Improved Outcome for ALL by Prolonging Therapy for *IKZF1* Deletion and Decreasing Therapy for Other Risk Groups

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ABSTRACT

PURPOSE The ALL10 protocol improved outcomes for children with ALL by stratifying and adapting therapy into three minimal residual disease–defined risk groups: standard risk, medium risk (MR), and high risk. *IKZF1*-deleted (*IKZF1*del) ALL in the largest MR group still showed poor outcome, in line with protocols worldwide, accounting for a high number of overall relapses. ALL10 showed high toxicity in Down syndrome (DS) and excellent outcome in *ETV6::RUNX1* ALL. Poor prednisone responders (PPRs) were treated as high risk in ALL10. In ALL11, we prolonged therapy for *IKZF1*del from 2 to 3 years. We reduced therapy for DS by omitting anthracyclines completely, for *ETV6::RUNX1* in intensification, and for PPR by treatment as MR.

METHODS Eight hundred nineteen patients with ALL (age, 1-18 years) were enrolled on ALL11 and stratified as in ALL10. Results were compared with those in ALL10.

RESULTS The five-year overall survival (OS), event-free survival (EFS), cumulative risk of relapse (CIR), and death in complete remission on ALL11 were 94.2% (SE, 0.9%), 89.0% (1.2), 8.2% (1.1), and 2.3% (0.6), respectively. Prolonged maintenance for *IKZF1*del MR improved 5-year CIR by 2.2-fold (10.8% *v* 23.4%; $P = .035$) and EFS (87.1% *v* 72.3%; $P = .019$). Landmark analysis at 2 years from diagnosis showed a 2.9-fold reduction of CIR (25.6%-8.8%; $P = .008$) and EFS improvement (74.4%-91.2%; $P = .007$). Reduced therapy did not abrogate 5-year outcome for *ETV6::RUNX1* (EFS, 98.3%; OS, 99.4%), DS (EFS, 87.0%; OS, 87.0%), and PPR (EFS, 81.1%; OS, 94.9%).

CONCLUSION Children with *IKZF1*del ALL seem to benefit from prolonged maintenance therapy. Chemotherapy was successfully reduced for patients with *ETV6::RUNX1*, DS, and PPR ALL. It has to be noted that these results were obtained in a nonrandomized study using a historical control group.

ACCOMPANYING CONTENT

Data Supplement

Protocol

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INTRODUCTION

Survival rates for children with ALL are 90% or higher with contemporary chemotherapy. The Dutch Childhood Oncology Group (DCOG) ALL10 Protocol (online only) improved outcome by stratifying children with ALL into standard-risk (SR), medium-risk (MR), and high-risk by minimal residual disease (MRD) levels and reducing therapy for SR and intensifying therapy for patients who were MR and high-risk.[1] However, genetic abnormalities and also recently described copy number alterations (CNAs) in B-cell differentiation and cell cycle genes influence outcome strongly, with *IKZF1* deletions being the most important.[2,3] Our ALL10 study resulted in an overall 92% 5-year survival rate, but outcome for *IKZF1*-deleted (*IKZF1*del) ALL was poor because of early relapses in line with other recent studies.[1,4-10] The prognostic relevance is found mainly in the large MR group where *IKZF1*del ALL has an approximately three-fold increased risk of relapse often occurring shortly after ending 2-year chemotherapy. As most relapses in childhood ALL occur in this group, more effective therapy for *IKZF1*del ALL is needed.

Other findings in ALL10 were a high toxicity in children with Down syndrome (DS) in concordance with earlier findings and an excellent outcome in *ETV6::RUNX1* ALL (5-year survival > 98%).[11] A poor prednisone response (PPR) was used as high risk criterion, but this is questionable in the MRD era.

The ALL11 Protocol had several modifications compared with ALL10. Therapy was intensified for *IKZF1*del ALL by adding a

CONTEXT

Key Objective

Does prolonged maintenance chemotherapy improves outcome in children with *IKZF1*-deleted ALL, a genetic high-risk type of ALL? Can therapy be reduced for other specific types of ALL including *ETV6::RUNX1*-rearranged ALL, children with Down syndrome (DS), and prednisone poor responders (PPRs)?

Knowledge Generated

Adding a third year of maintenance chemotherapy led to an almost three-fold reduction of the relapse rate in *IKZF1*-deleted ALL. Deintensification of therapy was performed by partly or fully omitting anthracyclines in *ETV6::RUNX1* ALL and children with DS ALL and by treating PPR ALL according to medium-risk chemotherapy instead of very intensive high risk chemotherapy courses. These reductions in therapy did not abrogate the outcome in these three groups.

Relevance *(S. Bhatia)*

Targeted risk stratified therapy can maintain/improve outcomes while offering an opportunity to reduce long-term morbidity.*

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

third year of maintenance therapy with infusion of methotrexate (MTX) once every 3 weeks and intermittent 6-mercaptopurine (6-MP) as described earlier.[12] Therapy was reduced for children with DS without *IKZF1*del by fully omitting anthracyclines, for *ETV6::RUNX1* ALL by deleting anthracyclines in intensification, and for PPR by shifting them from high risk to MR. Two questions were studied by a randomized design, which will be reported separately: The first was whether a continuous schedule of polyethylene glycol (PEG)–asparaginase reduces allergy and silent inactivation and the second was whether prophylactic immunoglobulins reduces infections.

METHODS

Patients

From April 2012 to July 2020, 887 consecutive children age 1-18 years with newly diagnosed ALL were considered for enrollment on ALL11. Infants younger than 1 year (Interfant protocol) and *BCR::ABL*-positive ALL cases (EsPhALL protocol) were excluded.[13,14] Eight hundred nineteen children were enrolled; Reasons for not being eligible are shown in Figure 1. Patients were treated in seven Dutch pediatric oncology centers until June 2018; thereafter, all patients were treated at the Princess Máxima Center in Utrecht. ALL11 was approved by institutional review boards, and verbal and written informed consent was provided by parents and patients. CNAs were assessed by multiplex ligation–dependent probe amplification (MLPA; MRC Holland, Amsterdam, the Netherlands) in the central laboratory of the DCOG, which was transferred to the Princess Máxima Center in June 2018; Quality controls were performed by MLPA and single nucleotide polymorphism arrays in two other laboratories with 100% concordance.

Therapy and Aims of the Study

Treatment was based on the DOCG ALL10[1] including identical stratification by MRD. Treatment details are given in the Data Supplement (Supplemental Fig S1, online only).

