Severe toxicity and poor efficacy of reinduction chemotherapy are associated with overall poor outcomes in relapsed B-cell acute lymphoblastic leukemia: a report from the Children's Oncology Group AALL1331 trial

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Abstract

Children's Oncology Group AALL1331 utilized an intensive chemotherapy induction (Block 1) based on UK ALLR3 induction for children, adolescents, and young adults with acute lymphoblastic leukemia in first relapse, followed by risk-stratified therapy. High/intermediate-risk patients were subsequently randomized to receive two blocks of chemotherapy or two blocks of blinatumomab followed by a hematopoietic stem cell transplant. Low-risk patients were randomized to chemotherapy or chemotherapy cycles intercalated with three blinatumomab blocks. Patients who had early treatment failure were eligible to receive blinatumomab for up to two salvage cycles. We reviewed Block 1 responses, risk stratification, randomization rates, adverse events, event-free survival and overall survival for all enrolled patients. AALL1331 enrolled 661 patients: 24 died during Block 1 and 42 experienced early treatment failure. Overall, 531/661 (80.3%) attained complete remission with 586 risk-assigned and only 471 were randomized. Of 532 patients with bone marrow involvement, 290 (54.5%) were positive for minimal residual disease (≥0.01%) after Block 1. Grade 3, 4 or 5 adverse events occurred in Block 1 in 44.9%, 24.1%, and 3.6% of patients, respectively, with febrile neutropenia, infections, and sepsis being most frequent. Notably, 190 enrolled patients (28.7%) did not proceed with post-induction therapy, including 115 (17.4%) risk-stratified but not randomized. These patients had dismal survival. More effective and less toxic reinduction strategies are needed for B-cell acute lymphoblastic leukemia in first relapse. Trial registration number: NCT02101853.

Introduction

B-cell acute lymphoblastic leukemia (B-ALL) is the most common childhood cancer. Despite improvements in therapy, approximately 10-15% of newly-diagnosed B-ALL patients relapse.[1-3] Survival for relapsed patients remains suboptimal with 5-year overall survival (OS) rates of 35-60%.[3-14] The most important predictors of outcome after relapse are time from diagnosis, site of relapse, and minimal residual disease (MRD) status after reinduction therapy.[11-19] Blinatumomab, a bispecific T-cell engager targeting CD19, has shown efficacy in pediatric patients with multiply relapsed/refractory B-ALL.[19,20] Children's Oncology Group (COG) AALL1331 enrolled patients with first relapse of B-ALL using

risk-adapted therapy after a common Block 1 reinduction which was modeled closely on the UK ALLR3 mitoxantrone reinduction.[11] We reported previously that for high- and intermediate-risk (HR and IR) patients (N=216), replacing two cycles of intensive chemotherapy with blinatumomab after Block 1 followed by hematopoietic stem cell transplant (HSCT) significantly improved OS and reduced toxicities.[21] We also reported that the replacement of one block of intensive chemotherapy and intercalation of two additional blocks of blinatumomab into continuation chemotherapy increased disease-free survival and OS for low-risk (LR) patients (N=255) with bone marrow (BM) relapse, with or without extramedullary (EM) relapse, also with reduced toxicities, while patients with isolated EM relapse fared poorly with or without blinatumomab.[22] However, these reports did not include data on all 661 eligible patients who initially enrolled on AALL1331. Herein, we describe the outcomes of the entire cohort of eligible patients who enrolled on AALL1331, including the 190 patients who never proceeded to risk stratification/randomization after Block 1 reinduction.

Methods

Eligibility and trial oversight

Patients between 1 and 30 years old with a first relapse of B-ALL were eligible. Site of relapse was defined as previously described (*Online Supplementary Table S1*).[21,22] Patients with Down syndrome, Philadelphia chromosome (*BCR::ABL1*)-positive ALL, previous HSCT, or previous blinatumomab treatment were not eligible. The protocol and amendments were approved by the National Cancer Institute (NCI) Pediatric Central Institutional Review Board (IRB) and by each center's IRB/independent ethics committee. Written informed consent/assent was obtained for Block 1 chemotherapy prior to starting therapy. Following completion of induction therapy and risk assignment, a second consent was required for post-induction therapy.

Treatment and risk assignment

All patients received a 4-week reinduction (Block 1) adapted from the mitoxantrone arm of UKALLR3,[11] which included vincristine, dexamethasone, pegaspargase, mitoxantrone, and risk-based intrathecal chemotherapy (*Online Supplementary Table S2*). Patients were risk-assigned at the end of Block 1 (Figure 1). End-of-induction response was evaluated locally by morphology and centrally by flow cytometric MRD with MRD negativity defined as <0.01%. Evaluation for EM disease included lumbar puncture and testicular examination. Testicular biopsy was required for those with equivocal examinations. Randomization was performed after risk stratification for eligible patients. The end-of-induction risk groups with randomization are shown in Figure 2.

Patients who had early treatment failure were eligible to receive up to two salvage cycles of blinatumomab. Patients who were HR or IR after Block 1 were randomized to receive two blocks of chemotherapy adapted from UKALLR3 (Arm A) or two blocks of blinatumomab (Arm B) followed by HSCT (*Online Supplementary Figure S1*).[21] LR patients received post-induction therapy adapted from UKALLR3 without HSCT with randomization to receive two intensive chemotherapy blocks (Block 2 and Block 3) followed by two continuation cycles and maintenance chemotherapy (Arm C) or Block 2 chemotherapy with 4 weeks of blina-

