original reports

Children's Oncology Group Trial AALL1231: A Phase III Clinical Trial Testing Bortezomib in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia and Lymphoma

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abstract

PURPOSE To improve the outcomes of patients with T-cell acute lymphoblastic leukemia (T-ALL) and lymphoblastic lymphoma (T-LL), the proteasome inhibitor bortezomib was examined in the Children's Oncology Group phase III clinical trial AALL1231, which also attempted to reduce the use of prophylactic cranial radiation (CRT) in newly diagnosed T-ALL.

PATIENTS AND METHODS Children and young adults with T-ALL/T-LL were randomly assigned to a modified augmented Berlin-Frankfurt-Münster chemotherapy regimen with/without bortezomib during induction and delayed intensification. Multiple modifications were made to the augmented Berlin-Frankfurt-Münster backbone used in the predecessor trial, AALL0434, including using dexamethasone instead of prednisone and adding two extra doses of pegaspargase in an attempt to eliminate CRT in most patients.

RESULTS AALL1231 accrued 824 eligible and evaluable patients from 2014 to 2017. The 4-year event-free survival (EFS) and overall survival (OS) for arm A (no bortezomib) versus arm B (bortezomib) were 80.1% ± 2.3% versus 83.8% ± 2.1% (EFS, $P = .131$) and 85.7% ± 2.0% versus 88.3% ± 1.8% (OS, $P = .085$). Patients with T-LL had improved EFS and OS with bortezomib: 4-year EFS (76.5% ± 5.1% *v* 86.4% ± 4.0%; $P = .041$); and 4-year OS (78.3% ± 4.9% *v* 89.5% ± 3.6%; $P = .009$). No excess toxicity was seen with bortezomib. In AALL0434, 90.8% of patients with T-ALL received CRT. In AALL1231, 9.5% of patients were scheduled to receive CRT. Evaluation of comparable AALL0434 patients who received CRT and AALL1231 patients who did not receive CRT demonstrated no statistical differences in EFS ($P = .412$) and OS ($P = .600$).

CONCLUSION Patients with T-LL had significantly improved EFS and OS with bortezomib on the AALL1231 backbone. Systemic therapy intensification allowed elimination of CRT in more than 90% of patients with T-ALL without excess relapse.

J Clin Oncol 00. © 2022 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Data Supplement

Protocol

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

Accepted on February 11, 2022 and published at ascopubs.org/journal/jco on March 10, 2022: DOI https://doi.org/10.1200/JCO.21.02678

INTRODUCTION

Historically, overall survival (OS) for children with T-cell acute lymphoblastic leukemia (T-ALL) and lymphoblastic lymphoma (T-LL) was inferior to B-ALL and B-LL; however, rates are now similar with contemporary therapy.[1-4] Unfortunately, relapsed T-ALL/T-LL outcomes remain dismal (5-year OS < 35%).[5-7] Consequently, Children's Oncology Group (COG) trials have focused on preventing relapse in newly diagnosed patients via refinement of risk stratification, introduction of novel agents, and intensification of chemotherapy.

COG AALL0434 reported outstanding outcomes for children and young adults with T-ALL and T-LL, establishing Capizzi-style escalating methotrexate plus pegaspargase (C-MTX) as superior to high-dose methotrexate (HDMTX) on the augmented Berlin-Frankfurt-Münster (aBFM) backbone, and that adding six 5-day courses of nelarabine improved disease-free survival (DFS).[8-11] Although DFS and OS were excellent, relapse remained the major cause of treatment failure and was rarely salvaged. Moreover, > 90% of AALL0434 patients with T-ALL received cranial radiotherapy (CRT), which has significant long-term morbidity.[12,13]

CONTEXT

Key Objective

Bortezomib was shown to be effective in patients with relapsed T-cell acute lymphoblastic leukemia (T-ALL) and lymphoblastic lymphoma (T-LL), leading to the investigation of its efficacy in a randomized phase III clinical trial, AALL1231 for newly diagnosed children and young adults with T-ALL/T-LL. Cranial radiation (CRT) has significant long-term morbidity and mortality, and is currently included as part of standard therapy for the majority of children with T-ALL in many cooperative groups.

Knowledge Generated

The proteasome inhibitor bortezomib improved event-free survival and overall survival in children and young adults with T-LL when combined with modified augmented Berlin-Frankfurt-Münster chemotherapy. CRT can be safely and effectively eliminated in more than 90% of children with T-ALL with intensification of systemic chemotherapy.

Relevance

Bortezomib is safe and effective in the treatment of newly diagnosed children and young adults with T-LL. With modern chemotherapy regimens, more than 80% of children and young adults with T-ALL can be cured without CRT.

COG AALL1231 (ClinicalTrials.gov identifier: NCT02112916) was a successor phase III trial with the primary objective to compare event-free survival (EFS) in children and young adults with T-ALL/T-LL who were randomly assigned to a modified aBFM backbone with/without the proteasome inhibitor bortezomib during induction and delayed intensification (DI). The use of bortezomib was based on compelling biologic rationale, strong preclinical data, and encouraging safety and efficacy in relapsed T-ALL/T-LL in COG AALL07P1.[14-18] A secondary objective of AALL1231 was to determine whether prophylactic CRT can be safely and effectively eliminated in the 85%-90% of patients with T-ALL classified as standard-risk (SR) or intermediate-risk (IR; risk group definitions are provided in the Data Supplement, online only). Because of poor historical outcomes, very high-risk (VHR) T-ALL/T-LL patients with refractory disease received additional intensified chemotherapy courses. We report the results of the bortezomib randomization and outcomes after therapy intensification that allowed elimination of CRT in approximately 90% of patients.

PATIENTS AND METHODS

Eligibility and Trial Oversight

Patients with newly diagnosed T-ALL or T-LL age 1-30 years were eligible. CNS status was defined on cerebrospinal fluid obtained before starting systemic chemotherapy or clinical signs of CNS leukemia. AALL1231 was conducted under a National Cancer Institute held Investigational New Drug (IND) application for bortezomib (NSC#68129; IND#58443). AALL1231 was approved by the Cancer Therapy and Evaluation Program, the Pediatric Central Institutional Review Board (IRB), and participating center IRBs. Written informed consent and assent (if applicable) were obtained before study entry.