Therapy reductions in ALL11 versus ALL10 were as follows:

- The maximum cumulative dose of anthracyclines was lowered from 300 to 240 mg/m^2 by reducing the number of doses in MR intensification once every three weeks.
- For *ETV6::RUNX1*-positive ALL MR cases, anthracyclines were deleted from intensification once every three weeks.
- For DS cases, anthracyclines were fully omitted (except for one MR case with *IKZF1*del).
- PPR cases were assigned to MR instead of high risk.
- Cranial irradiation was omitted for all patients. In November 2016, the Protocol was amended so that CNS2 patients no longer receive extra intrathecal therapy in induction and high risk Protocol II.
- Only patients stratified to high risk by MRD and patients with T-ALL not in complete remission (CR) after induction were eligible for stem-cell transplantation (SCT). Thirty-two of 40 patients eligible for SCT and one additional patient were transplanted. Four events (two deaths in CR, two relapse) occurred before SCT, four received chimeric antigen receptor T-cell (CAR-T) therapy, and one patient was not transplanted. Nine received total body irradiation (TBI) plus etoposide as conditioning, and 23 a TBI-free conditioning regimen.[15]

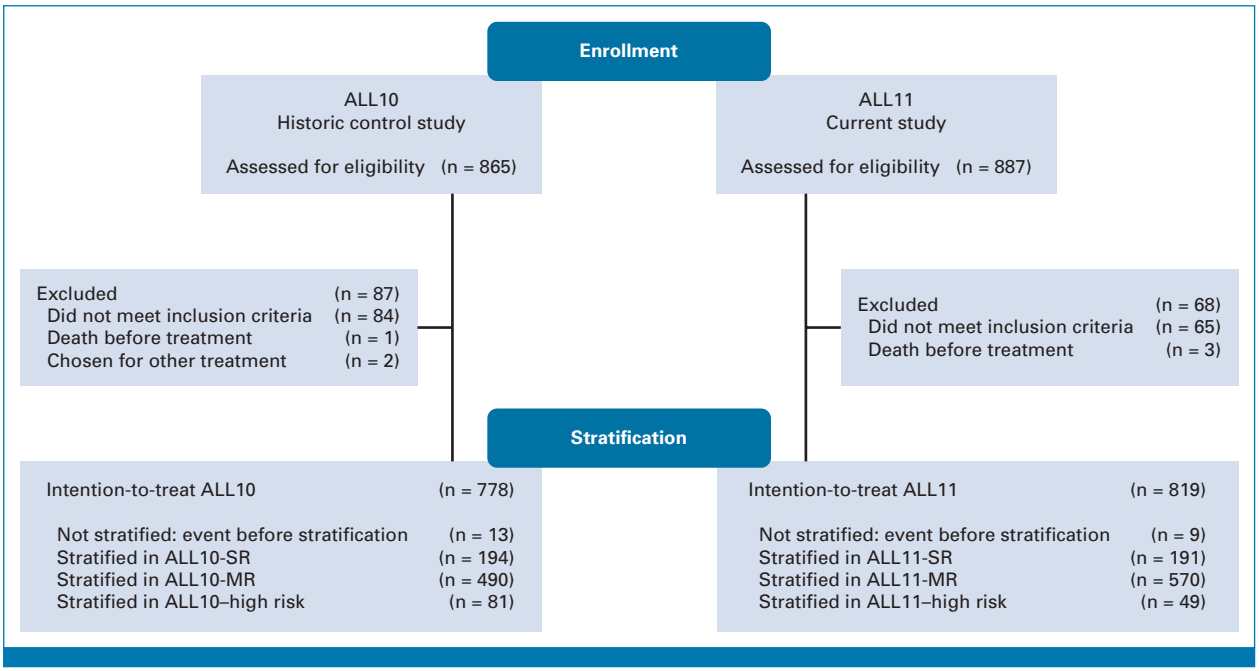

FIG 1. Flow diagram. MR, medium risk; SR, standard risk.

Therapy was intensified for *IKZF1*del cases:

- *IKZF1*del MR cases received one extra year of maintenance therapy with intermittent 6-MP and MTX.[12] This was given first for the most frequent types of *IKZF1*del (exon 4-7 and 1-8 deletion) and after Protocol amendment in June 2014 for also other rare types of *IKZF1*del.

Modifications in asparaginase:

- Eight doses of 5,000 U/m² Native Escherichia coli asparaginase once every three days in induction (approximately 24 days of asparagine depletion) in ALL10 were replaced by three doses of 1.500 U/m² PEG-asparaginase once every two weeks (approximately 42 days of asparagine depletion). ALL10 postinduction asparaginase already consisted of PEG-asparaginase; in ALL11, postinduction PEG-asparaginase was reduced by one dose in SR and MR to compensate for the longer asparaginase exposure in induction.
- Therapeutic drug monitoring of asparaginases was used to individualize dosing with a target trough level of asparaginase activity of 0.100-0.250 U/mL.

Statistical Analysis

Events were defined as induction failure (defined as event at day 0), relapse, death, or secondary malignancy. Event-free survival (EFS) and overall survival (OS) were estimated from diagnosis to first event or last follow-up. A competing risk model with two competing events was used to estimate the cumulative incidence of relapse (CIR) and death in remission (CID).[16] For the cumulative incidence of isolated bone marrow (BM), isolated CNS, and combined BM-CNS relapses, three additional competing risks models with three competing events were used (relapse of interest, other relapses, and death). The primary end point is survival; secondary end points are EFS, CIR, death in induction, death in remission, and toxicity.

The effect of a third year of therapy for MR *IKZF1*del cases was analyzed by intention to treat including all patients with ALL10MR in the ALL10 cohort (intention 2-year therapy) versus all patients with ALL11MR in the ALL11 cohort (intention 3-year therapy). In addition, we estimated the effect of treatment for MR *IKZF1*del cases on EFS, OS, and CIR using a landmark analysis at 2 years after diagnosis (ie, at the start of the third year of therapy) with an as-treated approach including only patients alive without event at the landmark point.[17] At the start of ALL11 in 2012, the ALL10 MR arm was amended by adding a third year of therapy for patients still on treatment: Seven MR patients with ALL10 were treated accordingly and included in the 3-year MR group for comparison of 3- versus 2-year therapy in the landmark analysis. Two of 66 *IKZF1*del cases in ALL11MR received no third year of therapy and were included in the 2-year MR group.

Median follow-up time was assessed by the reverse Kaplan-Meier method.[18] EFS/OS was estimated by Kaplan-Meier's methodology, the effect of covariates on EFS/OS by Cox models, differences in CIR between risk groups by Gray's log-rank test,[19] and the effect of risk factors on the CIR by Fine and Gray's[20] model. Statistical analyses were performed using SPSS-Rel. 20.0.2012 (SPSS Inc, Chicago, IL) and R software environment version R-4.2.2.[21] The library survminer[22] was used to visualize EFS, OS, CIR, and CID. Analyses concerning the competing risk model were performed with mstate[23] and cmprsk library in R.

RESULTS

Patient Characteristics

Table 1 presents EFS, OS, and CIR data. Distribution of SR (23.6%), MR (70.4%), and high risk (6.0%) was marginally different than in ALL10 (24.9%, 63.0%, and 10.4% respectively), mainly because PPR was no longer a high risk criterion and because of a higher number of adolescents in ALL11 who are known to have higher MRD. The trend of enrolling more 15- to 18-year-old adolescents (1.4%, 4.1%, 3.6%, and 7.3% on ALL7, ALL8, ALL9, and ALL10, respectively) continued in ALL11 (10.9%).

Outcome

The estimated median follow-up time was 68.3 months (95% CI, 65.0 to 71.6). Outcome data are shown in Table 1. Four patients (0.5% *v* 1.7% in ALL10) died during induction, and one patient (0.1% *v* 0.3% in ALL10) did not achieve CR, resulting in a 99.4% CR rate versus 97.9% in ALL10. Eighteen patients died in CR (2.2%), 60 relapsed (8.9%), and there were 2 second malignancies.