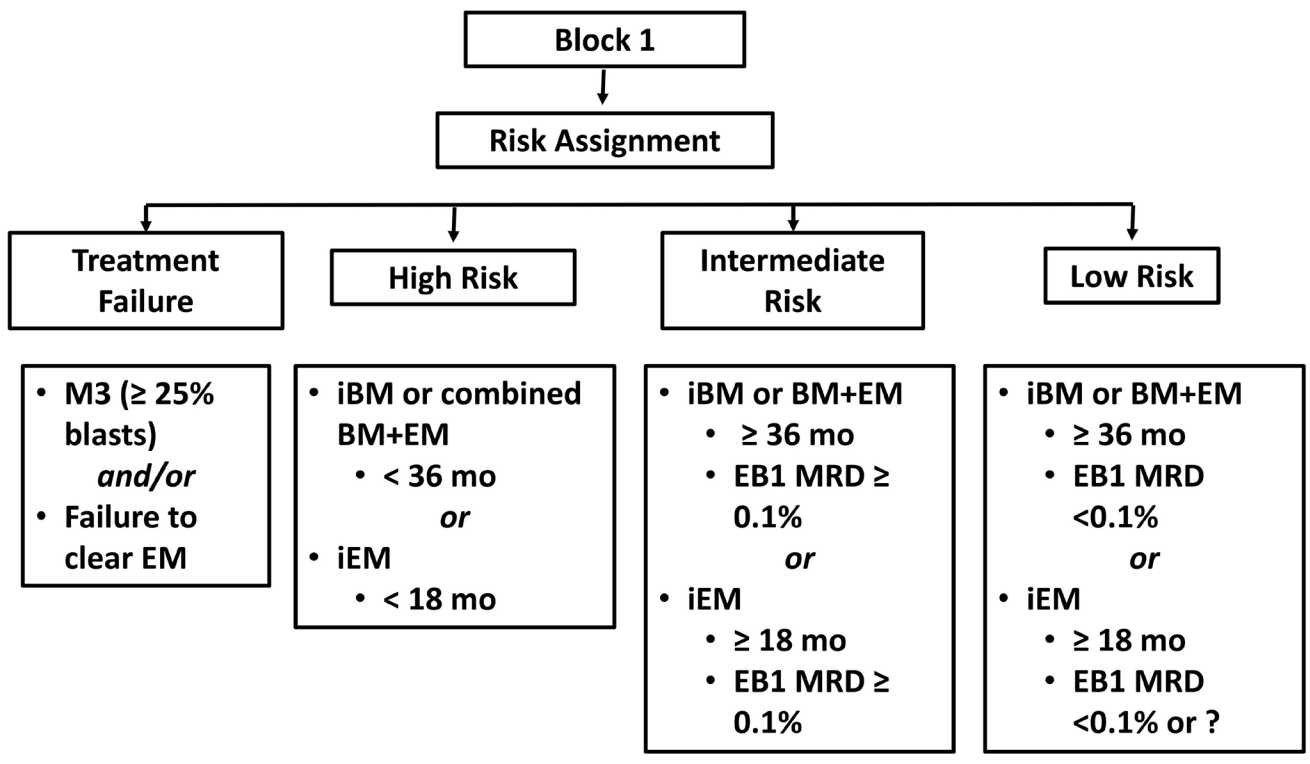

Figure 1. Risk stratification after Block 1. EM: extramedullary relapse; iBM: isolated bone marrow relapse; BM+EM: bone marrow with extramedullary relapse; mo: months from diagnosis to relapse; iEM: isolated extramedullary relapse; EB1: end of block 1; MRD: minimal residual disease; ?: unknown.

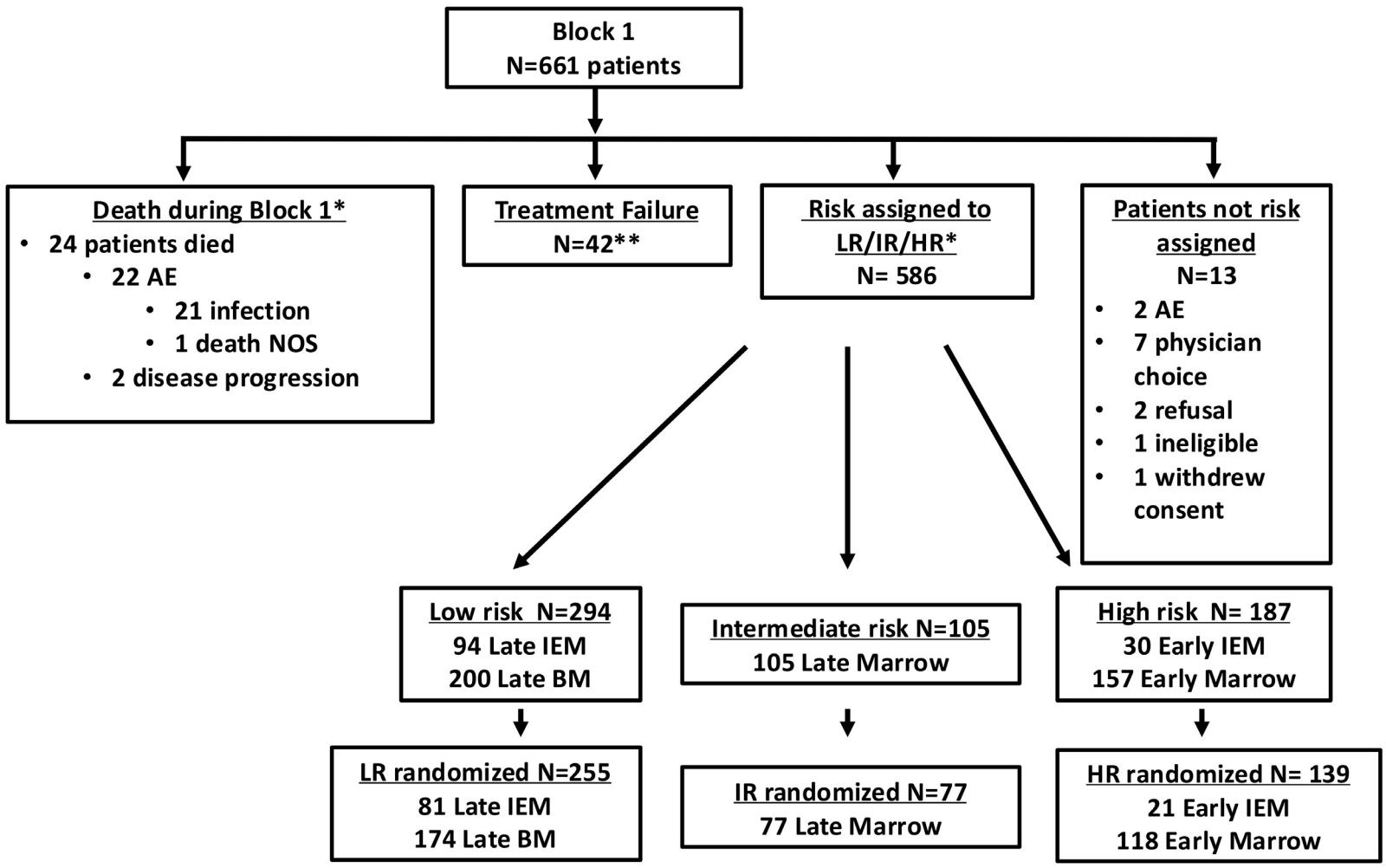

Figure 2. Consort diagram of enrolled patients. *Four patients who died were risk stratified: 1 low risk, 1 intermediate risk, 2 high risk. **One additional patient not counted in the 42 treatment failures had treatment failure and died due to adverse events. N: number, AE: adverse events; NOS: not otherwise specified; LR: low risk; IR: intermediate risk; HR: high risk; MRD: minimal residual disease; IEM: isolated extramedullary; BM: bone marrow.

tumomab replacing Block 3 followed by continuation chemotherapy intercalated with two 4-week blinatumomab blocks, followed by maintenance therapy (Arm D) (*Online Supplementary Figure S2*).[22] LR patients with central nervous system (CNS) disease received cranial radiotherapy (18 Gy) after maintenance cycle 1. Patients with testicular leukemia persisting after Block 1 received testicular radiation during Block 2.

