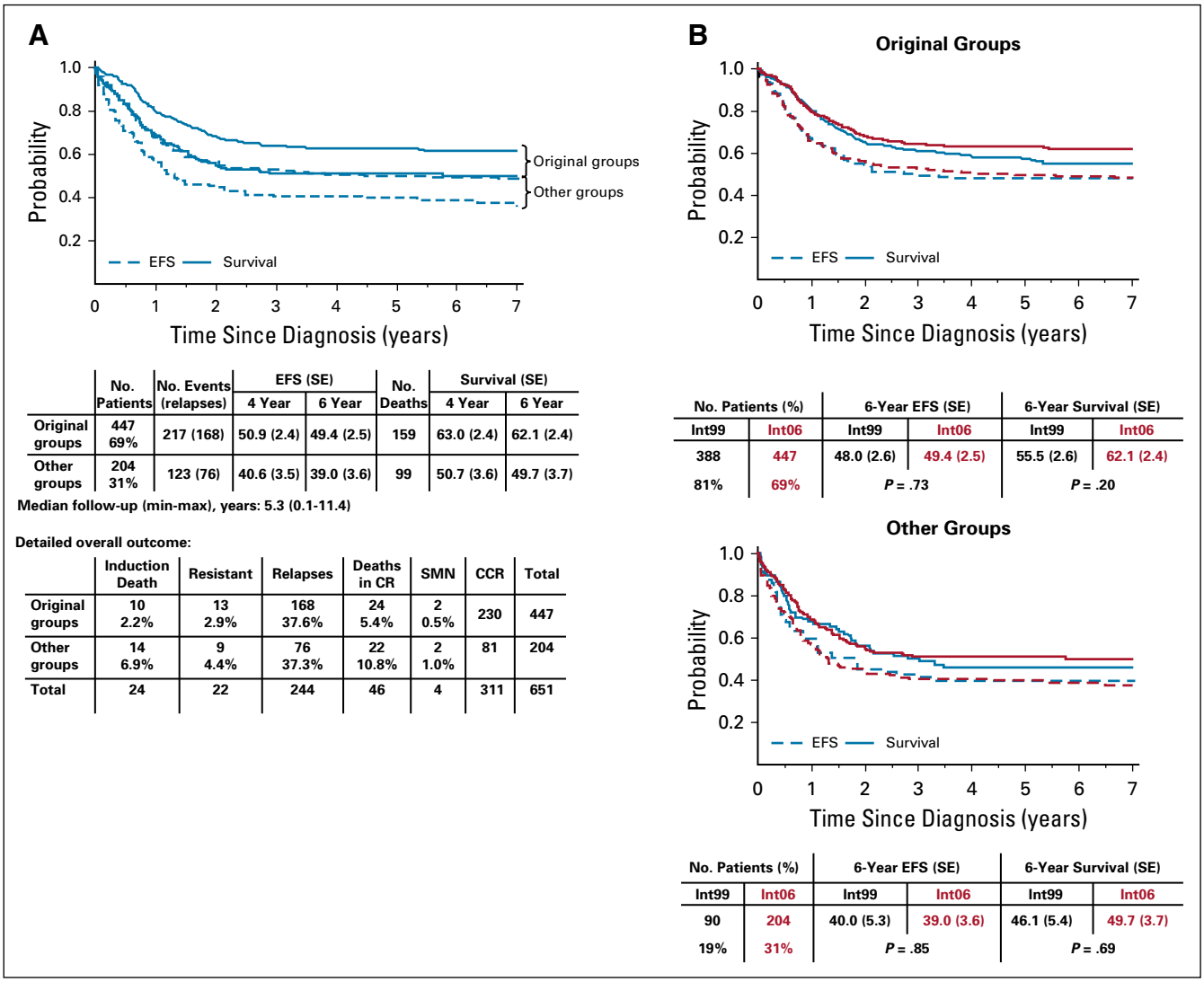
The 6-year EFS of all 164 patients in the HR group was 20.9% (3.4), with the intention to perform transplantation in all patients in the HR group who reached CR (n = 143). Only 76 out of 143 received SCT, because many (n = 54) experienced an early event before SCT could be performed. Donor source included matched sibling donor in 10, a matched unrelated donor in 54, and an HLA partially matched donor in 12 patients. Of the 76 patients undergoing transplantation, relapse occurred in 26 (34.2%), 14 (18.4%) died in CR from transplantation-related toxicity, and two developed a second malignancy, with a 4-year DFS after SCT of 44.0% (6.0).