The five-year EFS, CIR, CID, and OS were 89.0% (SE, 1.2), 8.1% (SE, 1.1), 2.3% (SE, 0.6), and 94.2% (SE, 0.9; Fig 2A), respectively, versus 87.0% (SE, 1.2), 8.4% (SE, 1.0), 2.9% (SE, 0.6), and 91.9% (SE, 1.0) on ALL10, respectively. The 5-year CIR for BM relapse was 5.7% (SE, 0.9%), that for isolated CNS relapse was 0.6% (0.3%), and that for combined BM + CNS relapse was 0.8% (0.3%). The five-year EFS, OS, and CIR for SR patients (n = 191) were 95.0% (SE, 1.7), 97.5% (SE, 1.3), and 4.2% (SE, 1.6), respectively; those for MR patients (n = 570) were 90.7% (SE, 1.3), 96.4% (SE, 0.8), and 7.8% (SE, 1.3), respectively; and those for high risk patients (n = 49) were 60.6% (SE, 7.6), 71.1% (SE, 7.0), and 27.4% (SE, 7.1; Figs 2B-2D), respectively.

Outcome by Patient Characteristics

Outcomes did not differ between boys and girls (Table 2). Children age 10-14 years and especially age 15-18 years had a higher CIR than children age 1-10 years and therefore a

TABLE 1. Overview of Events and 5-Year Outcome Data in ALL11

	Risk Group According to Protocol (intention to treat)				
Parameter	SR	MR	High Risk	Event Before Stratification	Total
Intention to treat, No. (%)	191 (100)	570 (100)	49 (100)	9	819 (100)
Nonresponder	0	0	1	0	1 (0.1)
Death in induction[a]	0	0	0	4	4 (0.5)
CR according to protocol	191	570	48	5	814 (99.4)
Death in CR[b]	1	7	5	5	18 (2.2)
Relapse	9 (5[c])	39 (16[c])	12 (8[c])	0	60 (7.3)
Isolated BM	5	28	8		41
Isolated CNS	1	3	1		5
Isolated testis	0	1	0		1
Isolated others	0	1	0		1
Combined BM-CNS	1	4	2		7
Combined BM-testis	1	2	0		3
Combined BM-others	1	0	1		2
Second malignancy	1	1	0	0	2 (0.3)
Alive in CR	180 (94.2)	523 (91.8)	31 (63.3)	0	734 (89.6)
Survival, % (SE)	n = 191	n = 570	n = 49		n = 819
Cumulative 3-year EFS	97.1 (1.3)	94.3 (1.0)	64.4 (7.0)		92.1 (1.0)
Cumulative 3-year OS	98.2 (1.0)	97.4 (0.7)	74.3 (6.5)		95.2 (0.8)
3-Year CIR	2.9 (1.3)	4.5 (0.9)	23.6 (6.3)		5.2 (0.8)
Cumulative 5-year EFS	95.0 (1.7)	90.7 (1.3)	60.6 (7.6)		89.0 (1.2)
Cumulative 5-year OS	97.5 (1.3)	96.4 (0.8)	71.1 (7.0)		94.2 (0.9)
5-Year CIR	4.2 (1.6)	7.8 (1.3)	27.4 (7.1)		8.1 (1.1)

Abbreviations: BM, bone marrow; CIR, cumulative risk of relapse; CR, complete remission; EFS, event-free survival; MR, medium risk; OS, overall survival; SR, standard risk; X-ALD, X-linked adrenoleukodystrophy.

[a]Death in induction: two death during Protocol 1A because of a Varicella infection and a GI bleeding, and two during Protocol IB because of causes that started in IA: multiorgan failure and cerebral Aspergillus.

[b]Death in CR: 10 because of an infection (one Down syndrome), two pancreatitis, two encephalopathy, one multiorgan failure/haemophagocytosis, one respiratory failure, one pulmonary bleeding, and 1 as a result of X-ALD, which was diagnosed after inclusion in the study. Death in CR occurred in five cases in IB, two in Protocol M, one in SR (3 years after stop of therapy because of X-ALD), four in MR at weeks 1-18, five in high risk blocks, and one 3 years after stem-cell transplantation.

[c]Death.

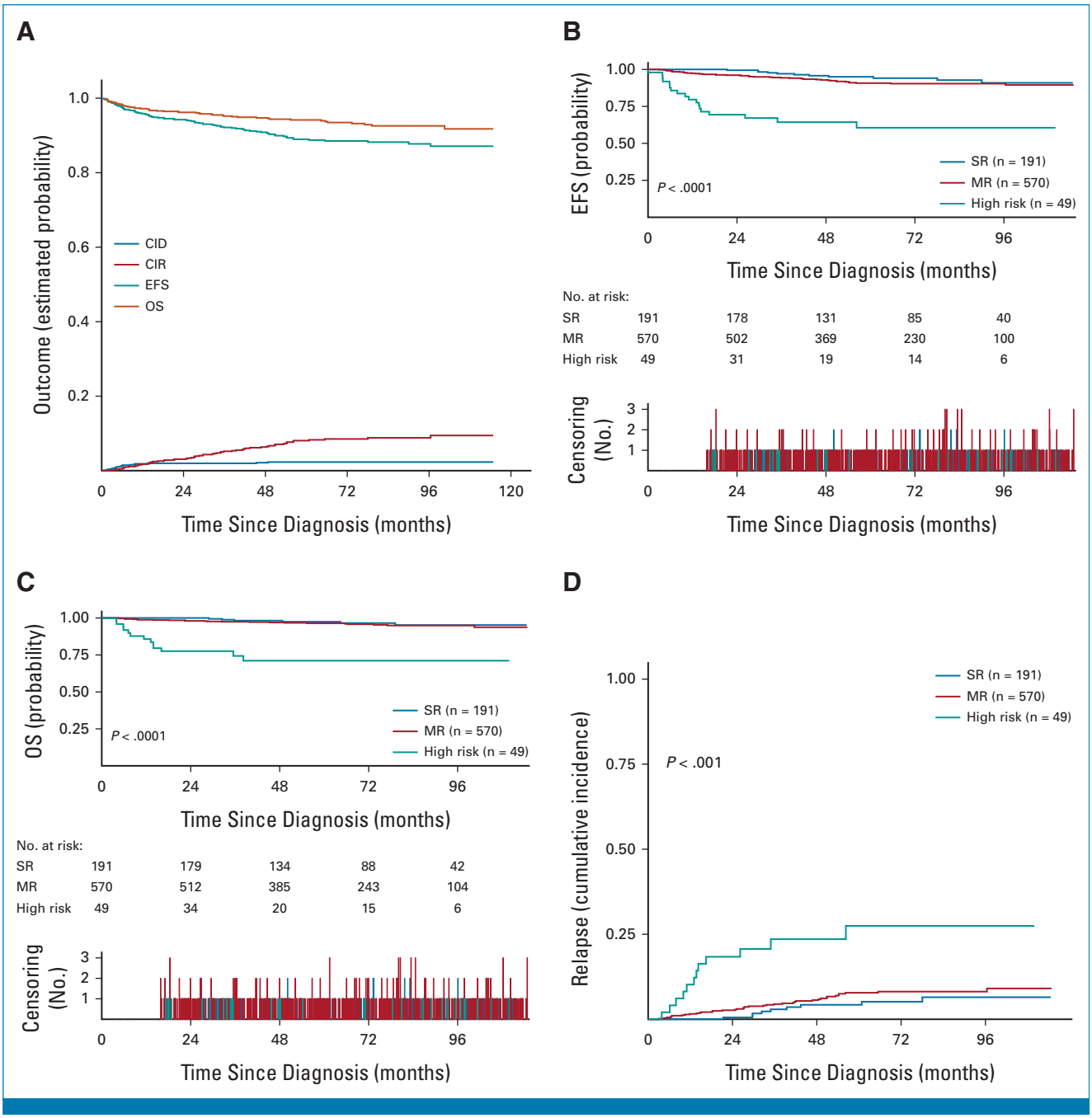

FIG 2. Outcome on ALL11. Kaplan-Meier curves of patients treated on ALL11 showing the outcome of (A) all patients, (B) EFS by risk group, (C) OS by risk group, and (D) cumulative incidence of relapse by risk group. CID, cumulative incidence of death; CIR, cumulative incidence of relapse; EFS, event-free survival; MR, medium risk; OS, overall survival; SR, standard risk.