Treatment

Patients were randomly assigned 1:1 at enrollment to receive/not receive bortezomib during induction and DI before starting therapy (except for intrathecal therapy or limited duration of corticosteroids). Four doses of bortezomib were given at 1.3 mg/m^2/dose per block. During induction bortezomib was given on Days 1, 4, 8, and 11. During DI, bortezomib was given on Days 1, 4, 15, and 18. Patients with T-ALL and T-LL were separately classified as SR, IR, and VHR for treatment assignment on the basis of disease characteristics and treatment response. Minimal residual disease (MRD) and early T-cell precursor (ETP) status were assessed centrally by flow cytometry at the University of Washington (BLW) reference laboratory using published methods[19]; detailed analyses will be reported separately. Several changes were made to the AALL0434 aBFM backbone to enhance CNS-directed systemic therapy and limit CRT. AALL0434 used prednisone during induction and maintenance. AALL1231 used dexamethasone during these phases on the basis of decreased relapse rates on UKALL2003 and AIEOP-BFM-ALL 2000.[20,21] Because asparaginase intensification improves T-ALL outcomes, patients received two additional doses of pegaspargase (day 18 of induction and DI).[22-24] SR AALL1231 patients with T-ALL/T-LL received a single interim maintenance (IM) phase with C-MTX, followed by DI and maintenance. Because of concerns about potential increased CNS relapse without CRT, IR patients received IM#1 with HDMTX, DI, IM#2 with C-MTX and maintenance.

VHR T-ALL patients with induction failure (day 29 M3 marrow [≥ 25% blasts]) or persistent MRD ≥ 0.1% at end of consolidation (EOC; approximately 3 months of therapy) received three BFM-based intensification blocks postconsolidation.[25-27] After these blocks, patients with detectable MRD were removed from protocol therapy as treatment failures. Patients with undetectable MRD continued on therapy and received DI followed by C-MTX IM and maintenance. Patients with T-LL with stable disease on day 29 imaging were considered VHR and received the same chemotherapy as VHR T-ALL with reimaging at the end of Intensification. Patients with proven persistent residual T-LL were removed from protocol therapy; the

TABLE 1. Patient Characteristics by Bortezomib Randomized Cohort

Characteristic	No Bortezomib (arm A) n = 416	Bortezomib (arm B) n = 408
Age, years, No. (%)		
< 10	178 (42.8)	177 (43.4)
10-16	151 (36.3)	156 (38.2)
≥ 16	87 (20.9)	75 (18.4)
Sex, No. (%)		
Male	326 (78.4)	295 (72.3)
Female	90 (21.6)	113 (27.7)
WBC (× 1,000/μL), No. (%)		
< 50	242 (58.2)	237 (58.1)
≥ 50	174 (41.8)	171 (41.9)
CNS, No. (%)		
CNS1	317 (76.4)	315 (77.4)
CNS2	77 (18.5)	66 (16.2)
CNS3	21 (5.1)	26 (6.4)
Race, No. (%)		
American Indian or Alaskan Native	3 (0.7)	2 (0.5)
Asian	20 (4.8)	12 (2.9)
Native Hawaiian or Other Pacific Islander	2 (0.5)	1 (0.2)
Multiple races	7 (1.7)	6 (1.5)
Black or African American	55 (13.2)	50 (12.3)
White	283 (68.0)	289 (70.8)
Unknown	46 (11.1)	48 (11.8)
Ethnicity, No. (%)		
Hispanic or Latino	68 (16.4)	74 (18.1)
Not Hispanic or Latino	316 (76.0)	304 (74.5)
Unknown	32 (7.7)	30 (7.4)
T-ALL bone marrow morphology day 29, No. (%)	Total 298	Total 299
M1 (< 5% blasts)	279 (93.6)	284 (95.0)
M2 (5%-25% blasts)	12 (4.0)	12 (4.0)
M3 (≥ 25 blasts)	7 (2.4)	3 (1.0)
T-ALL bone marrow MRD % day 29, No. (%)		
< 0.01	181 (61.1)	194 (65.1)
0.01 to < 0.1	25 (8.4)	21 (7.0)
0.1 to < 1	28 (9.5)	24 (8.1)
1 < 10	39 (13.2)	37 (12.4)
≥ 10	23 (7.8)	22 (7.4)
T-ALL bone marrow MRD % EOC, No. (%)		
< 0.01	256 (93.4)	271 (94.4)
0.01 to < 0.1	6 (2.2)	3 (1.1)
0.1 to < 1	6 (2.2)	6 (2.1)
1 < 10	5 (1.8)	5 (1.7)
≥ 10	1 (0.4)	2 (0.7)

(continued on following page)

TABLE 1. Patient Characteristics by Bortezomib Randomized Cohort (continued)

Characteristic	No Bortezomib (arm A) n = 416	Bortezomib (arm B) n = 408
T-ALL bone marrow MRD % end VHR blocks, No. (%)		
Undetectable	4 (44.4)	4 (44.4)
Detectable	5 (55.5)	5 (55.5)
T-ALL ETP status, No. (%)		
ETP	44 (14.3)	30 (9.8)
Near ETP	45 (14.6)	40 (13.0)
Not ETP	211 (68.5)	220 (71.7)
Unknown	8 (2.6)	17 (5.5)
T-LL day 29 response, No. (%)	Total 105	Total 97
Complete response	45 (42.9)	43 (44.3)
Partial response	60 (57.1)	52 (53.6)
Stable disease/no response	0 (0)	2 (2.1)

NOTE. Definitions of M1, M2, M3, and CNS1, 2, 3 are in the clinical trial protocol.

Abbreviations: EOC, end of consolidation; ETP, early T-cell precursor; MRD, minimal residual disease; Ph+, Philadelphia chromosome–positive; SMN, secondary malignancy; T-ALL, T-cell acute lymphoblastic leukemia; T-LL, T-cell lymphoblastic lymphoma; VHR, very high-risk.

remainder continued chemotherapy. CRT was only given to VHR T-ALL (prophylactic CRT; 12 Gy) and CNS3 T-ALL/T-LL (18 Gy) patients during maintenance. Patients with persistent testicular leukemia at the end of induction (EOI) received testicular radiation (24 Gy) during consolidation. The Data Supplement provides treatment details.

Treatment duration was the same for all arms and risk groups. Females with T-ALL/T-LL and males with T-LL were treated for two years from the start of IM#1 (SR/IR) or intensification block-1 (VHR); males with T-ALL were treated 1 year longer.

