original reports

Children's Oncology Group AALL0434: A Phase III Randomized Clinical Trial Testing Nelarabine in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia

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abstract

PURPOSE Nelarabine is effective in inducing remission in patients with relapsed and refractory T-cell acute lymphoblastic leukemia (T-ALL) but has not been fully evaluated in those with newly diagnosed disease.

PATIENTS AND METHODS From 2007 to 2014, Children's Oncology Group trial AALL0434 (ClinicalTrials.gov identifier: NCT00408005) enrolled 1,562 evaluable patients with T-ALL age 1-31 years who received the augmented Berlin-Frankfurt-Muenster (ABFM) regimen with a 2 × 2 pseudo-factorial randomization to receive escalating-dose methotrexate (MTX) without leucovorin rescue plus pegaspargase (C-MTX) or high-dose MTX (HDMTX) with leucovorin rescue. Intermediate- and high-risk patients were also randomly assigned after induction to receive or not receive six 5-day courses of nelarabine that was incorporated into ABFM. Patients who experienced induction failure were nonrandomly assigned to HDMTX plus nelarabine. Patients with overt CNS disease (CNS3; ≥ 5 WBCs/μL with blasts) received HDMTX and were randomly assigned to receive or not receive nelarabine. All patients, except those with low-risk disease, received cranial irradiation.

RESULTS The 5-year event-free and overall survival rates were 83.7% ± 1.1% and 89.5% ± 0.9%, respectively. The 5-year disease-free survival (DFS) rates for patients with T-ALL randomly assigned to nelarabine (n = 323) and no nelarabine (n = 336) were 88.2% ± 2.4% and 82.1% ± 2.7%, respectively (P = .029). Differences between DFS in a four-arm comparison were significant (P = .01), with no interactions between the MTX and nelarabine randomizations (P = .41). Patients treated with the best-performing arm, C-MTX plus nelarabine, had a 5-year DFS of 91% (n = 147). Patients who received nelarabine had significantly fewer isolated and combined CNS relapses compared with patients who did not receive nelarabine (1.3% ± 0.63% *v* 6.9% ± 1.4%, respectively; P = .0001). Toxicities, including neurotoxicity, were acceptable and similar between all four arms.

CONCLUSION The addition of nelarabine to ABFM therapy improved DFS for children and young adults with newly diagnosed T-ALL without increased toxicity.

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ASSOCIATED CONTENT

Appendix

Protocol

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

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INTRODUCTION

Dramatic increases in survival for pediatric acute lymphoblastic leukemia (ALL) have been achieved, from survival rates 50% in the 1980s to 90% today, and have been accomplished largely without using new agents.[1-13] T-cell ALL (T-ALL) is composed of 15% of pediatric and 25% of adult ALLs.[14] Compared with children and adolescents with B-lineage ALL (B-ALL), event-free survival (EFS) and overall survival (OS) rates were historically inferior for those with T-ALL, even with more intensified therapies.[4,5,10,13,15] Recurring genomic lesions, age, and presenting leukocyte count do not predict relapse for T-ALL, but minimal residual disease (MRD) is highly prognostic and is used for risk stratification.[1,11,16,17] Early T-precursor (ETP) T-ALL was initially reported to be prognostic of a poor outcome.[18] Relapse frequently occurs during active treatment and often involves extramedullary sites, and salvage therapies typically fail.[4,10,16,19,20]

Nelarabine is a DNA-terminating nucleoside prodrug for araguanosine metabolized into arabinosylguanine nucleotide triphosphate, preferentially accumulating in T lymphoblasts secondary to slowed degradation kinetics.[21] Nelarabine was first studied in a single-agent

CONTEXT

Key Objective

Is Nelarabine safe and effective in the treatment of newly diagnosed T-cell acute lymphoblastic leukemia?

Knowledge Generated

The addition of nelarabine to ABFM therapy improved DFS for children and young adults with newly diagnosed T-ALL without increased toxicity. Nelarabine decreased CNS relapses.