lower EFS and OS ($P < .0001$; Data Supplement, [Supplemental Figs 2A-2C]). National Cancer Institute (NCI)–SR and NCI–high risk B-lineage ALL differed in outcome with the 5-year EFS of 94.9% (SE, 1.1) versus 80.5% (SE, 1.8; $P < .0001$), the OS of 97.8% (SE, 0.7) versus 90.9% (SE, 2.0; $P < .0001$), and the CIR of 3.8% (SE, 1.0) versus 14.1% (SE, 2.6; $P < .0001$), respectively. Children with T-ALL and proB ALL had a higher 5-year CIR and lower 5-year EFS and OS than children with common/pre-B ALL (Data Supplement [Supplemental Figs 3A-3C]). Children with CNS3 but not CNS2 and traumatic lumbar puncture with leukemic cells (TLP)+ had a lower EFS and OS compared with children with CNS1. There were one death in induction, one isolated CNS relapse, and one combined BM + CNS relapse in nine CNS3 patients.

Detailed outcome data by patient characteristics by risk group are given in the Data Supplement (Supplemental Table S1).

TABLE 2. Outcome by Patient Characteristics and Univariate Hazard Ratio for OS, EFS, and OS Along With Their 95% CI

Parameter	Patients, No. (%)	5-Year EFS, % (SE)	End Point: EFS (univariate Cox), Estimated HR (95% CI)	*P* EFS	5-Year OS, % (SE)	End Point: OS (univariate Cox), Estimated HR (95% CI)	*P* OS	5-Year CIR, % (SE)	End Point: CIR (Fine and Gray), Estimated HR (95% CI)	*P* CIR
Sex										
Male	484 (59.1)	89.3 (1.5)	Ref	.916	94.4 (1.1)	Ref	.9060	8.2 (1.4)	Ref	.711
Female	335 (40.9)	88.5 (1.9)	1.024 (0.665 to 1.577)		93.9 (1.4)	1.034 (0.592 to 1.806)		7.9 (1.6)	0.906 (0.539 to 1.524)	
Age, years										
1-4	388 (47.4)	92.4 (1.4)	Ref	< .001	96.1 (1.0)	Ref	<.0010	5.6 (1.3)	Ref	< .001
5-9	215 (26.3)	92.9 (1.9)	1.086 (0.592 to 1.992)		96.6 (1.3)	0.809 (0.349 to 1.875)		4.6 (1.5)	0.996 (0.475 to 2.089)	
10-14	127 (15.5)	81.7 (3.8)	2.551 (1.453 to 4.479)		91.4 (2.6)	2.150 (1.026 to 4.504)		13.9 (3.5)	2.627 (1.357 to 5.084)	
15-18	89 (10.9)	73.3 (5.6)	3.495 (1.942 to 6.289)		82.8 (4.5)	3.972 (1.957 to 8.063)		20.4 (5.1)	3.624 (1.813 to 7.243)	
WBC										
<25	561 (68.5)	91.5 (1.3)	Ref	.0020	96.1 (0.9)	Ref	.0010	6.3 (1.1)	Ref	.004
25-50	87 (10.6)	87.6 (4.0)	1.460 (0.737 to 2.893)		91.8 (3.3)	1.941 (0.836 to 4.505)		6.2 (3.1)	0.779 (0.279 to 2.179)	
>50	171 (20.9)	81.1 (3.2)	2.260 (1.420 to 3.598)		89.0 (2.5)	2.907 (1.606 to 5.263)		15.0 (3.0)	2.332 (1.362 to 3.994)	
Phenotype										
ProB-ALL	15 (1.8)	66.7 (12.2)	5.036 (1.990 to 12.743)		66.7 (12.2)	9.136 (3.463 to 24.099)		13.3 (8.8)	2.422 (0.542 to 10.824)	
C-ALL	478 (58.4)	90.4 (1.5)	Ref	<.001	95.5 (1.0)	Ref	<.0010	7.1 (1.3)	Ref	.100
PreB-ALL	210 (25.6)	90.8 (2.2)	1.031 (0.599 to 1.772)		97.4 (1.2)	0.786 (0.352 to 1.757)		7.3 (2.0)	1.067 (0.569 to 2.002)	
T-ALL	116 (14.2)	82.6 (3.7)	1.987 (1.156 to 3.417)		86.3 (3.3)	2.829 (1.476 to 5.422)		12.8 (3.2)	2.057 (1.078 to 3.925)	
Phenotype (lineage)										
B-lineage	703 (85.8)	90.0 (1.2)	Ref	.018	95.4 (0.8)	Ref	.0020	7.3 (1.1)	Ref	.027
T-lineage	116 (14.2)	82.6 (3.7)	1.849 (1.110 to 3.081)		86.3 (3.3)	2.648 (1.450 to 4.837)		12.8 (3.2)	1.965 to (1.066 to 3.623)	
NCI_lineage										
B-lineage, NCI standard risk	459 (56.0)	94.9 (1.1)	Ref	<.001	97.8 (0.7)	Ref	<.0010	3.8 (1.0)	Ref	<.001
B-lineage, NCI high risk	244 (29.8)	80.5 (2.8)	3.573 (2.164 to 5.901)		90.9 (2.0)	3.985 (1.993 to 7.970)		14.1 (2.6)	3.417 (1.882 to 6.205)	
T-lineage	116 (14.2)	82.6 (3.7)	3.414 (1.870 to 6.234)		86.3 (3.3)	5.291 (2.476 to 11.306)		12.8 (3.2)	3.547 (1.731 to 7.267)	
CNS status (liquor)										
CNS1	354 (44.6)	89.2 (1.8)	Ref	.128	94.4 (1.3)	Ref	.0150	7.7 (1.6)	Ref	.229
CNS2	319 (40.2)	88.1 (2.0)	1.246 (0.779 to 1.992)		95.0 (1.3)	1.233 (0.652 to 2.332)		9.7 (1.8)	1.399 (0.811 to 2.415)	
CNS3	9 (1.1)	66.7 (15.7)	3.969 (1.217 to 12.949)		77.8 (13.9)	6.657 (1.959 to 22.619)		25.0 (15.3)	3.920 (0.820 to 18.728)	
TLP+	90 (11.3)	92.2 (2.8)	1.007 (0.465 to 2.179)		92.2 (2.8)	1.631 (0.681 to 3.906)		3.3 (1.9)	0.710 (0.245 to 2.057)	
TLP−	21 (2.6)	94.4 (5.4)	0.487 (0.067 to 3.566)		93.8 (6.1)	0.884 (0.118 to 6.627)		5.6 (5.4)	0.714 (0.096 to 5.342)	
Ploidy[a]										
Diploid (46, normal)	105 (14.4)	88.3 (3.2)	Ref	a	91.1 (2.8)	Ref	a	10.9 (3.1)	Ref	a
Pseudodiploid (46, abnormal)	276 (37.9)	85.7 (2.3)	1.215 (0.642 to 2.298)		92.0 (1.7)	1.044 (0.499 to 2.185)		9.7 (2.1)	0.794 (0.391 to 1.616)	
Near-haploid (<30)[a]	5 (0.7)	80.0 (17.9)	NA		80.0 (17.9)	NA		20.0 (17.9)	NA	