Outcomes and statistical analysis

Adverse events (AE) were graded with the NCI Common Terminology Criteria for Adverse Events version 4.0, and AE ≥ grade 3 were categorized as severe. Here we describe end of Block 1 MRD, Block 1 AE, event-free survival (EFS) and OS of the entire eligible cohort (N=661) including 190 patients who were not randomized using a data cutoff of March 31, 2023. In these analyses, EFS and OS were calculated from date of enrollment or from end of Block 1, as appropriate. Events included any treatment failure, relapse, second malignancy, or death due to any cause. The association between end of Block 1 response or AE during Block 1 with clinical characteristics was evaluated using Pearson's χ^2 test, Fisher's exact test or logistic regression as appropriate. Analyses of the association between EFS and OS and patients' or clinical characteristics were based on log-rank tests or univariate and multivariable Cox regression analyses.[23] For the construction of reduced multivariable models, a stepwise backward model selection procedure was used to select patients' or disease characteristic variables for each outcome with a threshold of 0.15 for stay.[24] All reported *P* values are two-sided. Statistical analyses were performed using STATA software.[25]

Results

Between January 2014 and September 2019, AALL1331 enrolled 669 patients, with 661 eligible starting Block 1 reinduction. The clinical characteristics at enrollment are shown in Table 1; 209 patients (31.6%) had a BM±EM relapse <36 months from diagnosis and 323 (48.9%) had a BM±EM relapse ≥36 months from diagnosis. Eighty-four of the 209 patients had an early BM±EM relapse <18 months from diagnosis. Thirty-two patients (4.8%; 31 CNS, one testicular) had an isolated EM relapse <18 months after the initial diagnosis and 97 patients (14.7%; 78 CNS, 18 testicular, 1 combined CNS/testicular) had an isolated EM relapse ≥18 months after the initial diagnosis. Overall, 15.6% of patients were 18 years or older.

Forty-two patients (6.4%) were considered to have had early treatment failure after Block 1 (Figure 2). One death from an AE occurred in an additional patient who was also

Table 1. Patients' baseline characteristics at enrollment.

Patients' characteristics	All eligible enrollments N=661	BM relapse <36 months N=209	BM relapse ≥36 months N=323	IEM relapse <18 months N=32	IEM relapse ≥18 months N=97
Age at enrollment, years					
Median (range)	10 (1-27)	8 (1-27)	11 (4-27)	9 (1-25)	9 (2-26)
1-9, N (%)	308 (46.6)	117 (56.0)	125 (38.7)	17 (53.1)	49 (50.5)
10-17, N (%)	250 (37.8)	62 (29.7)	138 (42.7)	12 (37.5)	38 (39.2)
18-20, N (%)	61 (9.2)	20 (9.6)	31 (9.6)	2 (6.3)	8 (8.2)
21-30, N (%)	42 (6.4)	10 (4.8)	29 (9.0)	1 (3.1)	2 (2.1)
Age at initial diagnosis, years					
Median (range)	6 (0-26)	6 (0-26)	6 (0-22)	7.5 (0-24)	6 (0-23)
0-1, N (%)	29 (4.4)	22 (10.5)	3 (0.9)	3 (9.4)	1 (1.0)
1-9, N (%)	415 (62.8)	106 (50.7)	234 (72.4)	14 (43.8)	61 (62.9)
10-17, N (%)	188 (28.4)	64 (30.6)	79 (24.5)	13 (40.6)	32 (33.0)
18-20, N (%)	18 (2.7)	11 (5.3)	5 (1.5)	1 (3.1)	1 (1.0)
21-30, N (%)	11 (1.7)	6 (2.9)	2 (0.6)	1 (3.1)	2 (2.1)
Sex, N (%)					
Male	380 (57.5)	107 (51.2)	171 (52.9)	27 (84.4)	75 (77.3)
Female	281 (42.5)	102 (48.8)	152 (47.1)	5 (15.6)	22 (22.7)
Race, N (%)					
American Indian or Alaska Native	5 (0.9)	2 (1.2)	2 (0.7)	0	1 (1.1)
Asian	36 (6.3)	8 (4.7)	23 (8.1)	0	5 (5.6)
Native Hawaiian or other Pacific Islander	2 (0.3)	0	0	0	2 (2.2)
Black or African American	60 (10.5)	26 (15.1)	24 (8.4)	4 (15.4)	6 (6.7)
White	462 (80.8)	134 (77.9)	233 (81.8)	22 (84.6)	73 (82.0)
Multiple races	7 (1.2)	2 (1.2)	3 (1.1)	0	2 (2.2)
Unknown	89	37	38	6	8
Ethnicity, N (%)					
Hispanic or Latino	216 (33.9)	76 (37.8)	97 (30.9)	11 (36.7)	32 (34.4)
Not Hispanic or Latino	422 (66.1)	125 (62.2)	217 (69.1)	19 (63.3)	61 (65.6)
Unknown	23	8	9	2	4
Race/ethnicity, N (%)					
Hispanic of all races	216 (32.7)	76 (36.4)	97 (30.0)	11 (34.4)	32 (33.0)
Non-Hispanic White	305 (46.1)	84 (40.2)	160 (49.5)	13 (40.6)	48 (49.5)
Non-Hispanic Black	56 (8.5)	25 (12.0)	23 (7.1)	4 (12.5)	4 (4.1)
Non-Hispanic Asian	33 (5.0)	8 (3.8)	20 (6.2)	0	5 (5.2)
Non-Hispanic other	5 (0.8)	1 (0.5)	1 (0.3)	0	3 (3.1)
Other/unknown	46 (7.0)	15 (7.2)	22 (6.8)	4 (12.5)	5 (5.2)
Obesity, N (%)					
Non-obese	487 (74.2)	143 (70.1)	251 (77.7)	21 (65.6)	72 (74.2)
Obese	169 (25.8)	61 (29.9)	72 (22.3)	11 (34.4)	25 (25.8)
Unknown	5	5	0	0	0

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Patients' characteristics	All eligible enrollments N=661	BM relapse <36 months N=209	BM relapse ≥36 months N=323	IEM relapse <18 months N=32	IEM relapse ≥18 months N=97
NCI risk group at diagnosis, N (%)					
High Risk	319 (48.7)	121 (58.5)	120 (37.6)	24 (75.0)	54 (55.7)
Standard Risk	336 (51.3)	86 (41.5)	199 (62.4)	8 (25.0)	43 (44.3)
Unknown	6	2	4	0	0
Site of relapse and duration of CR1, N (%)					
BM, CR1 <18 months	84 (12.7)	84 (40.2)	0	0	0
BM, CR1 18-36 months	125 (18.9)	125 (59.8)	0	0	0
BM, CR1 ≥36 months	323 (48.9)	0	323 (100)	0	0
IEM, CR1 <18 months	32 (4.8)	0	0	32 (100)	0
IEM, CR1 ≥18 months	97 (14.7)	0	0	0	97 (100)
Testicular disease at first relapse, N (%)					
No	623 (94.3)	206 (98.6)	308 (95.4)	31 (96.9)	78 (80.4)
Yes	38 (5.7)	3 (1.4)	15 (4.6)	1 (3.1)	19 (19.6)
CNS status at first relapse, N (%)					
CNS 1	422 (63.8)	155 (74.2)	249 (77.1)	1 (3.1)	17 (17.5)
CNS 2	67 (10.1)	28 (13.4)	38 (11.8)	0	1 (1.0)
CNS 3	172 (26.0)	26 (12.4)	36 (11.1)	31 (96.9)	79 (81.4)
Upfront COG trial, N (%)					
No	158 (23.9)	59 (28.2)	69 (21.4)	10 (31.3)	20 (20.6)
Yes	503 (76.1)	150 (71.8)	254 (78.6)	22 (68.8)	77 (79.4)
Cytogenetic group at initial diagnosis, N (%)					
ETV6::RUNX1	91 (15.1)	19 (10.0)	54 (18.4)	4 (13.3)	14 (15.6)
DT/TT	60 (10.0)	8 (4.2)	45 (15.4)	1 (3.3)	6 (6.7)
KMT2A rearranged	39 (6.5)	28 (14.7)	5 (1.7)	5 (16.7)	1 (1.1)
Hypodiploidy	8 (1.3)	5 (2.6)	3 (1.0)	0	0
None of the above	405 (67.2)	130 (68.4)	186 (63.5)	20 (66.7)	69 (76.7)
Unknown	58	19	30	2	7