Relevance

Nelarabine is safe and effective in the treatment of newly diagnosed T-ALL in children and young adults with excellent disease free survival.

phase I trial for relapsed or refractory T-ALL and produced a 42% complete and partial remission rate.[22] These results were confirmed in a phase II trial in relapsed or refractory T-ALL, with an observed complete and partial remission rate of 55% in first relapse (650 mg/m^2 daily for 5 days).[23] Although active, nelarabine was associated with significant risk of central and peripheral neuropathies, occasionally fatal, in patients with relapsed disease that were not clearly related to dose.[22-25] The Children's Oncology Group (COG) AALL00P2 pilot study added nelarabine (six 5-day courses of 400-650 mg/m^2/d) to intensive chemotherapy in patients with newly diagnosed T-ALL and found it to be safe and feasible, with a 5-year EFS rate of 73% in high-risk patients.[26] The rate of grade ≥ 3 peripheral neurotoxicity was 15%. COG AALL0434 was a phase III trial with a 2×2 pseudo-factorial randomization testing nelarabine in patients with newly diagnosed T-ALL. Patients were randomly assigned to receive escalating-dose methotrexate (MTX) plus pegaspargase (C-MTX) or high-dose MTX (HDMTX), and patients with intermediate-risk (IR) and high-risk (HR) disease were randomly assigned to receive or not receive nelarabine.[1] We previously reported on patient characteristics of the entire cohort, on the safety of integrating nelarabine into this regimen, and that C-MTX was associated with significantly better disease-free survival (DFS) and OS as compared with HDMTX.[1,27] We now report the results of the nelarabine randomization.

PATIENTS AND METHODS

Trial Oversight

This study was conducted by COG under an Investigational New Drug (IND) application for nelarabine (compound 506U78, IND 52611) held by the National Cancer Institute. AALL0434 was approved by the Cancer Therapy and Evaluation Program, the US Food and Drug Administration, the Pediatric Central Institutional Review Board, and institutional review boards at each participating center. In accordance with the Declaration of Helsinki, informed consent or assent was obtained before study entry.

Patients

COG AALL0434 enrolled 1,596 patients with T-ALL from January 2007 to July 2014 (CONSORT diagram provided in Fig 1). Eligible patients included newly diagnosed, untreated (except corticosteroids) patients age 1-31 years.[1] AALL0434 was amended in 2010 to include patients with T-cell lymphoblastic lymphoma, with a plan to analyze and report those patients separately. All participants underwent a 28-day, prednisone-based, four-drug induction (Appendix Table A1, online only). After a second-stage postinduction consent, participants underwent risk stratification as low risk (LR), IR, HR, or induction failure (IF; M3 marrow with $>$ 25% blasts; Appendix Table A2, online only). Appendix Tables A3 and A4 (online only) summarize ineligibility reasons and reasons for going off therapy after induction for patients with T-ALL. AALL0434 used a sequential design to evaluate nelarabine during the safety and efficacy phases.[27] In the safety phase, only HR patients participated in the nelarabine randomization. During the efficacy phase, HR and IR patients participated in the nelarabine randomization. Low-risk patients did not participate in this randomization. Six hundred fifty-nine IR or HR patients were randomly assigned to receive or not receive six 5-day courses of nelarabine 650 mg/m^2/d (arm A: C-MTX; arm B: C-MTX plus nelarabine; arm C: HDMTX; arm D: HDMTX plus nelarabine; Appendix Table A1). Two courses were given in consolidation, on days 1-5 and 43-47; one course was given in delayed intensification, on days 29-33; and three courses were given on days 29-33 of the first three maintenance cycles. All IR and HR patients received 12 Gy of prophylactic cranial radiation therapy (CRT). Participants with overt CNS involvement (CNS3; ≥ 5 WBCs/μL with blasts or clinical signs of CNS involvement) or persistent, postinduction testicular leukemia were nonrandomly assigned to receive HDMTX on arms C or D with 18 Gy of CRT during delayed intensification for those with CNS3 or 24 Gy of testicular radiation during consolidation. Treatment duration was the same for all arms and was 2 years from the start of interim maintenance for