(continued on following page)

TABLE 2. Outcome by Patient Characteristics and Univariate Hazard Ratio for OS, EFS, and OS Along With Their 95% CI (continued)

Parameter	Patients, No. (%)	5-Year EFS, % (SE)	End Point: EFS (univariate Cox), Estimated HR (95% CI)	*P* EFS	5-Year OS, % (SE)	End Point: OS (univariate Cox), Estimated HR (95% CI)	*P* OS	5-Year CIR, % (SE)	End Point: CIR (Fine and Gray), Estimated HR (95% CI)	*P* CIR
Low hypodiploid (30-39)[a]	2 (0.3)	50.0 (35.4)	NA		50.0 (35.4)	NA		50.0 (35.4)	NA	
Hypodiploid (40-45)	24 (3.3)	86.9 (7.1)	1.103 (0.314 to 3.874)		100.0	0.000		13.1 (7.1)	1.221 (0.339 to 4.392)	
Hyperdiploid (47-50)	117 (16.0)	96.2 (1.9)	0.522 (0.208 to 1.309)		99.1 (0.9)	0.283 (0.078 to 1.029)		3.8 (1.9)	0.580 (0.230 to 1.462)	
High hyperdiploid (51-65)	189 (25.9)	91.8 (2.2)	0.615 (0.285 to 1.328)		97.2 (1.2)	0.360 (0.131 to 0.992)		6.1 (2.0)	0.467 (0.196 to 1.110)	
Near-triploid (66-79)[a]	7 (1.0)	100.0	NA		100.0	NA			NA	
Near-tetraploid (80-100)[a]	4 (0.5)	100.0	NA		100.0	NA			NA	
Genetics[a]			a	a		a			a	a
ETV6::RUNX1	179 (23.9)	98.3 (1.0)			99.4 (0.6)			1.1 (0.8)		
DS	23 (3.1)	*87.0 (7.0)*			87.0 (7.0)			0.0		
KMT2A-rearranged[b]	17 (2.3)	*62.7 (12.3)*			70.1 (11.2)			19.6 (10.3)		
TCF3::PBX1	23 (3.1)	95.7 (4.3)			100.0			4.3 (4.3)		
High hyperdiploid (51-65)	185 (24.7)	91.7 (2.2)			97.2 (1.3)			6.2 (2.1)		
T-ALL	96 (12.8)	83.6 (3.9)			87.0 (3.5)			13.4 (3.7)		
B-others	226 (30.2)	85.6 (2.5)			93.5 (1.8)			12.3 (2.4)		
IKZF1-del (gene deletions)										
Wild-type	623 (86.6)	89.4 (1.3)	Ref	.012	94.7 (0.9)	Ref	.0014	7.7 (1.2)	Ref	.053
Deleted	96 (13.4)	80.2 (4.6)	1.966 (1.163 to 3.323)		86.4 (3.9)	2.757 (1.483 to 5.126)	.0010	13.5 (4.1)	1.867 (0.997 to 3.496)	
IKZF1 (gene alterations)										
Normal	623 (86)	89.4 (1.3)	Ref	.022	94.7 (0.9)	Ref	.0030	7.7 (1.2)	Ref	.083
Alteration	101 (14)	81.4 (4.3)	1.844 (1.091 to 3.116)		87.3 (3.7)	2.585 (1.390 to 4.805)		12.6 (3.8)	1.750 (0.934 to 3.277)	
BTG1										
Normal	686 (91.6)	88.7 (1.3)	Ref	.485	94.0 (0.9)	Ref	.7860	8.1 (1.1)	Ref	.350
Alteration	63 (8.4)	85.3 (5.3)	1.280 (0.640 to 2.558)		91.6 (4.0)	1.136 (0.451 to 2.863)		11.4 (4.4)	1.452 (0.669 to 3.151)	
CDKN2A/B										
Normal	467 (64.5)	90.1 (1.5)	Ref	.053	95.5 (1.0)	Ref	.1550	6.7 (1.3)	Ref	.046
Alteration	257 (35.5)	85.8 (2.3)	1.552 (0.993 to 2.426)		91.4 (1.9)	1.519 (0.854 to 2.699)		10.5 (2.1)	1.725 (1.008 to 2.952)	
EBF1										
Normal	671 (92.9)	89.1 (1.3)	Ref	.380	94.0 (1.0)	Ref	.6900	7.6 (1.1)	Ref	.338
Alteration	51 (7.1)	82.7 (5.6)	1.389 (0.668 to 2.889)		94.0 (3.4)	0.788 (0.244 to 2.544)		13.6 (5.2)	1.520 (0.653 to 3.540)	
ETV6										
Normal	533 (73.8)	86.3 (1.6)	Ref	.003	92.6 (1.2)	Ref	.0190	9.8 (1.4)	Ref	.010
Alteration	189 (26.2)	95.0 (1.8)	0.354 (0.177 to 0.708)		98.1 (1.1)	0.329 (0.130 to 0.832)		3.1 (1.4)	0.348 (0.149 to 0.814)	
PAX5										
Normal	566 (76.6)	88.5 (1.5)	Ref	.567	94.0 (1.0)	Ref	.4550	8.1 (1.3)	Ref	.531

(continued on following page)

TABLE 2. Outcome by Patient Characteristics and Univariate Hazard Ratio for OS, EFS, and OS Along With Their 95% CI (continued)

Parameter	Patients, No. (%)	5-Year EFS, % (SE)	End Point: EFS (univariate Cox), Estimated HR (95% CI)	*P* EFS	5-Year OS, % (SE)	End Point: OS (univariate Cox), Estimated HR (95% CI)	*P* OS	5-Year CIR, % (SE)	End Point: CIR (Fine and Gray), Estimated HR (95% CI)	*P* CIR
Alteration	173 (23.4)	87.4 (2.7)	1.156 (0.703 to 1.900)		92.7 (2.2)	1.266 (0.683 to 2.347)		9.7 (2.4)	1.209 (0.667 to 2.190)	
RB1										
Normal	659 (91.4)	89.5 (1.3)	Ref	.006	94.6 (0.9)	Ref	.0290	7.6 (1.1)	Ref	.051
Alteration	62 (8.6%)	78.0 (6.0)	2.292 (1.263 to 4.158)		86.8 (5.2)	2.335 (1.091 to 4.998)		13.9 (5.4)	2.086 (1.005 to 4.328)	
PAR1										
Normal	517 (71.5)	87.3 (1.6)	Ref	.086	92.8 (1.2)	Ref	.0510	8.9 (1.4)	Ref	.151
Alteration	206 (28.5)	91.9 (2.1)	0.610 (0.347 to 1.072)		97.4 (1.2)	0.449 (0.201 to 1.002)		5.7 (1.9)	0.608 (0.306 to 1.208)	
UKALL_CNA[2]										
GR (CNA-GR)	244 (35.3)	91.5 (1.9)	Ref	.060	95.4 (1.3)	Ref	.2660	5.2 (1.6)	Ref	.040
PR (CNA-PR)	447 (64.7)	86.2 (1.8)	1.630 (0.979 to 2.712)		93.0 (1.3)	1.439 (0.757 to 2.735)		10.1 (1.6)	1.935 (1.016 to 3.686)	
CNA_*IKZF1*										
CNA-GR	244 (35.3)	*91.5 (1.9)*	Ref	.074	95.4 (1.3)	Ref	.0420	5.2 (1.6)	Ref	.108
CNA-PR with *IKZF1*	97 (14.0)	82.9 (4.3)	2.114 (1.095 to 4.080)		89.4 (3.4)	2.470 (1.127 to 5.415)		10.7 (3.7)	2.195 (0.958 to 5.028)	
CNA-PR others	350 (50.7)	87.2 (2.0)	1.496 (0.876 to 2.553)		94.1 (1.3)	1.162 (0.582 to 2.321)		9.8 (1.8)	1.861 (0.953 to 3.634)	
BFM_IKZFplus[24]										
IKZF1-negative	623 (86.4)	89.4 (1.3)	Ref	.044	94.7 (0.9)	Ref	.0034	7.7 (1.2)	Ref	.144
IKZF1 without *PAX5/CDKN2A/-B/PAR1*	33 (4.6)	78.4 (8.8)	1.796 (0.777 to 4.154)		92.4 (5.1)	2.162 (0.768 to 6.085)		17.7 (8.2)	2.167 (0.905 to 5.187)	
IKZF1plus	65 (9.0)	81.8 (5.0)	1.990 (1.072 to 3.693)		84.1 (5.0)	2.999 (1.484 to 6.059)		10.8 (4.2)	1.639 (0.740 to 3.629)	