Outcome and Statistical Analysis

Treatment-related adverse effects were graded using Common Terminology Criteria for Adverse Events version 5. EFS was the primary outcome and defined as time from study enrollment to first event: death in induction or remission, refractory disease (persistent disease after Intensification blocks; defined above), relapse, second malignant neoplasm, or last contact date for those who were event-free. OS was defined as time from study enrollment to death or last contact date. AALL1231 was designed to accrue 1,200 eligible, evaluable randomly assigned patients to provide 90.5% power to detect an improvement in 4-year EFS from 85% to 90% with an alpha of .05 (one-sided; hazard ratio [HR] = 0.6483). Power calculation for the randomized ± bortezomib comparison was based on a one-sided log-rank test since the primary objective was to determine whether the addition of bortezomib improved outcome. Unless specified, one-sided log-rank tests were used for survival comparisons. Efficacy/futility interim analyses were scheduled at approximately 20%, 40%, 60%, 80%, and 100% of the expected event horizon (217 total events) in the overall randomized cohort. AALL1231 did not include nelarabine. Accrual was suspended in December 2017 when AALL0434 established that nelarabine improved T-ALL DFS.[10] AALL1231 permanently closed to accrual in May 2019 after the data safety monitoring committee determined it would be statistically unfeasible to add nelarabine and isolate bortezomib's impact.

Proportions were compared using a chi-square test or Fisher's exact test. Survival rates were estimated using the Kaplan-Meier method and standard errors of Peto et al.[28,29] Survival rates are presented as rates ± SEs. Multivariable analyses used Cox regression included treatment arm risk group. Per-protocol, subgroup analyses of overall outcomes, including by race, ethnicity, and sex, were performed. Cumulative incidence (CI) rates were computed using the CI function for competing risks, with comparisons between groups made using the K-sample test. A $P < .05$ was considered statistically significant for comparisons. Analyses were performed using SAS version-9.4 (SAS Institute, Cary NC). Graphics were generated using R version-2.13.1.[30] This report includes data current as of September 30, 2021.

As predefined in the protocol aims, AALL1231-treated patients were compared to AALL0434-treated to assess the impact of eliminating CRT in most patients with T-ALL; a subset analysis was performed comparing similar patients who received CRT in AALL0434 and no CRT in AALL1231. The AALL0434 patients with T-ALL constituting this group were those who did not receive nelarabine, and were not low-risk (LR; Data Supplement), CNS3, day 29 M3, or EOC MRD ≥ 0.1%. AALL1231 patients with T-ALL were included if they did not receive bortezomib and were IR (excluding CNS3) or SR (excluding those who met

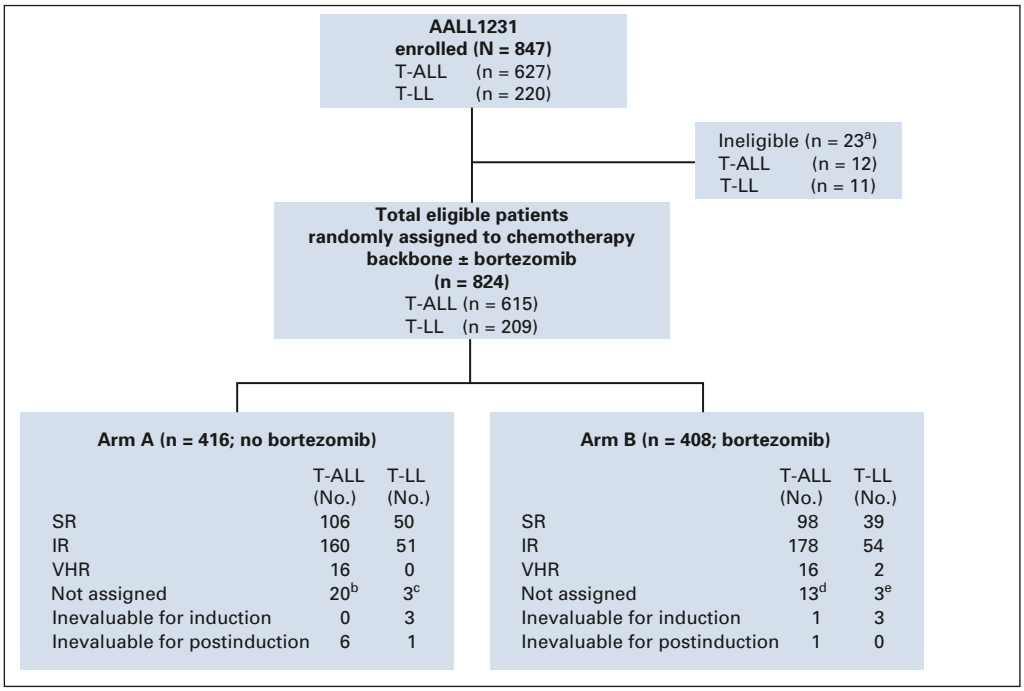

FIG 1. CONSORT diagram for the study. [a]Ineligible reasons: nine disease type or histology, one patient characteristics, six prior therapies, four stage extent of disease, one timing of start of protocol therapy, and two other (not enrolled in AALL08B1). [b]Two induction death, 14 off protocol therapy in induction, one off study in consolidation, and three off protocol therapy in consolidation. [c]One induction death, one off therapy in induction, and one off study in consolidation. [d]Five induction death, two consolidation death, five off protocol therapy in induction, and one off study in consolidation. [e]Two off protocol therapy in induction and one off study in induction. Arm A, control arm; Arm B, bortezomib arm; IR, intermediate-risk; SR, standard-risk; T-ALL, T-cell acute lymphoblastic leukemia; T-LL, T-cell lymphoblastic lymphoma; VHR, very high-risk.

AALL0434 LR definition). Similar subset analyses were performed comparing the different arms on both studies (AALL0434:± nelarabine, HDMTX *v* C-MTX; AALL1231: ± bortezomib). Data were collected retrospectively for patients removed from protocol therapy for physician or patient/family preference to determine reasons for removal, alternative therapies delivered, and impact on outcome.

Detailed eligibility criteria and criteria for response, relapse, and removal from protocol therapy are included in clinical trial Protocol document (online only).

RESULTS

Participants

COG AALL1231 enrolled 847 patients between September 2014 and December 2017. Of these, 824 were eligible and evaluable (Data Supplement); T-ALL:n = 615; T-LL: n = 209 (Table 1) with 416 randomly assigned to arm A (no bortezomib) and 408 to arm B (bortezomib; CONSORT diagram: Fig 1). Except for a slightly higher percentage of males on arm A, the randomized arms were similar (Table 1). Overall, 35.6% of patients were SR, 53.8% IR, and 4.1% VHR with a similar distribution between T-ALL and T-LL. Fifty-four patients (6.6%) were unable to be risk stratified (Data Supplement).