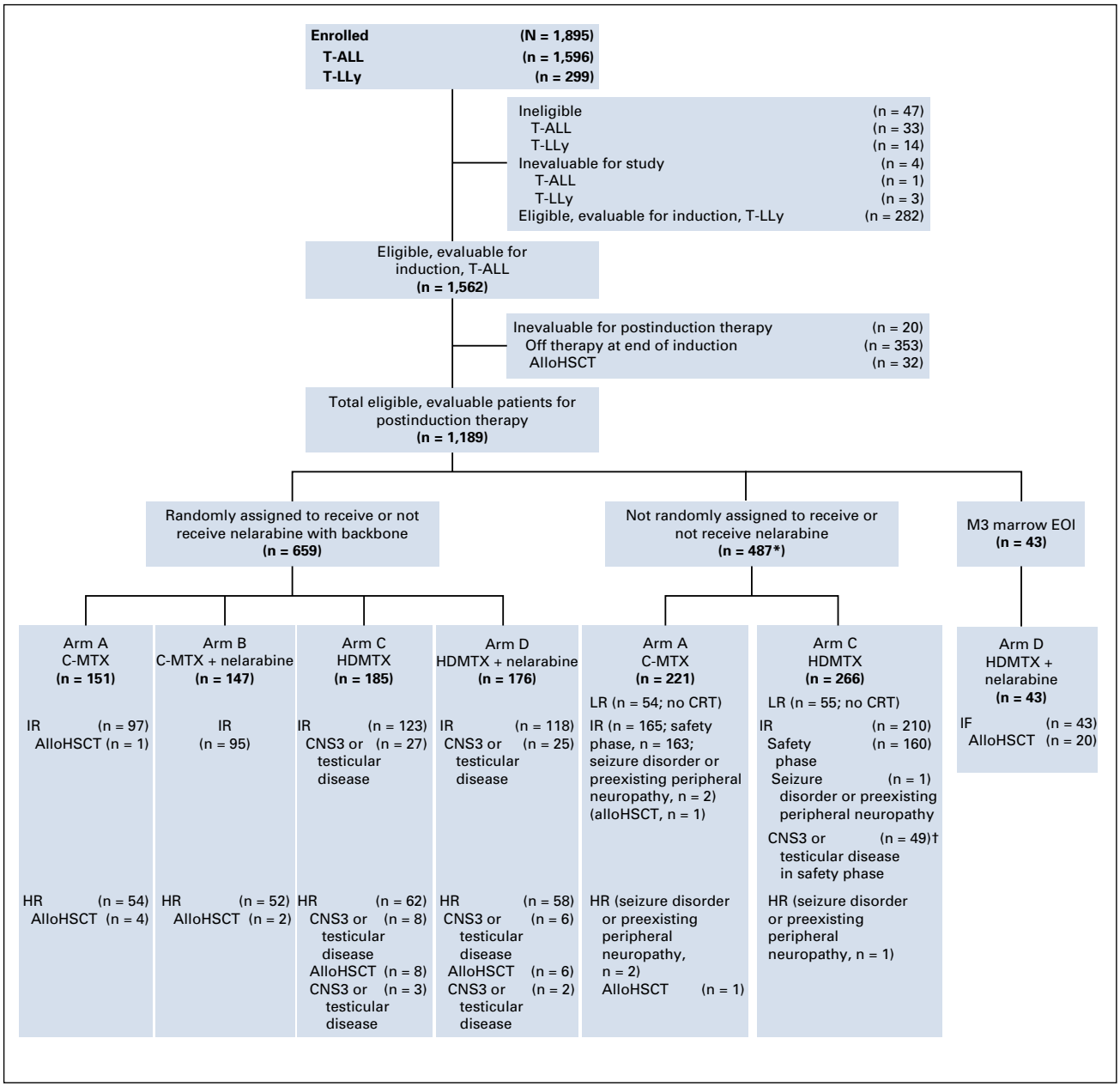

FIG 1. CONSORT diagram for study. (*) Includes patients who were not eligible to receive nelarabine (randomized to arms A and C only) either during the safety phase (intermediate risk [IR]) or efficacy phase (seizure disorder or preexisting peripheral neuropathy). (†) IR patients with CNS3 and testicular disease were assigned to arm C during the safety phase. The most commons reasons why patients came off study between the first and second stages of randomization were because the physician determined it was in the best interests of the patient and the participant declined to participate in the randomization. AlloHSCT, allogeneic hematopoietic stem-cell transplantation; C-MTX, escalating-dose methotrexate without leucovorin rescue plus pegaspargase; CRT, cranial radiation therapy; EOI, end of induction; HDMTX, high-dose methotrexate with leucovorin rescue; HR, high risk; IF, induction failure; LR, low risk; T-ALL, T-cell acute lymphoblastic leukemia; T-LLy, T-Cell lymphoblastic lymphoma.

females and 3 years for males. Patients with IF were nonrandomly assigned to arm D and could remain on study if an M1 or M2 marrow (≤ 25% blasts) was achieved by the end of consolidation. Participants with a preexisting, medication-dependent seizure disorder were ineligible for the nelarabine randomization.[1] No participants were assigned risk based on cytogenetics, immunophenotype, or genomic alterations.[4,28-34] Centrally determined ETP status was available for 1,125 patients (81%) and categorized as ETP, near ETP (ETP but with high CD5 expression), or not ETP.[35] Although COG AALL0434 did not include an allogeneic hematopoietic stem-cell transplantation (alloHSCT) option, approximately 4% of patients were taken off protocol therapy for transplantation by investigator choice. Retrospectively collected data were available on 1,390 patients (89%) to identify who was taken off therapy, either

during induction or after induction therapy, and subsequently underwent alloHSCT in first remission.