Abbreviations: CIR, cumulative risk of relapse; CNA, copy number alteration; DS, Down syndrome; EFS, event-free survival; GR, good risk; HR, hazard ratio; NA, not available; NCI, National Cancer Institute; OS, overall survival; PR, poor risk; TLP, traumatic lumbar puncture; UKALL, United Kingdom ALL.

[a]Ploidy/Genetics: Because of small numbers, some groups are not included in the statistical models, and only descriptive statistics are shown.

[b]*KMT2A* subtype: n= 8 AF4, n = 2 AF9, n = 2 add11, n = 2 del11, n = 3 unknown.

Outcome by Genetics and Prednisone Response

For children with DS, treatment without anthracyclines in ALL11 resulted in no relapses within 5 years and the 5-year EFS and OS of 87.0% (SE, 7.0), comparing favorably with outcome in ALL10 including anthracyclines (Figs 3A and 3B; Data Supplement [Supplemental Fig S4]). Three patients with DS ALL had an *IKZF1*del: one died in induction, one was stratified in SR, and one in MR. There were 1 of 23 deaths in induction (4.3%) and 2 of 23 deaths in CR (8.7.0%) in DS ALL (one in induction after having reached CR and one during intensification) versus 7 of 40 (17.5%) and 3 of 40 (7.5%) in ALL10, respectively.

Reduction of anthracyclines for *ETV6::RUNX1* in ALL11 MR did not abrogate the highly favorable outcome (Figs 3C and 3D and Data Supplement [Supplemental Fig S5]). Overall, for *ETV6::RUNX1*-rearranged ALL, outcome was even slightly better on ALL11 than on ALL10 with an EFS of 98.3% (SE, 1.0) versus 95.2% (SE, 1.8; $P = .052$), an OS of 99.4% (SE, 0.6) versus 98.2% (SE, 1.0; $P = .84$), and also a remarkably lower CIR of 1.1% (SE, 0.8) versus 4.8% (SE, 1.6; $P = .022$; Data Supplement [Supplemental Fig S6]).

Five-year CIR was low in *TCF3::PBX1* (4.3% [SE, 4.3]) and hyperdiploid (47-50 chromosomes; 3.8% [SE, 1.9]) and high hyperdiploid ALL (51-65 chromosomes; 6.1% [SE, 2.0]),

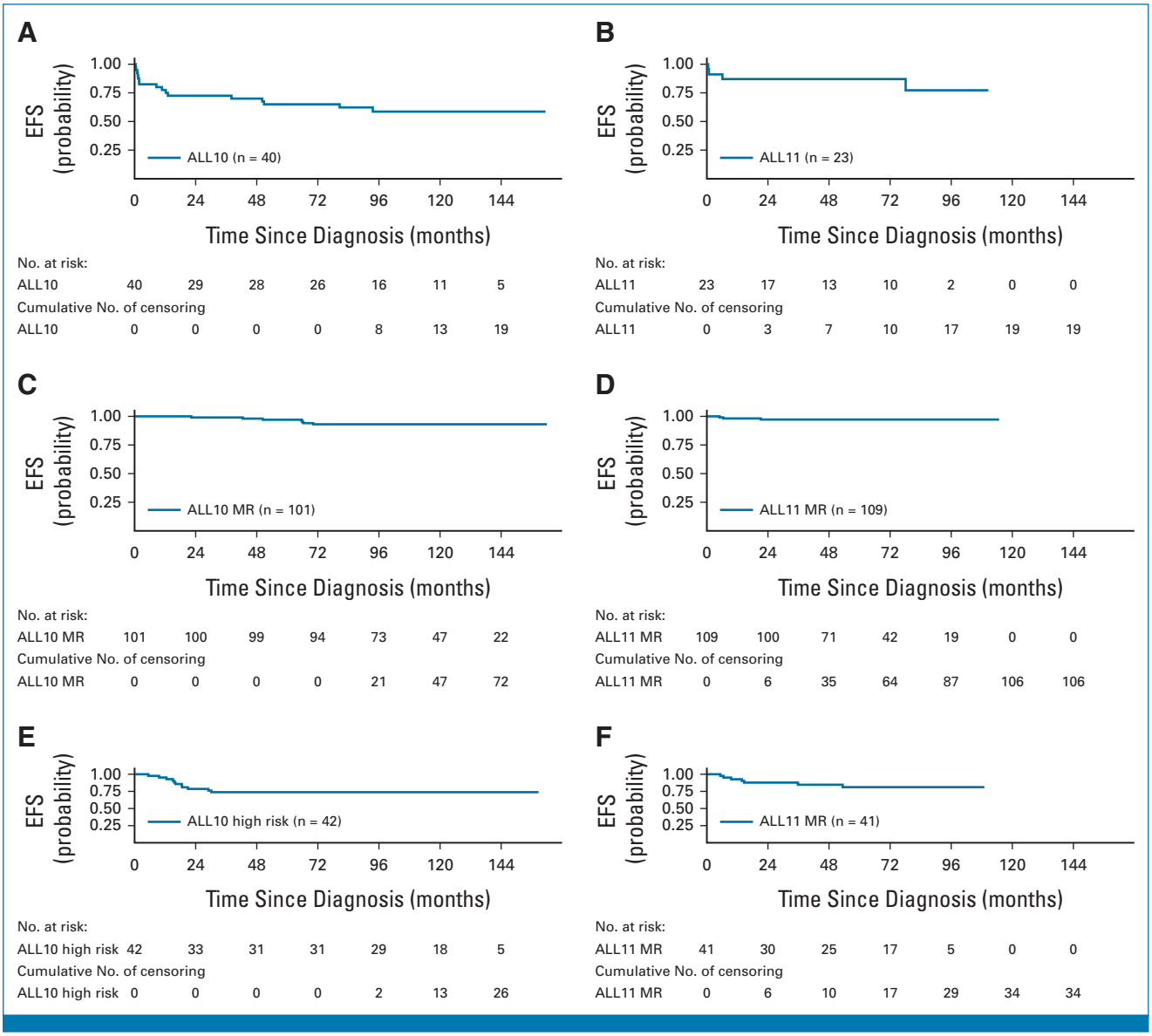

FIG 3. EFS of DS ALL, *ETV6::RUNX1*, and PPRs: ALL10 versus ALL11. Kaplan-Meier curves of patients treated with ALL10 versus ALL 11 Protocol for *DS ALL*, (A) ALL10 versus (B) ALL11 ($P = .17$); for *ETV6::RUNX1*-translocated ALL, (C) ALL10 versus (D) ALL11 ($P = .44$); and for *PPRs*, (E) ALL10 versus (F) ALL11 ($P = .342$). CID, cumulative incidence of death; CIR, cumulative incidence of relapse; DS, Down syndrome; EFS, event-free survival; HR, high risk; MR, medium risk; OS, overall survival; PPR, prednisone poor responder.

whereas 5-year CIR was high in *KMT2A*-rearranged cases (19.6% [SE, 10.3]; Data Supplement [Supplemental Fig S7]).