From June 2009, SCT was recommended for patients in the MR group with MRD 10^{-4} or greater at the start of OCTADA(D). Out of 23 patients in the MR group with this MRD level, 16 received SCT; 4-year DFS after SCT was 18.8% (12.5), with four patients in continuous complete remission.

Of the total cohort, 18% of 605 patients in first complete remission (CR1) received SCT, namely 89 (21%) of the 424 in CR1 in original groups and 22 (12%) of the 181 patients in CR1 in other groups. A total of 14.4% of patients who underwent transplantation died as a result of SCT-related toxicity, without differences between the original and other countries. In 2006 to 2011, 13 of 50 (26%) patients who underwent transplantation died in CR. The conditioning regimen was then changed from busulfan, cyclophosphamide, and melphalan into busulfan plus treosulfan, fludarabine, and thiotepa. In 2012 to 2016, three of 61 (5%) died in CR after SCT.

DISCUSSION

This trial is the largest study for infant ALL. The OS rate of 62% in West European countries and North American institutes is 12% higher than in other countries, mainly because of fewer toxic deaths, illustrating how regional handling of this protocol influences outcome. Although Interfant-06 is of high intensity, it is less intense than the high-risk Berlin-Frankfurt-Muenster regimen, previously used in Europe for *KMT2A*-rearranged ALL, which included three high-risk chemotherapy courses. The 6-year OS was 6% higher for patients treated in Interfant-06 compared with Interfant-99; however, this did not attain statistical significance. The Interfant-99 study resulted in a better outcome for infant ALL compared with outcome before 1999 in some of the national study groups.[1] After that, outcome has not improved significantly by either Interfant or other cooperative groups, such as the Children's Oncology Group (COG).[6]



	No. Patients	No. Events (relapses)	EFS (SE) 4 Year	EFS (SE) 6 Year	No. Deaths	Survival (SE) 4 Year	Survival (SE) 6 Year
Original groups	447 69%	217 (168)	50.9 (2.4)	49.4 (2.5)	159	63.0 (2.4)	62.1 (2.4)
Other groups	204 31%	123 (76)	40.6 (3.5)	39.0 (3.6)	99	50.7 (3.6)	49.7 (3.7)

Median follow-up (min-max), years: 5.3 (0.1-11.4)

Detailed overall outcome:

	Induction Death	Resistant	Relapses	Deaths in CR	SMN	CCR	Total
Original groups	10 2.2%	13 2.9%	168 37.6%	24 5.4%	2 0.5%	230	447
Other groups	14 6.9%	9 4.4%	76 37.3%	22 10.8%	2 1.0%	81	204
Total	24	22	244	46	4	311	651

No. Patients (%) Int99	Int06	6-Year EFS (SE) Int99	Int06	6-Year Survival (SE) Int99	Int06
388	447	48.0 (2.6)	49.4 (2.5)	55.5 (2.6)	62.1 (2.4)
81%	69%	*P* = .73		*P* = .20	

No. Patients (%) Int99	Int06	6-Year EFS (SE) Int99	Int06	6-Year Survival (SE) Int99	Int06
90	204	40.0 (5.3)	39.0 (3.6)	46.1 (5.4)	49.7 (3.7)
19%	31%	*P* = .85		*P* = .69	

FIG 4. Outcome by participating group in Interfant-06 (Int06) versus Interfant-99 (Int99). (A) Outcome by participating group in Interfant-06. Original groups refer to Western European Study groups and North American centers that founded Interfant (Associazione Italiana Ematologia Oncologia Pediatrica, Berlin-Frankfurt-Muenster Austria, Berlin-Frankfurt-Muenster Group Germany, German Cooperative Study Group for Childhood Acute Lymphoblastic Leukemia, Czech Working Group for Pediatric Hematology, Dutch Childhood Oncology Group, Dana Farber Cancer Institute, European Organisation for Research and Treatment of Cancer Children Leukemia Group, French Acute Lymphoblastic Leukemia Study Group, Nordic Society of Pediatric Hematology/Oncology, St Jude Children's Research Hospital, UK Children Cancer Study Group), and other groups are groups that joined Interfant later. (B) Outcome of Interfant-06 (red) versus Interfant-99. These groups represent Argentina, Chilean National Pediatric Oncology Group, Australian and New Zealand Childrens Haematology/Oncology Group, The Chinese University of Hong Kong, Polish Pediatric Leukemia/Lymphoma Study Group, and Seattle Children's Hospital and Research Institute. CCR, continuous complete remission; CR, complete remission; EFS, event-free survival; OS, overall survival; SMN, second malignant neoplasm.