Outcome and Statistical Analyses

Treatment-related adverse events were graded using Common Terminology Criteria for Adverse Events version 4. EFS was defined as time from study enrollment to first event (IF, induction death, relapse, second malignant neoplasm, or remission death) or date of last contact. The primary outcome for the randomized question was DFS, which was defined as the time from postinduction randomization to first event (relapse, second malignant neoplasm, or remission death) or date of last contact. OS was defined as the time from study enrollment or, for the randomized cohorts, from postinduction randomization to death or date of last contact. With a one-sided α of 5%, there was 80% power to detect an improvement in 4-year DFS from 82% to 89% (93 events) between the nelarabine and no nelarabine regimens for a total of 659 patients, with a minimum follow-up time of 3 years.

Study accrual duration was driven by the time needed to meet accrual targets for the nelarabine randomization. Interim analyses for efficacy and futility were scheduled when approximately 20%, 40%, 60%, 80%, and 100% of the expected events were observed. An αt^2 spending function with truncation at three standard deviations was used for interim monitoring.

Survival rates were estimated using the Kaplan-Meier method[36] and standard errors of Peto et al.[37] Survival rates are presented as rates ± SEs. The power calculation for the randomized nelarabine comparison was based on a one-sided log-rank test ($\alpha = .05$) because the objective was to determine whether the addition of nelarabine to a standard backbone improved outcomes. Unless otherwise specified, two-sided log-rank tests were used for comparison of survival curves. Multivariable analyses used Cox regression analyses, adjusting for treatment arm and risk group, and time-dependent covariates for time to alloHSCT. Per-protocol subgroup analyses of overall outcomes, including by race and sex, were also performed. Post hoc analyses used the log-rank test to compare DFS by age group within the nelarabine and no nelarabine randomized cohorts. Proportions were compared between groups using a χ^2 test or Fisher's exact test. Cumulative incidence rates were computed using the cumulative incidence function for competing risks, with comparisons between groups made using the *K*-sample test.[38] A $P < .05$ was considered significant for all comparisons. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary NC), and graphics were generated using R Version 2.13.1 (http://www.r-project.org). This report includes data current as of June 30, 2018.

TABLE 1. Patient Characteristics for the Nelarabine Randomized Cohort

Characteristic	No. of Patients (%)	
	Nelarabine (n = 323)	No Nelarabine (n = 336)
Age, years		
< 10	151 (46.8)	178 (53.0)
10-15	116 (35.9)	104 (30.9)
≥ 16	56 (17.3)	54 (16.1)
Sex		
Male	238 (73.7)	255 (75.9)
Female	85 (26.3)	81 (24.1)
WBC (× 1,000/μL)		
< 50	130 (40.3)	116 (34.5)
≥ 50	193 (59.7)	220 (65.5)
CNS		
CNS1	232 (71.8)	233 (69.4)
CNS2	62 (19.2)	75 (22.3)
CNS3	29 (9.0)	28 (8.3)
Race		
American Indian or Alaska native	1 (0.3)	2 (0.6)
Asian	15 (4.7)	21 (6.3)
Native Hawaiian or other Pacific Islander	4 (1.2)	1 (0.3)
Black or African American	41 (12.7)	40 (11.9)
White	223 (69.0)	236 (70.2)
Unknown	39 (12.1)	36 (10.7)
Ethnicity		
Hispanic or Latino	51 (15.8)	46 (13.7)
Not Hispanic or Latino	260 (80.5)	279 (83.0)
Unknown	12 (3.7)	11 (3.3)
AlloHSCT		
Yes	8 (2.5)	13 (3.9)
No	275 (85.1)	274 (81.5)
Unknown	40 (12.4)	49 (14.6)
BM, induction day 29		
M1	306 (94.7)	322 (95.8)
M2	17 (5.3)	14 (4.2)
MRD, induction day 29, %		
< 0.01	160 (49.5)	174 (51.8)
0.01 to < 0.1	16 (5.0)	14 (4.2)
0.1 to < 1.0	38 (11.7)	32 (9.5)
1.0 to < 10.0	91 (28.2)	86 (25.6)
≥ 10	18 (5.6)	30 (8.9)

Abbreviations: AlloHSCT, allogeneic hematopoietic stem-cell transplantation; BM, bone marrow; MRD, minimal residual disease.