Response and Survival

Overall response and survival. Overall 4-year EFS and OS were 81.9% ± 1.5% and 87.0 ± 1.3%, respectively (Fig 2A), and were similar for T-ALL and T-LL (Figs 2B and 2C). There were no outcome differences on the basis of race, ethnicity, or sex (Data Supplement). The 4-year EFS rates for no bortezomib (arm A) versus bortezomib (arm B) were 80.1% ± 2.3% versus 83.8% ± 2.1%; HR = 0.833; $P = .131$, respectively (Fig 3A). The Data Supplement provides a detailed breakdown of events. The 4-year OS rates for arm A versus arm B were 85.7% ± 2.0% versus 88.3% ± 1.8%; HR = 0.772; $P = .085$, respectively (Fig 3B). 95% of risk-stratified patients were SR or IR, and they had significantly improved EFS on arm B compared with arm A (Table 2). Survival was dismal for VHR patients, but better on arm A (Table 2). OS data by risk group are provided in the Data Supplement.

T-ALL response and survival. At the EOI (day 29), 94.3% (563/597) of patients with T-ALL achieved complete remission (M1); rates were similar between arms (Data Supplement). EOI MRD using a threshold of 0.01% and EOC MRD using a threshold of 0.1% were used for T-ALL risk stratification. Of the patients with T-ALL who had EOI

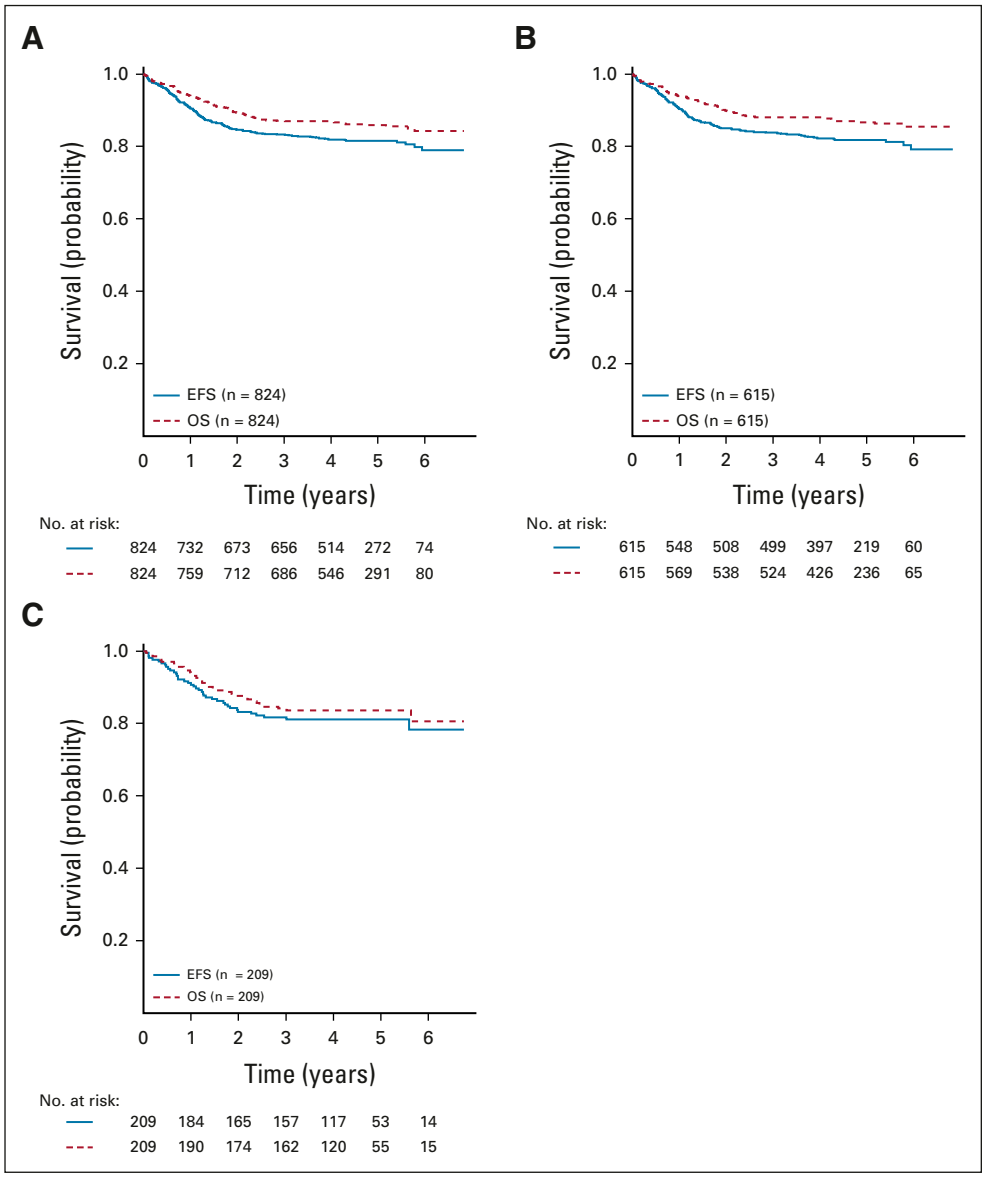

FIG 2. EFS and OS curves for all eligible and evaluable patients. (A) Four-year EFS and OS rates for all patients were 81.9% ± 1.5% and 87.0% ± 1.3%, respectively. (B) Four-year EFS and OS for patients with T-ALL were 82.2% ± 1.7% and 88.1% ± 1.5%, respectively. (C) Four-year EFS and OS for patients with T-LL were 81.2% ± 3.3% and 83.6% ± 3.1%, respectively. EFS, event-free survival; OS, overall survival; T-ALL, T-cell acute lymphoblastic leukemia; T-LL, T-cell lymphoblastic lymphoma.

MRD sent, 38.8% (115/296) and 34.9% (104/298) on arms A and B, respectively, had MRD ≥ 0.01% (P = .318; Data Supplement). EOC MRD was only sent on patients with EOI MRD ≥ 0.01%. Only 12 and 13 patients on arms A and B had EOC MRD ≥ 0.1% (P = .931; Data Supplement). The modified induction resulted in improved EOI MRD < 0.1% rates compared with AALL0434 (AALL1231 arm A: 69.6%; arm B: 72.2%; AALL0434: 64.6%; P = .02; Data Supplement). EOC MRD was only sent on a subset of AALL0434 patients and was not compared with AALL1231. EFS and OS were similar without/with bortezomib in T-ALL (Figs 3C and 3D).

T-LL response and survival. All but two (196/198; 99.9%) patients with T-LL were in CR/PR at EOI. Patients with T-LL treated with bortezomib had significantly better 4-year EFS (86.4% ± 4.0% *v* 76.5% ± 5.1%; HR = 0.563; P = .041) and OS (89.5% ± 3.6% *v* 78.3% ± 4.9%; HR = 0.421; P = .009; Figs 3E and 3F).