There were 38 PPRs (six had *IKZF1*del). Therapy reduction was also safe for PPR: the EFS, OS, and CIR at 5 years were 81.1% (SE, 6.6) versus 73.8% (SE, 6.8; $P = .42$), 94.9% (SE, 3.5) versus 81.0% (SE, 6.1; $P = .068$), and 16.4% (SE, 6.3) versus 11.9% (SE, 5.0; $P = .57$) for ALL11 MR versus ALL10 high risk, respectively (Figs 3E and 3F and Data Supplement [Supplemental Fig S8]). Five deaths in CR occurred in ALL10 high risk PPR (three after SCT, one after high risk 1 course, one because of secondary histiocytic sarcoma), and one in ALL11 PPR MR (in intensification).

Outcome by *IKZF1* Deletion and Other CNA

Outcome of *IKZF1*del MR patients improved significantly by adding a third year of therapy. This prolonged maintenance reduced the 5-year CIR by 2.2-fold from 23.4% (SE, 6.2) in ALL10 to 10.8% (SE, 4.6) in ALL11 ($P = .035$) and improved EFS from 72.3% (SE, 6.5) to 87.1% (SE, 5.0; $P = .019$) and OS from 83.0% (SE, 5.5) to 92.9% (SE, 4.0; $P = .078$; Figs 4A-4B and Data Supplement [Supplemental Fig S9]). Two relapses in ALL10 and one in ALL11 occurred within 2 years after diagnosis in the *IKZF1*del MR group. The landmark analysis at 2 years after diagnosis showed a 2.9-fold reduction of the 5-year CIR from 25.6% (SE, 7.4) to 8.8% (SE, 4.2; $P = .008$) and an improved EFS from 74.4% (SE, 7.4) to 91.2% (SE, 4.2; $P = .007$) and OS from 88.6% (SE, 5.4) to 95.5% (SE, 3.1; $P = .14$; Fig 4C and Data Supplement [Supplemental Fig S9]). During the third year of maintenance, no increased toxicity was observed except for an infection rate of 36.8% compared with 13.4%-32.4% in the earlier maintenance phases. GI toxicity in the third year did not differ from that in the second year of therapy (28.1% *v* 18.4%-46.7%; Data Supplement [Supplemental Table S2]). There were no differences between ALL10 and ALL11 in patient characteristics that might have contributed to the better outcome of *IKZF1*del MR patients (Data Supplement [Supplemental Table S3]). Differences in asparaginase in induction did not lead to lower end-of-induction or end-of-consolidation MRD in ALL11 versus ALL10, which might have contributed to differences in long-term outcome (Data Supplement [Supplemental Table S3]).

From the eight studied CNAs, alterations in *IKZF1* and *RB1* were associated with a poor outcome, *ETV6* alteration was associated with a good outcome, and the others (*CDKN2A/B*, *BTG1*, *EBF1*, *PAX5*, and *PAR1*) had no statistically significant prognostic relevance (Table 2). Combining these into the UKALL CNA classifier resulted in a 1.9-fold increased risk of 5-year CIR for the CNA poor-risk (CNA-PR) versus the good-risk (CNA-GR) group (Data Supplement [Supplemental Figs 10A-10C]; $P = .040$).[2] Using *IKZF1*del+ instead of *IKZF1* deletion only did not result in a higher CIR[24] (Data Supplement [Supplemental Figs 10D-10F]). Both CNA-PR involving *IKZF1* deletion and CNA-PR not involving *IKZF1* deletion had poorer outcome than CNA-GR cases (Data Supplement [Supplemental Figs 10G-10I]).

DISCUSSION

The most important finding of the ALL11 study is that the outcome of *IKZF1*del cases improved by adding a third 3-year maintenance therapy. *IKZF1* deletion has been associated with an unfavorable outcome on contemporary treatments by us and others.[4-10,24] *IKZF1* deletions are not only often associated with high risk genetics such as *BCR::ABL*-like and *KMT2A*-rearranged ALL but also found in favorable subtypes like high hyperdiploidy or remaining B-other cases.[7,10,25] The prognostic relevance of *IKZF1*del has mainly been shown in MR patients, and as this group comprises two third of all patients and the far majority of *IKZF1*del cases, most relapses occur in this group.[10] Because relapses in this *IKZF1*del group occurred shortly after the end of 2-year therapy, we added a third year of maintenance therapy.[4] The third year was a nonconventional type of maintenance therapy with a 6-hour MTX infusion every 3 weeks and intermittent use of 100 mg/m² 6MP once daily for 10 days followed by 11 days without 6MP. This schedule had a favorable outcome in boys in a Brazilian study.[12] The prolonged therapy appeared to significantly improve outcome for *IKZF1*del MR cases in ALL11 compared with ALL10: the 5-year CIR was reduced 2.2 fold from 23% to 11% and the EFS improved from 72% to 87%, and OS from 83% to 93%. When using a landmark analysis at 2 years, there was even a 2.9-fold reduction of the 5-year CIR rate from 26% to 9%. The third year of therapy did not result in toxicities except for a slightly higher infection rate. A question which cannot be answered is whether the better outcome could also have been achieved with a third year of standard continuous 6MP/MTX maintenance schedule. Whether adding dexamethasone-vincristine pulses improves outcome for *IKZF1*del patients remains contradictory.[26,27] Prolonged maintenance therapy beyond 2 years is not indicated for other types of ALL.[28,29] Whether patients with a high-risk CNA profile not including *IKZF1*del benefit from prolonged therapy is an interesting hypothesis.