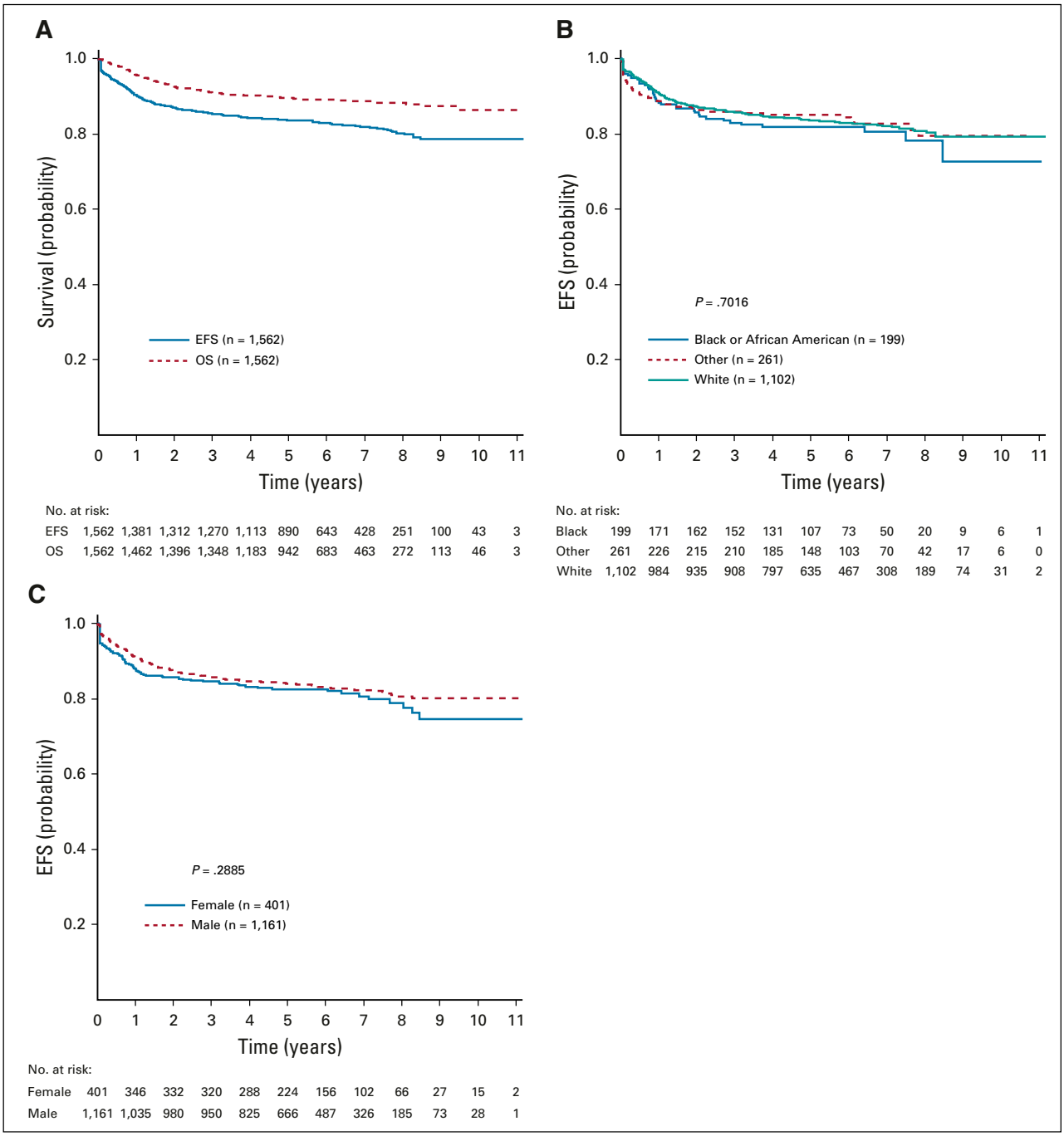

FIG 2. (A) Event-free survival (EFS) and overall survival (OS) curves for all patients with T-cell acute lymphoblastic leukemia; 5-year EFS and OS rates were 83.7% ± 1.1% and 89.5% ± 0.9%, respectively. (B) EFS by race and ethnicity; 5-year EFS rates were 83.7% ± 1.3% for White patients, 81.8% ± 3.4% for Black patients, and 85.1% ± 2.7% for other patients ($P = .702$). (C) EFS by sex; 5-year EFS rates were 82.6% ± 2.3% for females and 84.1% ± 1.3% for males ($P = .289$).