N: number; NCI: National Cancer Institutes; BM: bone marrow; IEM: isolated extramedullary; CR1: first complete remission; CNS: central nervous system; COG: Children's Oncology Group; DT/TT: double trisomy/triple trisomy of chromosomes 4 and 10 or 4, 10, and 17.

deemed to have had early treatment failure. Of these early treatment failures, 33 (78.6%) enrolled after a BM relapse in <36 months, with 23 (54.8%) of these relapsing <18 months from the initial diagnosis (*Online Supplementary Table S3*). Twenty-four patients (3.6%) died during Block 1. Of the 24 deaths, two were due to disease progression and 22 were due to AE, 21 (95.5%) of which were related to infection/sepsis. Among the 24 patients with induction death, three had an initial isolated CNS relapse, all others had BM involvement. Of 532 patients with BM±EM relapse, 290 patients (54.5%) were MRD-positive (≥0.01%) and 35 (6.6%) had unknown/not done MRD status at the end of Block 1. Most of the unknown/not done MRD cases were due to death, early treatment failure, or severe AE. The rate of MRD positivity was 67.9% for marrow relapses <18 months from diagnosis, 60% for marrow relapses between 18-36 months after diagnosis and 48.9% for marrow relapses >36 months after the initial diagnosis.

Five hundred eighty-six of 661 eligible patients (88.7%) initially enrolled were risk-assigned to LR, IR or HR. Two hundred ninety-four were LR (94 late isolated EM, 200 late BM), 105 were IR (all late BM relapses) and 187 were HR (30 early isolated EM and 157 early BM). Of the 24 reinduction deaths, five patients were risk-assigned before death (1 LR, 1 IR, 2 HR and 1 early treatment failure). Of the 24 deaths, 21 had BM±EM relapse (15 early/6 late) and three had isolated EM (1 early, 2 late). Thirteen patients were not risk-assigned because of AE (N=2), physicians' choice (N=7),

patients' refusal (N=2), ineligible (N=1), and withdrawal of consent (N=1).

After risk assignment, patients who consented were randomized to post-reinduction consolidation therapy. One hundred fifteen patients (19.6%) of the 586 who were risk-assigned were not randomized. Reasons for not proceeding with randomization included severe AE (N=6), physicians'/patients' choice (N=102), death (N=3) and other (N=4). Of the initial 661 eligible patients, only 471 patients (71%) were randomized for post-induction therapy, (255 LR, 77 IR and 139 HR).

Of the 42 patients who had early treatment failure, 22 received salvage blinatumomab on protocol with variable responses. After cycle 1 of salvage blinatumomab, three had MRD >1% (5.2%, 96.7%, and 96%), two had MRD between 0.1-0.99%, two had MRD <0.01%, and 15 had unknown MRD status. Only one additional patient had MRD <0.01% after a second cycle of salvage blinatumomab. Of these 42 patients with early treatment failure, one received HSCT on protocol after receiving salvage blinatumomab, and four others were reported to have received HSCT within 6 months after patients were off protocol. Three of the five patients receiving HSCT were alive as of the last follow-up date.

AE were frequent during Block 1 with 22 grade 5 events, the majority of which (N=21) were infectious toxicities, with one cause of death not otherwise specified. Importantly, 480 patients experienced a grade 3 or higher AE with 183 experiencing a grade 4 or higher AE. *Online Supplementary Table S4* shows grade 3-5 AE that were seen in at least 5% of patients. Grade 3-5 febrile neutropenia, infections, and sepsis were seen in 30.3%, 36.6% and 10.1% of patients, respectively. Additionally, metabolic/nutritional disorders, abnormal liver function, mucositis and hypotension were common. Clinical characteristics that correlated with grade 3-5 AE are shown in Table 2. Significantly higher rates of infection were seen in patients with BM relapses, particularly

Table 2. Grade 3-5 adverse events correlating with clinical characteristics.

Adverse events	Grade 3-5		Grade 4-5	
	Frequency %	*P*	Frequency %	*P*
Infections (total)*				
1-9 years, N=308	54.2	0.85	8.4	0.0008
10-18 years, N=270	51.9		15.6	
19-30 years, N=83	53.0		22.9	
BM relapse, N=532	55.3	0.024	13.2	0.99
IEM relapse, N=129	44.2		13.2	
BM early relapse, N=209	55.5	0.013	15.8	0.36
BM late relapse, N=323	55.1		11.5	
IEM early relapse, N=32	62.5		18.8	
IEM late relapse, N=97	38.1		11.3	
Infections and infestations				
1-9 years, N=308	32.5	0.058	7.8	0.0004
10-18 years, N=270	38.5		14.8	
19-30 years, N=83	45.8		22.9	
BM relapse, N=532	39.1	0.007	12.8	0.72
IEM relapse, N=129	26.4		11.6	
BM early relapse, N=209	46.4	<0.001	14.8	0.33
BM late relapse, N=323	34.4		11.5	
IEM early relapse, N=32	37.5		18.8	
IEM late relapse, N=97	22.7		9.3	
Sepsis				
1-9 years	6.5	0.007	6.2	0.005
10-18 years	12.2		11.9	
19-30 years	16.9		16.9	
Oral mucositis				
1-9 years	4.9	0.013	0	
10-18 years	5.2		0	
19-30 years	13.3		0	
Hyperglycemia				
1-9 years	11.7	0.001	2.9	0.61
10-18 years	18.9		3.0	
19-30 years	27.7		4.8	
Hyperbilirubinemia				
1-9 years	5.5	0.052	1.0	0.018
10-18 years	7.0		0.4	
19-30 years	13.3		4.8	
Gastrointestinal toxicity				
Male	14.0	<0.001	1.3	0.75
Female	24.9		1.8	
Hypoalbuminemia				
Male	3.7	0.002	0.3	1.00
Female	9.6		0	

*Includes infections and febrile neutropenia. N: number; BM early relapse: bone marrow relapse within 36 months; BM late relapse: bone marrow relapse at 36 months or beyond; IEM early relapse: isolated extramedullary relapse within 18 months; IEM late relapse: isolated extramedullary relapse at 18 months or beyond.

those with early BM relapse. Infections, sepsis, mucositis, hyperglycemia, hyperbilirubinemia, and grade 5 AE were more common in older patients. Grade 5 AE were seen in 2%, 4.1%, and 8.4% of patients 1-9, 10-18, and 19-30 years old, respectively. Girls had significantly higher rates of gastrointestinal toxicity (hepatic failure, portal hypertension, mucositis) and hypoalbuminemia.