Adverse Events

Overall grade ≥ 3 toxicity rates were similar between arms (arm A: 76.5%, arm B: 80.0%; P = .234). Twenty infection-related deaths occurred (induction: 5, consolidation: 4, DI: 8, and maintenance: 3), 10 per arm. Eleven deaths resulted from invasive fungal disease (9: arm A). Bortezomib can cause

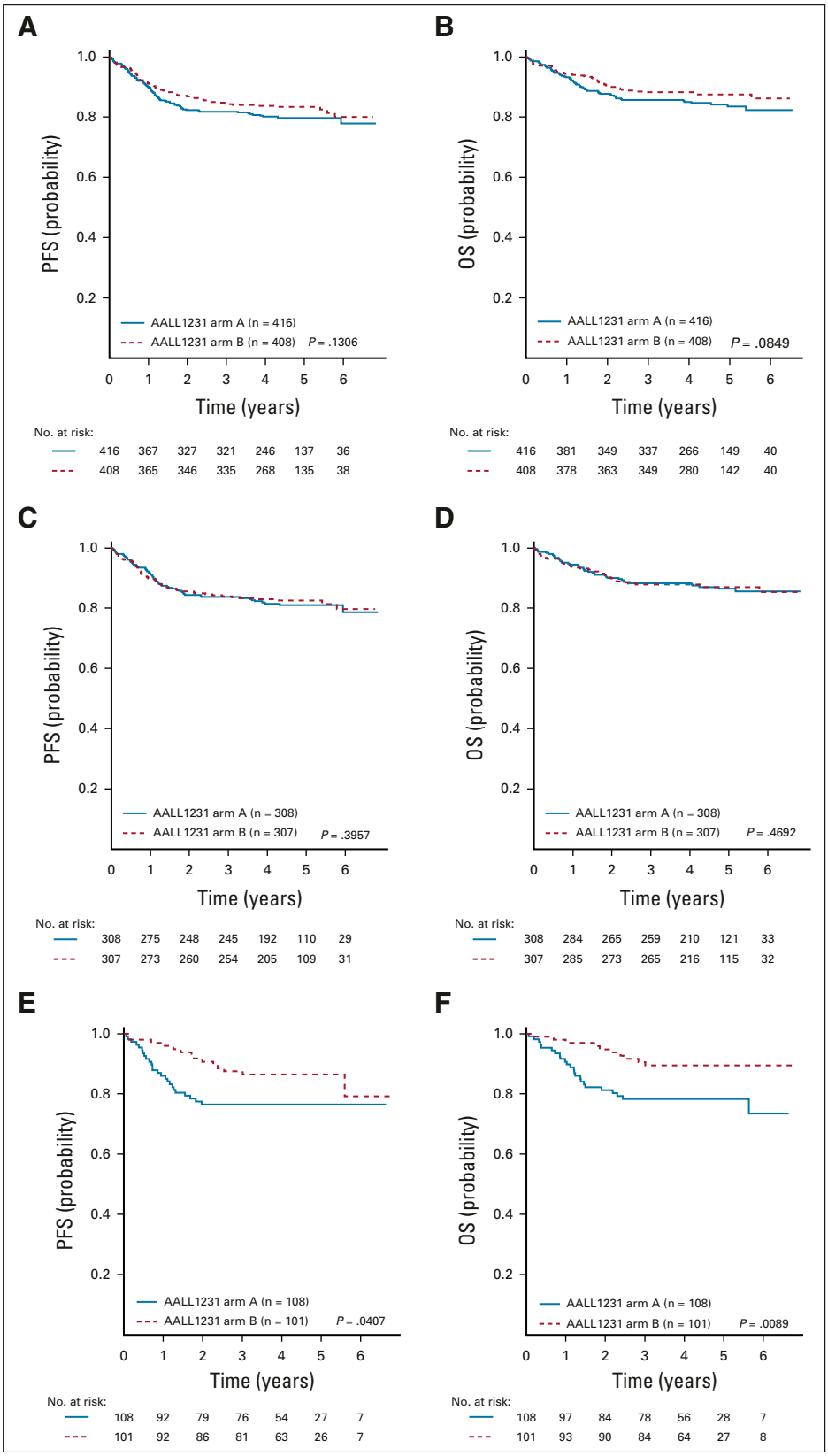

FIG 3. EFS and OS for no bortezomib (arm A) and bortezomib (arm B) randomized cohorts. (A) 4-year EFS rates for all patients were 83.8 ± 2.1% with bortezomib compared with 80.1 ± 2.3% without bortezomib (P = .131). (B) 4-year OS rates for all patients were 88.3 ± 1.8% with bortezomib compared with 85.7 ± 2.0% without bortezomib (P = .085). (C) 4-year EFS rates for patients with T-ALL were

FIG 3. (Continued). 82.9% ± 2.4% with bortezomib compared with 81.5% ± 2.5% without bortezomib (P = .396). (D) 4-year OS rates for patients with T-ALL were 87.9% ± 2.1% with bortezomib compared with 88.3% ± 2.1% without bortezomib (P = .469). (E) 4-year EFS rates for patients with T-LL (continued on following page)were 86.4% ± 4.0% with bortezomib compared with 76.5% ± 5.1% without bortezomib (P = .041). (F) 4-year OS rates for patients with T-LL were 89.5% ± 3.6% with bortezomib compared with 78.3% ± 4.9% without bortezomib (P = .009). T-ALL, T-cell acute lymphoblastic leukemia; T-LL, T-cell lymphoblastic lymphoma; EFS, event-free survival; OS, overall survival.

peripheral neuropathy and rarely short-term severe pulmonary toxicity.[31,32] The overall rate of peripheral neuropathy was as expected, and similar between arms (Data Supplement). The number of patients with grade 4+ pulmonary toxicity during induction and DI were 11 (arm A) and 15 (arm B; P = .393).