RESULTS

AALL0434 cohort risk stratification and randomization are presented in the CONSORT diagram (Fig 1). There were no unexpected variances in patient characteristics (Table 1). For the 1,562 eligible and evaluable patients with T-ALL, 5-year EFS was 83.7% ± 1.1% and 5-year OS was 89.5% ± 0.9% (Fig 2A). There was no difference in overall EFS by race or ethnicity and sex (Figs 2B and 2C).

Nelarabine Randomization

Patients randomly assigned to receive nelarabine (n = 323) had superior 5-year DFS compared with those not assigned

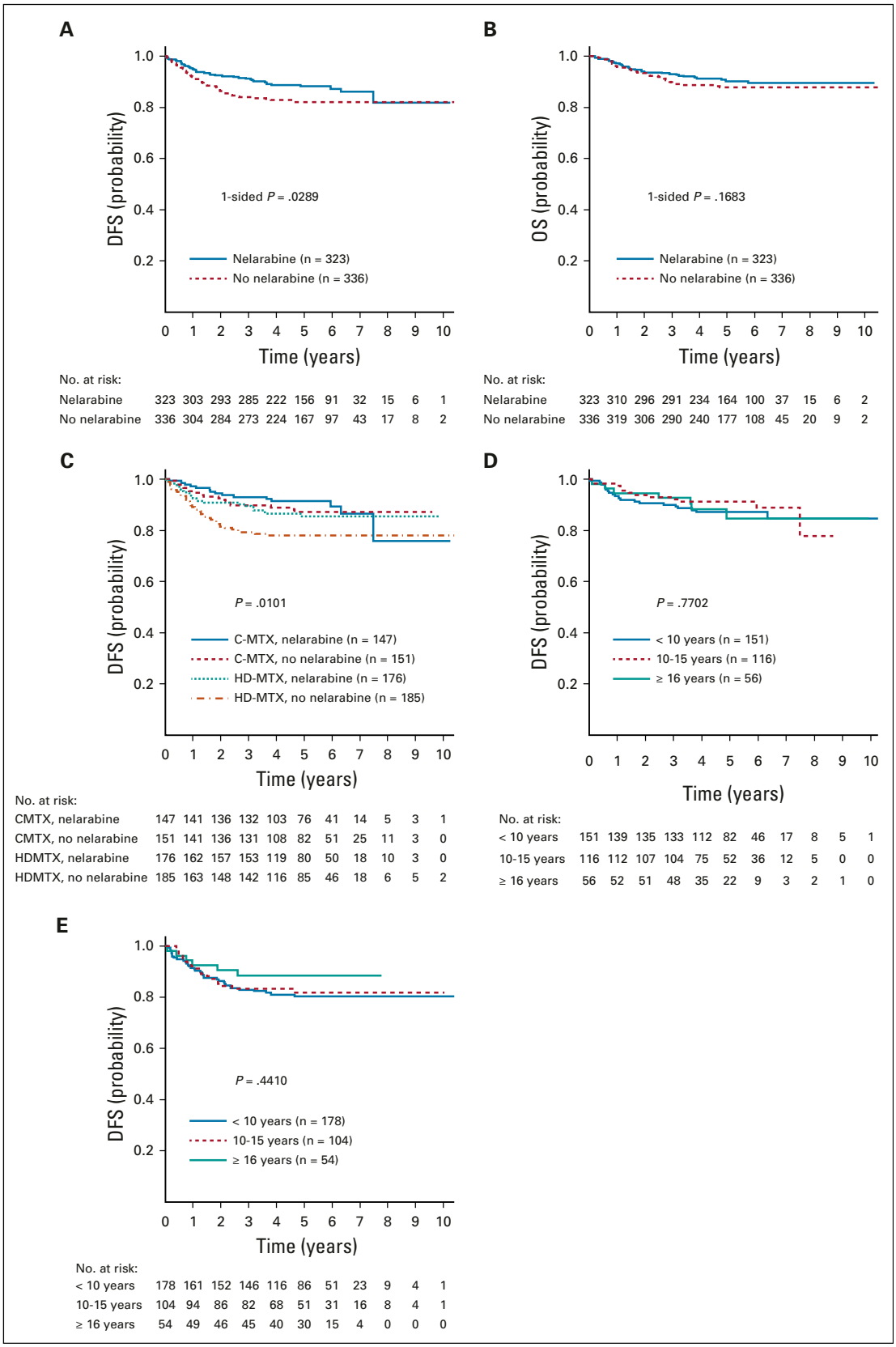

FIG 3. Disease-free survival (DFS) and overall survival (OS) comparisons for nelarabine versus no nelarabine in the randomized cohorts. (A) Five-year DFS rates were 88.2% ± 2.4% with nelarabine compared with 82.1% ± 2.7% without nelarabine ($P = .029$). (B) Five-year OS rates were 90.3% ± 2.2% with nelarabine compared with 87.9% ±without nelarabine ($P = .168$). (Continued on following page)