The association of clinical characteristics and grade 3-5 or grade 4-5 AE during Block 1, end of Block 1 MRD positivity, EFS and OS are shown in *Online Supplementary Tables S5-S11*. In univariate and multivariable analysis, race/ethnicity was significantly correlated with grade 3-5 or grade 4-5 AE in Block 1 in patients with BM relapse, with Hispanic and Non-Hispanic Asians having the highest risk of grade 3-5 AE and Hispanics having the highest risk of grade 4-5 AE. No other clinical characteristic was associated with overall increased risk of grade 3-5 or 4-5 AE in Block 1 in multivariable analyses.

Four-year EFS and OS from the date of enrollment for all 661 patients was 44.0±2.0% and 64.9±1.9%, respectively. Six-year EFS and OS was 41.1±2.0% and 62.0±2.0%, respectively, indicating that the majority of events happened in the first 4 years and that outcome was relatively stable after that time (Figure 3). However, outcomes varied significantly by time to relapse, site of relapse, risk assignment group and randomization status (Figure 4). Notably the 84 patients with a BM±EM relapse <18 months from diagnosis had the worst EFS and OS (9.6±3.3% and 16.1±4.1% at 4 years, respectively), accounting for 23 (54.8%) early treatment failures. In addition, ten patients were not risk-assigned and of the 51 risk-assigned patients, 15 were not randomized. Those with a BM±EM relapse ≥36 months from diagnosis had the best EFS and OS (62.8±2.8% and 84.8±2.1% at 4 years, respectively). Patients who had early treatment failure or were not risk-assigned had dismal outcomes. Patients with early treatment failure had a 4-year EFS of 0% (by definition since early treatment failure was an event) and an OS of 18.7±6.2%, and those who were not risk-assigned had a 4-year EFS and OS of 8.1±5.3% and 19.8±7.4%, respectively. Four-year EFS and OS by CNS status at first relapse is shown in *Online Supplementary Figure S3*. Patients with marrow relapse+CNS2 disease had worse outcomes than those with marrow relapse+CNS3 disease. Increasing levels of MRD were associated with lower EFS and OS (P<0.0001) (Figure 5).

Among patients with isolated BM relapse there was a higher risk of being MRD-positive and shorter time to first relapse. Interestingly, in multivariable analysis, age at enrollment, sex, race/ethnicity, obesity and cytogenetic subgroup at initial diagnosis were not associated with increased risk of being MRD-positive in patients with BM±EM relapse. In multivariable analysis of patients with a BM±EM relapse, inferior EFS was seen in older patients (worst in those ≥18 years old), males and those with a shorter time to first relapse (worst in those who relapsed <18 months from diagnosis). Additionally, in multivariable analysis of patients with BM±EM relapse, having an isolated BM relapse and shorter duration of time to first relapse was associated with reduced OS, but age ≥18 years was not. Obesity, defined as body mass index percentile ≥95%, was not significantly associated with EFS and OS in multivariable analysis of patients with BM±EM relapse; however, for patients with isolated EM relapse, obesity was associated with inferior EFS.

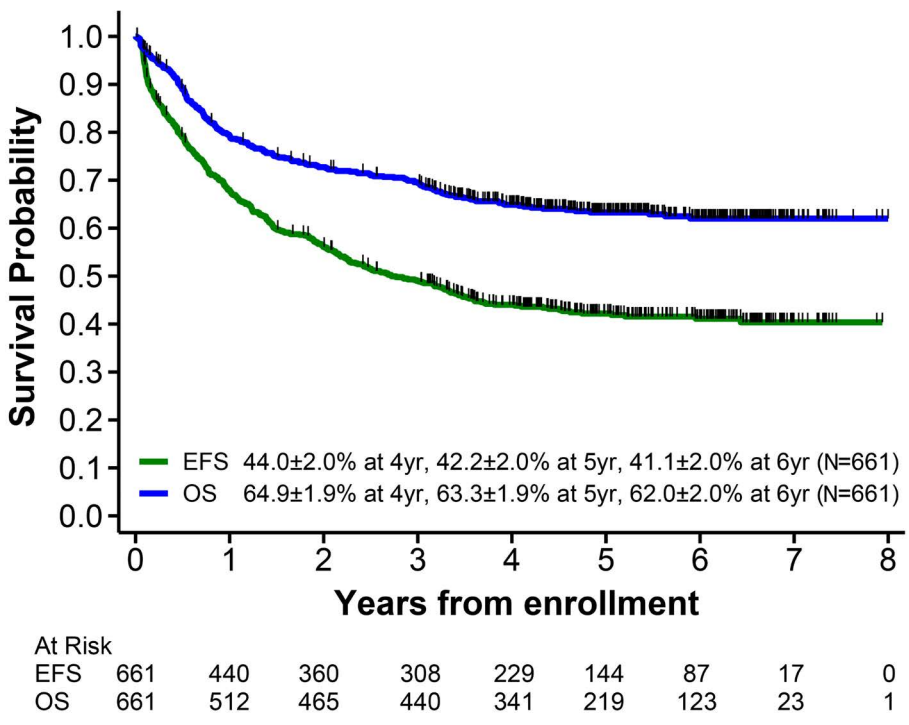


Figure 3. Event-free survival and overall survival from enrollment of all 661 patients. EFS: event-free survival; OS: overall survival; yr: years; N: number.

Discussion

COG AALL1331 is the largest comprehensive clinical trial for B-ALL in first relapse. The primary objective of COG AALL1331 was to determine whether substituting blinatumomab for intensive chemotherapy in consolidation after a common block of standard reinduction therapy would improve survival in children and young adults with first relapse of B-ALL. For all enrolled patients, the 3-year EFS and OS were 49.0±2.0% and 69.6±1.8%, respectively, and the 6-year EFS and OS rates from the date of enrollment were 41.1±2.0% and 62.0±2.0%, respectively. In comparison, estimated 3-year progression-free survival and OS on the mitoxantrone arm of UK ALLR3 were 64.6% and 69.0%, respectively.[11] Lower EFS on AALL1331 was no doubt partly due to inferior outcomes in patients with late isolated EM. However, the R3 mitoxantrone arm included only 105 patients and did not include patients over 18 years of age. Although race and ethnicity were not reported for the UKALL R3 trial, it is likely that the population differed from that enrolled in AALL1331, thus the trial populations are not directly comparable.