Comparison With AALL0434, Including Elimination of Prophylactic CRT

Although EOI MRD response was better in AALL1231 than in AALL0434, the overall 4-year EFS was similar between trials (AALL1231: 81.9% ± 1.5%; AALL0434: 84.4% ± 0.9%; P = .131; Fig 4A) and the 4-year OS in AALL1231 (87.0% ± 1.3%) was inferior to that in AALL0434 (90.0% ± 0.7%; P = .006; Fig 4B). Comparing events between trials, the inferior OS appears largely because of increased toxic death, which was comparable in T-ALL and T-LL, and the poor outcomes for the AALL1231 VHR risk group. In AALL0434, 37/1844 (2.0%) evaluable patients had deaths as first events (7: induction; 30: remission), whereas 50/824 (6.1%) AALL1231 patients had deaths as first events (12: induction; 38: remission). Induction mortality in AALL1231 versus AALL0434 was 1.5% and 0.4%, respectively (P = .002). Four-year CI rates of remission deaths in AALL0434 versus AALL1231 were 2.1% ± 0.4% and 3.9% ± 0.7%, P = .008 (Fig 4D). CI of relapse was similar (AALL0434: 8.4% ± 1.0%, AALL1231: 9.3% ± 0.8%, P = .562, Fig 4C). A detailed comparison of presenting features, toxicities, and events on the trials is provided in the Data Supplement.

Subset analyses were performed comparing similar patients scheduled to receive CRT in AALL0434 (90.8% of T-ALL; CNS3 T-LL were not eligible), but not in AALL1231, where only 9.5% were scheduled to receive CRT (CNS3 T-ALL/T-LL: 5.7%; VHR T-ALL: 4.1%; Table 3). Excluding patients receiving nelarabine (AALL0434) or bortezomib (AALL1231), the 4-year EFS (P = .412), OS (P = .600), CI of CNS relapse (P = .456), and overall relapse (P = .836) were not significantly different between the studies (Table 3). It is not possible to make a pure comparison as risk stratification was different and EOC MRD was not

TABLE 2. Outcome by Risk Group

Risk Group	Percent in Group	4-Year EFS Arm A	4-Year EFS Arm B	*P*
All patients (n = 824)				
Overall	100	80.1% ± 2.3% (n = 416)	83.8% ± 2.1% (n = 408)	.131
SR	35.5	84.4% ± 3.4% (n = 156)	91.2% ± 2.7% (n = 137)	.077
IR	53.8	83.9% ± 2.9% (n = 211)	88.7% ± 2.3% (n = 232)	.068
VHR	4.1	31.3% ± 13.0% (n = 16)	6.5% ± 6.3% (n = 18)	.044
No risk	6.6	60.0% ± 12.7% (n = 33)	34.1% ± 27.7% (n = 21)	.016
T-ALL only (n = 615)				
Overall	100	81.5% ± 2.5% (n = 308)	82.9% ± 2.4% (n = 307)	.396
SR	33.2	89.4% ± 3.4% (n = 106)	92.8% ± 2.9% (n = 98)	.359
IR	55.0	85.1% ± 3.2% (n = 160)	88.2% ± 2.7% (n = 178)	.164
VHR	5.2	31.3% ± 13.0% (n = 16)	7.8% ± 7.5% (n = 16)	.033
No risk	6.7	58.2% ± 13.3% (n = 26)	28.6% ± 24.2% (n = 15)	.015
T-LL only (n = 209)				
Overall	100	76.5% ± 5.1% (n = 108)	86.4% ± 4.0% (n = 101)	.041
SR	42.6	74.0% ± 7.6% (n = 50)	87.2% ± 5.8% (n = 39)	.054
IR	50.2	80.4% ± 6.7% (n = 51)	90.5% ± 4.8% (n = 54)	.101
VHR	1.0	NA (n = 0)	NA (n = 2)[a]	NA
No risk	6.2	68.6% ± 38.4% (n = 7)	NA (n = 6)[a]	.464

Abbreviations: EFS, event-free survival; IR, intermediate-risk; NA, not available; SR, standard-risk; T-LL, T-cell lymphoblastic lymphoma; VHR, very high-risk.

[a]Insufficient follow-up.