to nelarabine (n = 336; 88.2% ± 2.4% *v* 82.1% ± 2.7%, respectively; *P* = .029; Fig 3A). The 5-year OS for patients randomly assigned to receive nelarabine was 90.3% ± 2.2%, compared with 87.9% ± 2.3% for those not receiving nelarabine (*P* = .168; Fig 3B). There was no significant interaction between the MTX and nelarabine randomizations (*P* = .41). Analysis by treatment arm revealed that C-MTX with nelarabine had the best 5-year DFS at 91.4% ± 3.1% (n = 147), followed by C-MTX without nelarabine (87.2% ± 3.5%; n = 151), HDMTX with nelarabine (85.5% ± 3.6%; n = 176), and HDMTX without nelarabine (78.1% ± 4.0%; n = 185; *P* = .01; Fig 3C). DFS of the HDMTX without nelarabine arm was significantly lower than that of the other arms with no increase in higher risk patient characteristics, such as higher WBC (*P* = .07) or higher day 29 MRD (*P* = .66), compared with the other arms. No differences in DFS were observed across all age groups in those randomly assigned to receive (Fig 3D) or not receive (Fig 3E) nelarabine. There was no difference in 5-year EFS between patients eligible for the nelarabine randomization who did not participate and those who were randomly assigned (85.5% ± 3.2% *v* 85.1% ± 1.8%, respectively; *P* = .53).

Events in Randomized Cohorts

Among patients who underwent randomization, 39 of 323 patients receiving nelarabine had an event, compared with 58 of 336 patients treated without nelarabine (Table 2); relapse was the most common event (72.2%). Nelarabine was associated with a striking decrease in CNS relapses, with 5-year cumulative incidence rates of CNS relapse (isolated and combined) of 1.3% ± 0.63% in patients who received nelarabine compared with 6.9% ± 1.4% in patients who did not receive nelarabine (*P* = .0001; nelarabine: one CNS relapse; two CNS and marrow relapses; and one CNS, marrow, and other relapse; no nelarabine: 14 CNS relapses; eight CNS and marrow relapses; and one CNS, marrow, and other relapse; Fig 4). CNS3 patients were nonrandomly assigned to HDMTX, and six (21.4%) of 28 patients randomly assigned to HDMTX without nelarabine had a CNS relapse compared with only one (3.4%) of 29 patients randomly assigned to HDMTX with nelarabine (*P* = .052). Second malignancy rates were low and similar between groups (Appendix Table A5, online only).

Risk-Stratified Outcomes

Among the 1,189 eligible and evaluable patients with T-ALL with postinduction risk stratification data, 109 (9.2%) were LR, 808 (70.0%) were IR, 229 (19.3%) were HR, and 43 (3.6%) had IF. The 5-year DFS and OS rates for patients randomly assigned to receive versus not receive nelarabine were 90.8% ± 2.8% and 91.3% ± 2.7%, respectively, versus 86.3% ± 3.1% and 92.4% ± 2.4%, respectively (*P* = .077 and *P* = .617, respectively) for IR patients, and 83.5% ± 4.4% and 88.5% ± 3.8%, respectively, versus 74.1% ± 4.8% and 79.2% ± 4.6%, respectively (*P* = .106 and *P* = .051, respectively) for HR patients. For the 43 patients who experienced IF who were nonrandomly assigned to HDMTX with nelarabine, the 5-year EFS was 53.1% ± 9.4%. The 5-year DFS rates for CNS3 patients randomly assigned between the HDMTX-containing arms were 93.1% ± 6.5% for HDMTX with nelarabine and 67.9% ± 12.2% for HDMTX without nelarabine (*P* = .014; Appendix Fig A1, online only). Day 29 MRD was prognostically significant in both cohorts (Appendix Figs A2A and A2B, online only). For patients who received nelarabine, 5-year DFS was 92.3% ± 2.9% for MRD < 0.1% compared with 83.5% ± 3.9% with MRD ≥ 0.1% (*P* = .01); without nelarabine, DFS was 89.0% ± 3.1% for MRD < 0.1% compared with 73.4% ± 4.3% with MRD ≥ 0.1% (*P* = .0003).