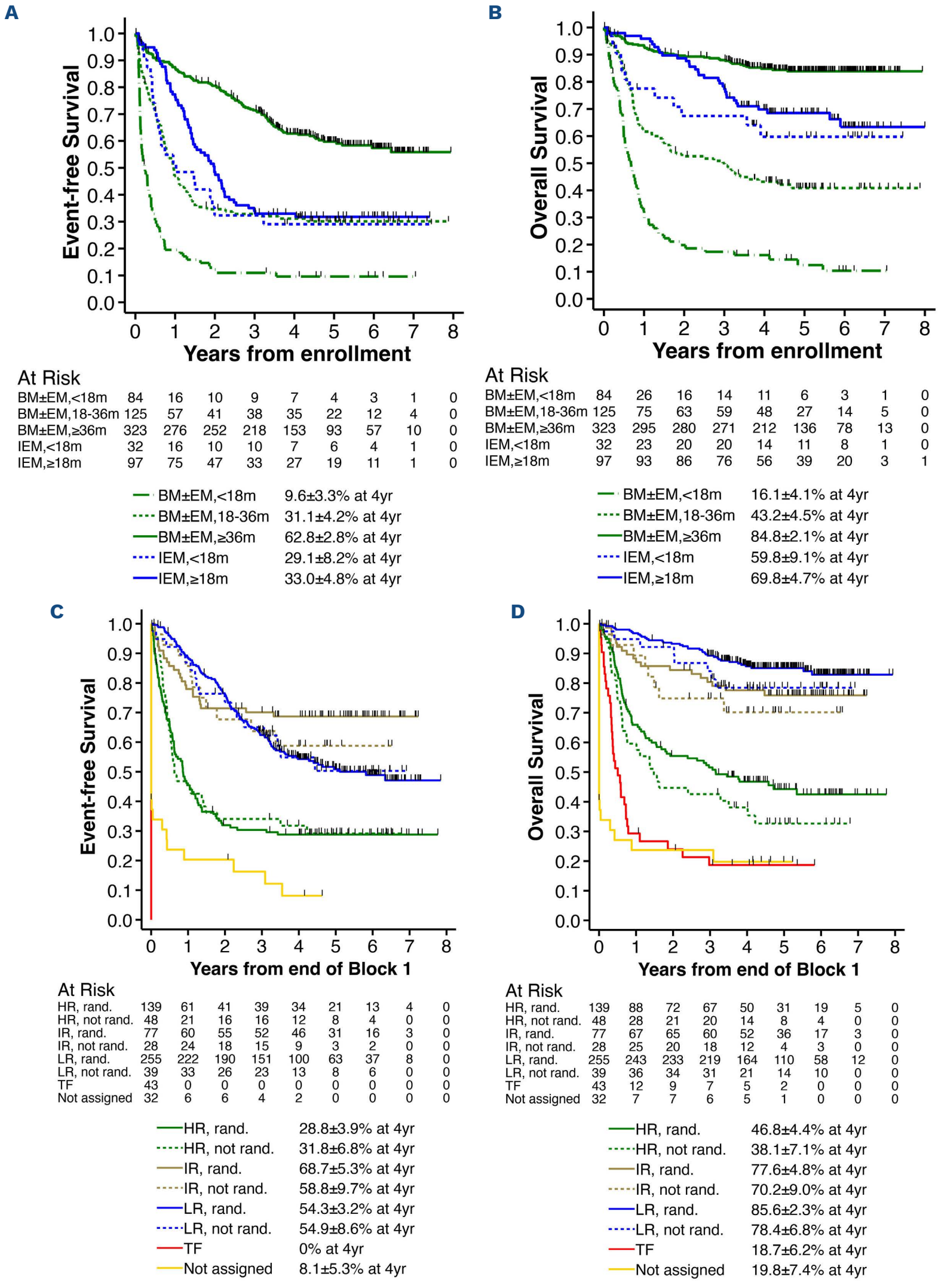


Figure 4. Survival from enrollment by site and time to relapse and from completion of Block 1 by risk assignment group and randomization status. (A, B) Event-free survival and overall survival from enrollment by site of relapse and time to relapse. (C, D) Event-free survival and overall survival from completion of Block 1 by risk assignment group and randomization status. BM: bone marrow; EM: extramedullary; IEM: isolated extramedullary; m: months; yr: years; HR: high risk; rand: randomized; IR: intermediate risk; LR: low risk; TF: treatment failure.

We previously showed that for subsets of randomized patients (HR/IR and LR with marrow disease), incorporation of blinatumomab improved outcomes with a favorable AE profile after Block 1 reinduction.[21,22] Poor outcome in LR patients with isolated EM was largely driven by poor outcomes in patients with isolated CNS relapse in both treatment arms. Importantly, a large group of patients (N=190, approximately 30%) who initially enrolled on this trial were not included in the HR/IR and LR analyses due to removal from protocol therapy during or soon after completing Block 1. We here present EFS and OS data on all eligible patients from the time of enrollment. Additionally, we performed *post hoc* analyses of the correlation between clinical characteristics and outcomes that were not previously published primary or secondary objectives.

AALL1331 was noteworthy because it enrolled all patients in first relapse, regardless of relapse site or time to relapse. The UK ALLR3 chemotherapy backbone was chosen due to superior outcome when compared to prior COG reinduction platforms.[11,26] In the UK ALLR3 trial, there were 105 patients on the mitoxantrone arm. Of these, three withdrew (reasons not given), eight failed induction (7.6%) and five died of treatment-related causes (4.8%).[11] The UK ALLR3 induction failure rate was 7.6%, similar to ours, but definitions of induction failure may be different, making direct comparison difficult. In addition, the toxic death rate of 4.8% on the UK AALLR3 is similar to ours (3.3%) and the R3 trial did not include patients over 18 years who had the highest rates of induction death on AALL1331. The UK ALLR3 trial does not provide data on MRD results for all enrolled patients at the end of phase I, nor does it provide separate AE data during phase I. An alternative reinduction strategy used by the ALL-REZ BFM trials included induction with F1/F2 courses that included dexamethasone, vincristine, methotrexate, cytarabine and asparaginase.[27] Outcome data on all patients (response and toxicity during the first block of reinduction) are not reported, again making direct comparison with AALL1331 Block 1 difficult. The COG AALL07P1 included HR B-ALL (N=103, early BM±EM relapse) as well as patients with T-cell relapses.[7] Block 1 of induction included bortezomib plus vincristine, prednisone, doxorubicin and PEG-asparaginase. Only 68±5% of 100 B-ALL patients less than 21 years old achieved a second remission and of these, only 29% were MRD-negative at the end of Block 1.

AALL1331 Block 1 therapy was associated with high AE rates (72.6% ≥ grade 3, 27.7% ≥ grade 4), and relatively poor responses, with 54.5% of patients with BM±EM relapse being MRD-positive at the end of reinduction. Based on these data, we believe that the toxicities of reinduction therapy using UKALL R3 in the COG patient population are unjustified given the unsatisfactory MRD responses. It is also concerning that all grade 5 AE but one were due to infection, with grade 3-5 febrile neutropenia (30.3%), infections (36.6%), and sepsis (10.1%) being frequent. In univariate analysis of specific AE, older age correlated with a higher risk of grade 3-5 infections, sepsis, mucositis, hyperglycemia, hyperbilirubinemia and death during Block 1. However, in multivariable analyses, age did not correlate with any grade 4-5 AE. One hundred and twenty-eight patients (19.4% of those enrolled) did not get risk-assigned or randomized, often due to AE or physicians' choice, in many cases due to toxicities experienced during reinduction.

Not unexpectedly, outcomes varied significantly by time to relapse, site of relapse, and risk group, as these variables are well known to be associated with outcomes in relapsed patients. It is noteworthy that patients who were not risk-assigned had a 4-year OS more similar to that of the group with early treatment failure group (19.8±7.4% and 18.7±6.2%, respectively), suggesting that these patients experienced significant negative events during Block 1 therapy that affected their overall outcome. The patients with early treatment failure who received salvage blinatumomab on study still had dismal outcomes, indicating the need to have better treatment approaches available to be started at the time of relapse.