The randomized use of two intensive myeloid-like chemotherapy courses did not lead to a statistically better outcome than the classic lymphoid-like course IB. The lower number of relapses with the myeloid-like courses was partly countered by more infectious deaths. The backbone of Interfant chemotherapy already contains low- and high-dose araC, the main component of AML therapy, and 180 mg/m^2 anthracyclines. Our study shows that infant patients with ALL do not benefit from early intensification of therapy with additional araC and daunorubicin or from the other drugs, mitoxantrone and etoposide, as given in these AML-like courses.

The role of SCT for infant *KMT2A*-rearranged ALL is limited.[7] The Japanese Pediatric Leukemia/Lymphoma Study Group previously applied SCT for all infant *KMT2A*-rearranged ALL patients, whereas the COG eliminated SCT from treatment.[8-10] In Interfant-99, SCT did not improve the outcome for patients in the MR group,[1] but a small subgroup with HR infant ALL seemed to benefit from SCT.[11] The current Interfant-06 study was not designed to compare SCT with chemotherapy. Approximately half of the patients in the HR group could not undergo transplantation in first CR because of an early

event, mainly relapse; thus, patients undergoing transplantation represented a positively selected population. The 6-year EFS of all patients in the HR group was 21%; for those who made it to transplantation, the 4-year DFS was 44%. In 2009, eligibility for SCT was extended to patients in the MR group with MRD 10^{-4} or greater after mercaptopurine, Ara-C, and methotrexate, and asparaginase, because all these patients experienced relapse in Interfant 99.[5] For these patients in the MR group who underwent SCT, the 4-year DFS was 19%. So, still the far majority of these patients in the MR group relapsed despite the use of SCT. The toxic death rate related to SCT was 14% and did not differ between the original groups and the other countries. Together, these findings justify restricting the use of SCT for the select HR group that comprises only 25% of all *KMT2A* infant ALL cases. SCT can also be part of salvage therapy, with intensive chemotherapy plus SCT shown to cure 20% of patients who relapsed in Interfant-99.[12]

This study shows that the outcome of infant ALL with germline *KMT2A* (LR group) is favorable, with a 6-year OS rate of 87% (Data Supplement). Infant ALL with germline *KMT2A* has a low incidence of the favorable ETV6/RUNX1 and hyperdiploid genetic subtypes,[13-15] and thus treatment according to Interfant or to the schedules used for children age 1 year and older must be carefully balanced.

The current study confirms that *KMT2A* status is the strongest factor predicting outcome, followed by diagnosis, WBC count at diagnosis, and prednisone responses.[16] It remains unclear as to why increasing age within infants is associated with a better outcome.[13] We cannot exclude whether dose reductions in the young contribute to the inferior outcome of younger infants. However, the fact that older children with *KMT2A*-rearranged ALL have a better outcome compared with infants is also not understood.[14]

The poor outcome of infant *KMT2A*-rearranged ALL requires more insight into its underlying biology. Successful inhibition of fms-like tyrosine kinase 3 in preclinical systems led to a clinical trial inhibiting this target, but without success.[17-22] A subset of patients have subclonal rat sarcoma mutations, and mitogen-activated protein kinase kinase inhibitors have shown promising efficacy in preclinical models.[23-27] Recently, preclinical research has focused on the abnormal epigenetic profile of *KMT2A*-rearranged ALL[28-33] and illustrated the potential of demethylating agents and histone deacetylase inhibitors.[34-38] Immunotherapeutic approaches directed against B-cell antigens, such as those that are based on blinatumomab[39] and chimeric antigen receptor T cells,[40] have shown high antileukemia potential in infant case reports. Lineage switch to myeloid leukemias has been reported under the pressure of such B-lineage–specific therapy; however, this switch can also be seen after standard chemotherapy against infant ALL.[41-43] The COG and Interfant study groups are currently studying the safety and feasibility of adding azacitidine and blinatumomab to standard Interfant chemotherapy. If successful, the COG, Interfant, and Japanese Pediatric Leukemia/Lymphoma Study Group will collaborate globally to investigate these drugs further in the context of a worldwide randomized study.

In conclusion, the OS rate for infants with ALL in West European countries and North American institutes in Interfant-06 is 62%, which is 12% higher than in other participating countries. Early intensification with two postinduction AML-type chemotherapy courses versus course IB did not lead to a significantly better outcome. Future studies will focus on the use of epigenetic drugs and immunotherapy on the Interfant backbone.[6]

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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