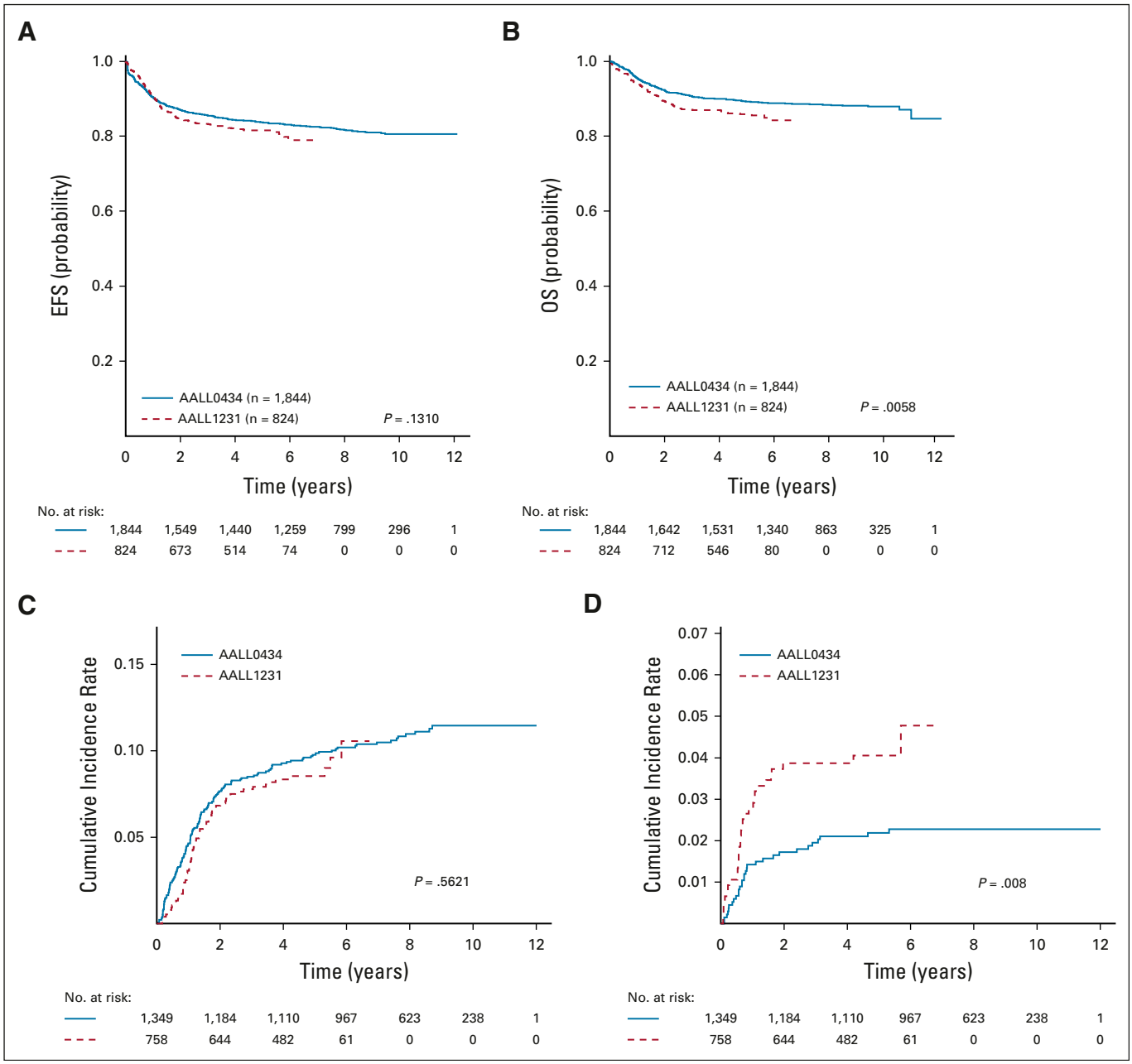

FIG 4. Comparison of outcomes between all patients in AALL1231 and AALL0434, the predecessor trial to AALL1231. (A) Four-year EFS rates in AALL1231 versus AALL0434 were 81.9% ± 1.5% and 84.4% ± 0.9%, respectively (P = .131). (B) Four-year OS rates in AALL1231 versus AALL0434 were 87.0% ± 1.3% and 90.0% ± 0.7%, respectively (P = .006). (C) Four-year CI rates of relapse in AALL1231 versus AALL0434 were 8.4% ± 1.0% and 9.3% ± 0.8%, respectively (P = .562). (D) Four-year CI rates of remission death in AALL1231 versus AALL0434 were 3.9% ± 0.7% and 2.1% ± 0.4%, respectively (P = .008). CI, cumulative incidence; EFS, event-free survival; OS, overall survival.

assessed for many AALL0434 patients. Table 3 includes comparisons of similar patients (CRT in AALL0434 *v* no CRT in AALL1231) by treatment arm.

Thirty percent (216 of 824) of AALL1231 patients were removed from protocol therapy for physician or patient/family preference, with 48% (104) of those removed occurring after the results of the AALL0434 nelarabine randomization were released. In comparison, 29% (527 of 1844) of AALL0434 patients were removed from protocol therapy for physician or patient/parent choice or for declining participation in the randomized questions. Retrospective data were collected for 98.6% (213/216) of AALL1231 patients removed from protocol therapy; 37.1% received nelarabine (only two had T-LL). There were no differences in use of nelarabine comparing arms A and B or outcomes for those who received nelarabine (Data Supplement).

TABLE 3. Elimination of Prophylactic Cranial Radiation

Outcomes Comparing Similar Patients Who Received CRT in AALL0434 and Who Did Not in AALL1231[a]

	AALL0434 no nel (n = 634)	AALL1231 no bort (n = 229)	*P*
4-year EFS	88.0% ± 1.3%	86.1% ± 2.6%	.412
4-year OS	91.6% ± 1.1%	91.5% ± 2.1%	.600
CI of CNS relapse	4.5% ± 0.8%	5.4% ± 1.5%	.456
CI of BM relapse	3.2% ± 0.7%	2.3% ± 1.0%	.364
CI of any relapse	9.1% ± 1.2%	8.1% ± 1.8%	.836

Outcomes by Treatment Arm Comparing Similar Patients Who Received CRT in AALL0434 and Did Not in AALL1231[b]

	AALL0434 no nel HDMTX (n = 318)	AALL0434 + nel HDMTX (n = 145)	AALL0434 no nel C-MTX (n = 316)	AALL0434 + nel C-MTX (n = 146)	AALL1231 no bort (n = 229)	AALL1231 + bort (n = 233)
4-year EFS	84.1% ± 2.1%	86.6% ± 2.9%	91.9% ± 1.6%	92.2% ± 2.3%	86.1% ± 2.6%	90.1% ± 2.2%
4-year OS	89.4% ± 1.8%	90.1% ± 2.6%	93.9% ± 1.4%	92.9% ± 2.2%	91.5% ± 2.1%	93.6% ± 1.8%
CI of CNS relapse	7.3% ± 1.5%	0.7% ± 0.7%	1.6% ± 0.7%	1.4% ± 1.0%	5.4% ± 1.5%	3.9% ± 1.3%
CI of BM relapse	4.8% ± 1.2%	5.0% ± 1.8%	1.6% ± 0.7%	1.4% ± 1.0%	2.3% ± 1.0%	1.7% ± 0.9%
CI of any relapse	13.4% ± 1.9%	8.5% ± 2.4%	4.8% ± 1.2%	5.6% ± 1.9%	8.1% ± 1.8%	6.0% ± 1.6%

Abbreviations: BM, bone marrow; bort, bortezomib; CI, cumulative incidence; C-MTX, Capizzi-style escalating methotrexate plus pegaspargase; CRT, cranial radiation; EFS, event-free survival; EOC, end of consolidation; HDMTX, high-dose methotrexate; IR, intermediate-risk; LR, low-risk; MRD, minimal residual disease; nel, nelarabine; OS, overall survival; SR, standard-risk; T-ALL, T-cell acute lymphoblastic leukemia.

[a]Includes patients with T-ALL in AALL0434 who received prophylactic CRT and did not receive nelarabine (exclude LR, CNS3, M3 day 29, and EOC MRD ≥ 0.1%); includes patients with T-ALL in AALL1231 who did not receive prophylactic CRT and did not receive bortezomib: IR T-ALL (exclude CNS3) and SR T-ALL (exclude those who met AALL0434 LR definition).

[b]Includes patients with T-ALL in AALL0434 who received prophylactic CRT (exclude LR, CNS3, M3 day 29, and EOC MRD ≥ 0.1%) by treatment arm; includes patients with T-ALL in AALL1231 who did not receive prophylactic CRT by treatment arm: IR T-ALL (exclude CNS3) and SR T-ALL (exclude those who met AALL0434 LR definition). These analyses do not include all patients in AALL0434 who received radiation or all patients in AALL1231 who did not receive radiation, but rather includes groups of similar patients who could be compared.