In multivariable analysis we confirmed several established risk factors for poor outcome, including shorter time to relapse. Not surprisingly, shorter time to relapse was also associated with higher rates of MRD positivity at the end of Block 1. Older age was associated with inferior EFS for patients with BM±EM relapse but was not associated with inferior OS. Patients with isolated marrow relapse had both higher MRD positivity at the end of Block 1 and lower OS, as compared to patients with BM and EM relapse. For patients with BM±EM relapse, Hispanic ethnicity was associated with more grade 4-5 AE in Block 1 and Hispanic or non-Hispanic Asian race/ethnicity was associated with more grade 3-5 AE. Lastly, the finding of inferior EFS and OS in male patients with BM and EM relapse is noteworthy. While this has not been reported in recent relapse trials, this may be due to smaller numbers of patients.[4,5,10,11] It will be important to evaluate this finding in ongoing relapse trials.

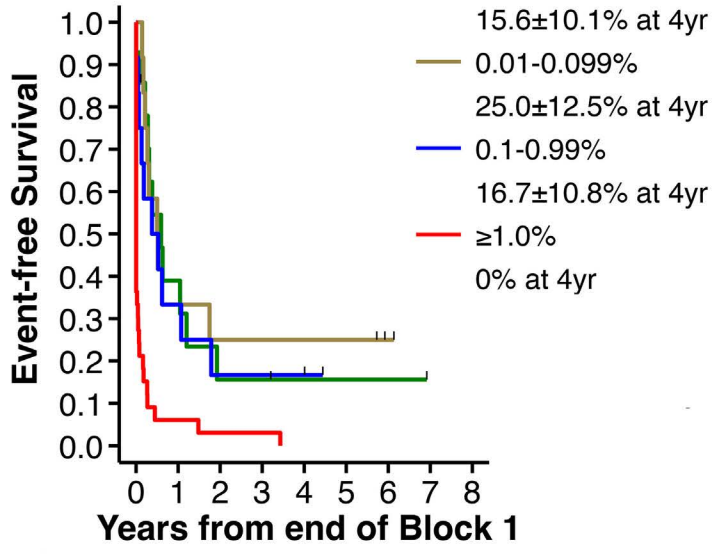
In summary, 72.6% of patients with relapsed B-ALL who received a common UK ALLR3 adapted Block 1 of induction chemotherapy experienced either death or grade 3-5 AE with only about 40% of patients achieving MRD-negative response. End of Block 1 MRD response was not sufficiently robust to justify using UK ALLR3 reinduction as standard re-induction therapy, particularly for late BM relapses in which the goal is to avoid HSCT.

Alternative approaches that result in better MRD clearance with lower toxicities are urgently needed. Ongoing efforts in several large consortia are investigating reduced intensity chemotherapy followed by earlier onset blinatumomab in efforts to achieve higher rates of MRD negativity without unacceptable AE rates. It will be important to see whether these approaches also result in improved long-term outcomes.

Disclosures

LEH participated in an advisory board for Amgen. LG owns

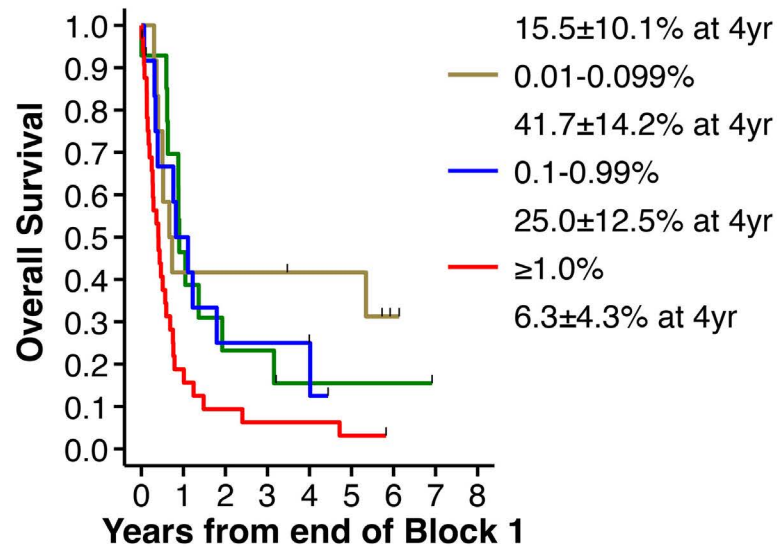
A



At Risk

<0.01%	14	5	2	2	1	1	1	0	0
0.01-0.099%	12	4	3	3	3	3	1	0	0
0.1-0.99%	12	4	2	2	1	0	0	0	0
≥1.0%	33	2	1	1	0	0	0	0	0

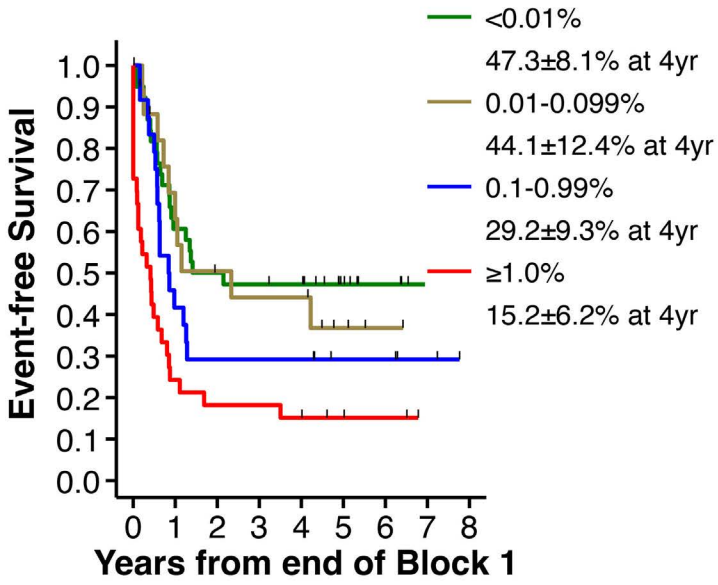
B



At Risk

<0.01%	14	6	3	3	1	1	1	0	0
0.01-0.099%	12	5	5	5	4	4	1	0	0
0.1-0.99%	12	6	3	3	2	0	0	0	0
≥1.0%	33	6	3	2	2	1	0	0	0