Even with the current strong improvement, *IKZF1* deletion still has a worse outcome, which may further improve by adding blinatumomab or inotuzumab. Our study shows no superiority in predicting relapses by the so-called *IKZF1*del+ profile compared with *IKZF1* deletion itself, in line with another recent study.[30] The discrepancy with Stanullas' findings may come from subtle differences in patient numbers and stratification and by not including *ERG* deletions in our study.[24] We confirmed the prognostic relevance of the CNA profile currently used for stratification in the ALLTogether1 study.[2,3]

The former ALL10 study showed a successfully reduced chemotherapy regimen in SR patients, which was confirmed in the ALL11 study by a 98% 5-year survival. Our ALL11 study

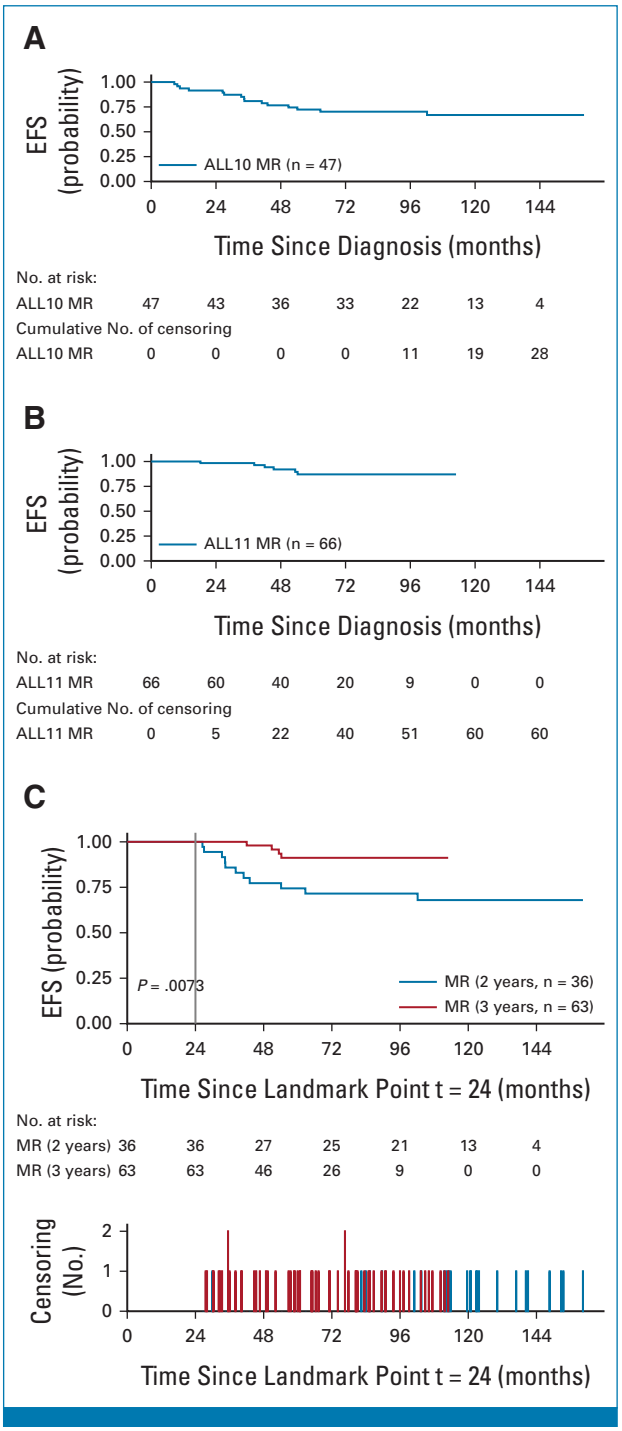

FIG 4. EFS of *IKZF1*-deleted MR patients: ALL10 versus ALL11. Kaplan-Meier curves of *IKZF1*-deleted MR patients treated with ALL10 (2-year therapy) versus ALL 11 (3-year therapy) by intention to treat, showing the EFS on (A) ALL10 versus (B) ALL11 ($P = .019$), and Kaplan-Meier curves for *IKZF1*-deleted MR patients as treated with landmark analysis including only patients who reached t = 24 months, showing (C) EFS when treated for 2 years versus 3 years ($P = .0073$). EFS, event-free survival; MR, medium risk.

showed that therapy can also be safely reduced for other patients. For MR patients with *ETV6::RUNX1*, anthracyclines were safely deleted from the intensification phase and there may be room for further de-escalating therapy.[31] For DS ALL, anthracyclines were safely fully omitted. Even without anthracyclines, two of 23 patients with DS ALL died in CR, reflecting their susceptibility to severe infections. Further therapy reductions may be difficult as patients with DS have relatively resistant ALL types.[32] Significant therapy reductions for PPR were also safe as the 5-year survival with MR therapy was 94%, which is at least comparable with outcomes with the intensive high risk chemotherapy courses in DCOG ALL10 and AIEOP/BFM ALL2010 trials.[1,33] This indicates that the use of PPR as the high risk criterion can be negated in MRD-guided Protocols.

Overall, the outcomes with ALL11 therapy are at least as good as the outcome on ALL10 despite the abovementioned therapy reductions for specific patient groups. In addition, no irradiation was used and only 4% of patients received SCT in first remission. The duration of exposure to asparaginase was higher in ALL11 induction versus ALL10, but the cumulative exposure did not differ, and the dose was lower by using drug monitoring.[34,35] The DFCI-based cumulative dose of 300 mg/m^2 anthracyclines in the MR group were reduced without jeopardizing the outcome of overall MR patients including those with unfavorable genetic abnormalities.

There are several limitations to our study; we used a historical control group, in which the composition of risk groups is similar. Difference in patient characteristics or in asparaginase dose intensity might theoretically contribute to the better outcome of *IKZF1*del MR patients. However, our data do no suggest this. Patient characteristics did not differ between ALL10 and ALL11. MRD at the end of induction and end of consolidation is not lower in ALL11 compared with that in ALL10, so there was no earlier eradication by PEGylated *E coli* Asparaginase in ALL11 compared with native *E coli* asparaginase in induction in ALL10. This is in line with our studies showing that both asparaginase regimes lead to trough levels of asparaginase that fully deplete serum asparagine.[34,36-38] As long as these trough asparaginase levels are sufficient for asparagine depletion, higher asparaginase levels obtained with PEG-asparaginase do not correlate with outcomes.[35] In ALL10, we used native *E coli* asparaginase in induction plus 15 doses of PEG-asparaginase in intensification. In ALL11, we used 14 doses of PEG-asparaginase in intensification to correct for the PEG-asparaginase dose at day 40.

There could also have been an impact of transitioning from care in seven centers to a single center; However, this took place only in June 2018, so this would only account for a limited number of events. In the 6 years before this change, there were 15 deaths in remission compared with three deaths in CR in the 4 years thereafter.

Outcome for CNS3 patients is still worse in line with other studies.[39] TLP+ was not of prognostic relevance in our study nor was CNS2 status, whereas these patients did not receive extra intrathecal therapy after the Protocol amendment. The outcome of the small high risk group has improved with intensive chemotherapy and SCT but is still unsatisfactory.[1,40-42]

In the ALLTogether1 Protocol, patients with high risk B-cell ALL are now eligible for CAR-T–cell studies.

We conclude from our ALL11 study that therapy was safely reduced for *ETV6::RUNX1* ALL, DS ALL, and PPR. Most importantly, children with *IKZF1*del ALL seem to benefit from a third year of therapy, suggesting to change therapy accordingly for this class of patients. It has to be noted that this was a nonrandomized study using a historical control group.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

All pseudonymized participant data as collected within this study are stored in the Datawarehouse of the Princess Máxima Center for Pediatric Oncology and will be available after approval of relevant research applications by the Biobank Data Access Committee (https://research.prinsesmaximacentrum.nl/en). This data set includes patient characteristics at diagnosis, therapy details, response to therapy, and toxicity and outcome parameters. Data are available immediately after publication, no end date. A relevant subset of anonymized participant data as collected within this study will be uploaded into the International Harmony Big Data Platform and will be available after approval of research applications by the Harmony Alliance (https://www.harmony-alliance.eu). This limited data set includes patient characteristics at diagnosis, response to therapy, and outcome parameters. Data will be available approximately 6-12 months after publication, no end date.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Improved Outcome for ALL by Prolonging Therapy for *IKZF1* Deletion and Decreasing Therapy for Other Risk Groups

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