DISCUSSION

Despite early closure prompted by nelarabine results in AALL0434, AALL1231 provided several important findings that affect T-ALL and T-LL treatment in children and young adults and have the potential to change standard of care. Although overall outcomes and outcomes in T-ALL were not statistically significantly improved on the bortezomib arm, outcomes for SR and IR T-ALL and T-LL patients treated with bortezomib were excellent despite elimination of prophylactic CRT for patients with T-ALL. Moreover, patients with T-LL had significantly improved EFS and OS with bortezomib. To our knowledge, this is the first trial demonstrating an OS benefit for newly diagnosed pediatric T-LL with a small molecule inhibitor. Indeed, the only drugs that have improved survival previously for newly diagnosed T-ALL/T-LL patients are cytotoxic chemotherapeutics, including the purine nucleoside analog nelarabine, which improved DFS in T-ALL.[3]

Bortezomib was well tolerated, and toxicities were comparable between arms. It is unclear why bortezomib was more impactful in T-LL. The benefit of bortezomib in T-LL was a reduction of relapse and disease progression (CI arm A *v* arm B: 16.0% ± 3.6% *v* 6.3% ± 2.5%; $P = .024$). In T-ALL, the cumulative incidence of relapse on arms A and B were 9.2% ± 1.7% versus 7.9% ± 1.5%, respectively ($P = .264$). Biologically, T-ALL and T-LL are often considered a spectrum of the same disease, which led to harmonization in therapy. A principal difference is that T-ALL, through poorly characterized mechanisms, has the ability to invade extralymphatic spaces more readily. It is possible that genetic or epigenetic alterations that affect lymphoblast interactions with the microenvironment are modulated by proteins dependent on the ubiquitin proteasome pathway. Ongoing studies are investigating these differences.

Although AALL0434 outcomes were outstanding, approximately 90% of children received CRT. The potential benefit of CRT is offset by substantial long-term adverse effects, including second cancers, irreversible endocrinopathies, neurocognitive decline, and neurotoxic effects. Pui et al[33] showed that previous irradiation was associated with a 20.9% cumulative risk of second neoplasms at 30 years, a higher mortality rate than the general population, and an increased unemployment rate. AALL1231 modified the chemotherapy backbone and eliminated radiation in all patients but CNS3 T-ALL/T-LL and VHR T-ALL with acceptable CNS relapse rates. The benefit of dexamethasone in T-ALL was previously demonstrated in the AIEOP-BFM-ALL 2000 trial, which randomly assigned patients to a

dexamethasone-based versus prednisone-based induction. Although increased treatment-related mortality was seen on the dexamethasone arm, this was balanced by a reduction in relapse and improved EFS and OS in prednisone good responders.[20] The induction death rates in AALL1231 were similar to those in AIEOP-BFM-ALL 2000, justifying the continued use of dexamethasone during induction. Remission death rates and rates of pancreatitis, thrombosis, and infections were higher than expected, and the changes made to the backbone to intensify postinduction therapy, including the additional pegaspargase, dexamethasone in maintenance, and intensification blocks, are unlikely to be justified in future studies. Patients with T-LL on arm A had inferior outcome compared with patients treated with similar therapy in AALL0434, as well as patients with T-ALL on arm A. Most of the changes to the backbone were designed to prevent CNS relapse and eliminate CRT in T-ALL. Accordingly, patients with T-LL might be less likely to benefit from these changes. Although treatment-related mortality was higher in T-LL in AALL1231 than in AALL0434, the difference was small and does not explain the inferior outcomes in the control arm. Genomic profiling and minimal disseminated disease analyses are ongoing to determine whether more patients with T-LL in AALL1231 had higher-risk disease biology as has been recently defined by other groups.[34]

The inferior OS in AALL1231 compared with that in AALL0434 without a change in EFS was unexpected. AALL1231 had more toxic deaths than AALL0434, and the differences approximate the OS difference. Relapse has a greater impact on EFS compared with OS when outcomes are reported before extended follow-up. Toxic deaths, by contrast, affect EFS and OS equally with earlier follow-up. The higher rates of EOI MRD negativity in AALL1231 compared with AALL0434 did not translate to improved survival, confirming the principle that MRD is important in risk allocation but is not necessarily a surrogate for EFS/OS in trials.[35] AALL1231 also confirmed the importance of EOC MRD in risk allocation.[25]

The UKALL-2003 trial demonstrated excellent outcomes with C-MTX, no HDMTX, and no CRT in T-ALL.[36,37] Incorporating the advances from AALL0434, AALL1231, and UKALL-2003 will allow for the continued refinement of T-ALL/T-LL upfront therapy with the continued elimination of CRT in most patients. Patients who were removed from protocol therapy and treated with nelarabine had outcomes similar to those who were not treated with nelarabine. It is unclear as to whether nelarabine adds similar benefit on a dexamethasone-based backbone with C-MTX as it did on a prednisone-based backbone. As nelarabine conferred a dramatic reduction in CNS relapse in AALL0434, it is attractive to study further in regimens without CRT.[10]

VHR patient outcomes were dismal in AALL1231. Approximately 10%-15% of patients were expected to be VHR; yet, only 4.1% of patients were assigned to the VHR group. Intensification of induction therapy selected for a small number of highly refractory patients. The BFM HR blocks included high-dose cytarabine, etoposide, ifosfamide, and intrathecal triple therapy that patients would not have otherwise received; they were not effective in this population. These patients urgently need a new approach for cure.

In conclusion, AALL1231 demonstrated that bortezomib is an active drug in some patients with T-cell lymphoblastic disease. Importantly, prophylactic CRT can be safely and effectively eliminated in most patients with T-ALL. Incorporating bortezomib into standard therapy for de novo T-LL appears advantageous. Future COG T-ALL/T-LL trials will build on the positive findings from AALL0434 and AALL1231, balancing intensity while mitigating toxicity to maintain high cure rates without routine CRT.

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PRIOR PRESENTATION

Presented in part at the American Society of Hematology Virtual Annual Meeting, December 5-8, 2020 and ASCO Virtual Annual Meeting, June 4-8, 2021.

SUPPORT

Supported by NIH grants U10CA180886 (M.L.L. and D.T.T.) and U10CA180899 (M.D., Z.C., H.A., C.W., and M.L.L.), U24CA196173 (M.L.L. and D.T.T.), R01CA193776 (D.T.T., M.L.H., T.M.H., B.L.W., and M.D.), X01HD100702 (D.T.T., M.L.L., S.P.H., M.D., S.S.W., K.P.D., and E.R.), the Leukemia and Lymphoma Society (D.T.T.), R03CA256550 (D.T.T., M.L.L., S.P.H., M.D., S.S.W., K.P.D., and E.R.), and R01CA264837 (D.T.T.), and St Baldrick's Foundation funding (M.L.L. and S.P.H.). S.P.H. is the Jeffrey E. Perelman Distinguished Chair in Pediatrics at The Children's Hospital of Philadelphia. E.A.R. is a KiDS of NYU Foundation Professor at NYU Langone Health.

CLINICAL TRIAL INFORMATION

NCT02112916

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.02678.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Children's Oncology Group Trial AALL1231: A Phase III Clinical Trial Testing Bortezomib in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia and Lymphoma

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

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No other potential conflicts of interest were reported.