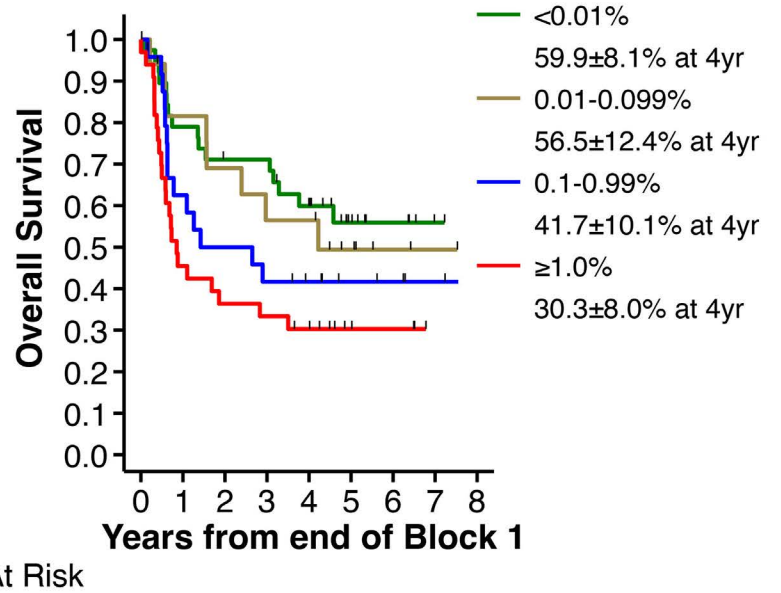
C



At Risk

<0.01%	39	23	18	17	16	9	5	1	0
0.01-0.099%	18	10	8	7	7	3	1	0	0
0.1-0.99%	24	10	7	7	7	4	4	2	0
≥1.0%	33	8	6	6	4	3	2	0	0

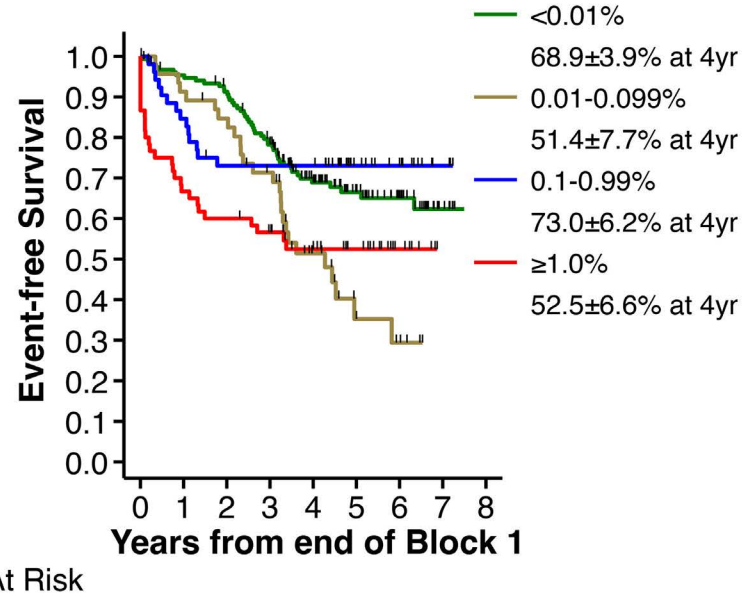
D



At Risk

<0.01%	39	30	26	26	20	10	5	1	0
0.01-0.099%	18	13	11	9	9	5	2	1	0
0.1-0.99%	24	15	12	10	8	5	4	2	0
≥1.0%	33	15	12	11	8	4	3	0	0

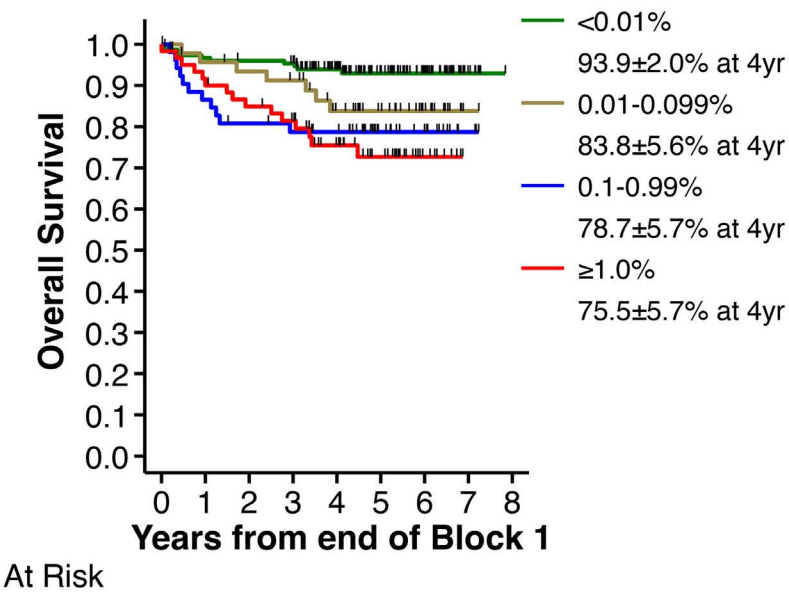
E



At Risk

<0.01%	154	142	134	112	72	46	30	7	0
0.01-0.099%	46	42	38	31	16	7	4	0	0
0.1-0.99%	52	44	37	35	32	17	11	3	0
≥1.0%	60	40	36	32	23	17	7	0	0

F



At Risk

<0.01%	154	144	142	139	103	65	38	8	0
0.01-0.099%	46	44	42	40	30	22	12	1	0
0.1-0.99%	52	45	41	38	35	19	12	3	0
≥1.0%	60	54	50	46	33	22	8	0	0

Continued on following page.

Figure 5. Survival by end of Block 1 minimal residual disease status according to time of relapse among patients with bone marrow relapse with or without extramedullary relapse. (A, B) Event-free survival (EFS) and overall survival (OS) by end of Block 1 minimal residual disease (MRD) status for time to relapse (bone marrow with or without extramedullary relapse [BM±EM]) <18 months. (C, D) EFS and OS by end of Block 1 MRD status for time to relapse 18-36 months among patients with BM±EM relapse. (E, F) EFS and OS by end of Block 1 MRD status for time to relapse ≥36 months among patients with BM±EM relapse. Yr: years.

common stock in Amgen and OnKure and receives institutional research support from Agios/Servier. EAR receives research support from Pfizer and serves on a Data and Safety Monitoring Board for BMS. SPH owns common stock in Amgen and has received honoraria from Amgen, Jazz, and Servier. MLL has received honoraria from Jazz for participation on advisory boards. PAB is employed by and owns common stock in BMS. LJ serves on a Data and Safety Monitoring Board at Pfizer. DTT serves on advisory boards (unpaid) for Amgen, BEAM, Jazz, Servier, Sobi, J&J, and Novartis, receives research funding from BEAM and holds multiple patents or patents pending on chimeric antigen receptor T cells.

Contributions

LEH, LG, EAR, DB, DTT, SPH, MLL and PAB designed the research. LEH, TB, LG, EAR, DB, DTT, SPH, MLL and PAB performed the research. LEH, TB, XX, SPH, MLL, PAB and LJ analyzed the data and performed the statistical analysis. LEH, TB SPH, MLL and LJ wrote the manuscript. All authors read, commented on and approved the manuscript.

Acknowledgments

LG is the Ergen Chair in Pediatric Oncology at the Children's Hospital Colorado. EAR is a KiDS of NYU Foundation Professor at NYU Langone Health. SPH is the Jeffrey E. Perelman Distinguished Chair in Pediatrics at The Children's Hospital of Philadelphia. MLL is the Aldarra Foundation, June and Bill Boeing, Founders, Endowed Chair in Pediatric Cancer Research of Seattle Children's Hospital.

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Data-sharing statement

Full details on data sharing are provided in the Online Supplementary Material.

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