Treatment-Related Adverse Events

Overall toxicity and neurotoxicity were acceptable and similar between all four randomized arms. Grade ≥ 3 nontargeted toxicity rates were similar on both nelarabine arms (41.2% with nelarabine *v* 46.1% without nelarabine; *P* = .2). For the targeted neuropathy toxicities, grade 3 or 4 peripheral motor (*P* = .223) and sensory (*P* = .664) neuropathy rates were similar in the nelarabine and no nelarabine arms (Appendix Tables A6 and A7, online only). There was no significant difference in rates of grade ≥ 3 central neurotoxicity (leukoencephalopathy, encephalopathy, reversible posterior leukoencephalopathy syndrome, CNS necrosis, cerebral edema, Guillain-Barre syndrome, and pyramidal tract syndrome) in arms with versus without nelarabine (3.4% *v* 2.1%, respectively; *P* = .298; Appendix Tables A6 and A7). However, two patients with IF who were nonrandomly assigned to receive nelarabine on arm D developed symptoms of central neurocognitive decompensation either during or immediately after a nelarabine cycle during consolidation therapy and eventually died.

AlloHSCT at Investigator Discretion

Among the 1,390 eligible and evaluable patients with T-ALL for whom survey information was available, 333 (24%) were taken off protocol therapy during induction before

FIG 3. (Continued). (C) Five-year DFS rates for the 4 randomized arms were as follows: escalating-dose methotrexate without leucovorin rescue plus pegaspargase (C-MTX) with nelarabine, 91.4% ± 3.1% (n = 147); C-MTX without nelarabine, 87.2% ± 3.5% (n = 151); high-dose methotrexate with leucovorin rescue (HDMTX) with nelarabine, 85.5% ± 3.6% (n = 176); and HDMTX without nelarabine, 78.1% ± 4.0% (n = 185; *P* = .01). (D) DFS by age group in patients randomly assigned to nelarabine; 5-year DFS rates were as follows: age < 10 years, 87.1% ± 3.5%; age 10-15 years, 91.3% ± 3.7%; and age ≥ 16 years, 84.8% ± 7.1% (*P* = .77). (E) DFS by age group in patients not randomly assigned to nelarabine; 5-year DFS rates were as follows: age < 10 years, 80.3% ± 3.8%; age 10-15 years, 81.9% ± 4.9%; and age ≥ 16 years, 88.6% ± 5.5% (*P* = .441).

TABLE 2. List of DFS Events by Arm

Type of Events	No. of Patients			
	Arm A (C-MTX)	Arm B (C-MTX+Nel)	Arm C (HDMTX)	Arm D (HDMTX+Nel)
Relapse	11	10	32	17
CNS	1	0	13	1
BM	5	2	9	10
BM and CNS	1	1	7	1
Lymph nodes	1	1	0	0
Mediastinum	1	0	0	1
Marrow, CNS, lymph nodes	1	0	0	0
Marrow, lymph nodes	0	0	1	0
Marrow, CNS, mediastinum	0	0	0	1
Marrow, other site, specify: refractory disease	0	0	1	0
Marrow, other site, specify: blood	0	0	1	0
Other site, specify[a]	1	6	0	3
SMN	3	5	2	2
Remission death	4	0	6	5
Total	18	15	40	24

Abbreviations: BM, bone marrow; C-MTX, escalating-dose methotrexate without leucovorin rescue plus pegaspargase; DFS, disease-free survival; HDMTX, HDMTX, high-dose methotrexate with leucovorin rescue; Nel, nelarabine; SMN, second malignant neoplasm.

[a]Pleural fluid, mandible, ileum, or peripheral blood.

randomization. Thirty-two of these patients (9.6%) underwent alloHSCT. Of 917 patients with T-ALL randomized or assigned after induction to one of the four treatment arms, 23 (2.5%) were taken off protocol therapy and underwent alloHSCT. Multivariable Cox regression analyses on this cohort (adjusting for treatment arm and risk group and using time-dependent covariates for time to alloHSCT) showed worse DFS for those who received alloHSCT compared with patients who received protocol chemotherapy (hazard ratio, 3.32; 95% CI, 1.34 to 8.23; $P = .009$; Table 3). For patients who experienced IF, there was no difference in outcome for those receiving HDMTX plus nelarabine (n = 23) compared with those receiving alloHSCT (n = 20; hazard ratio, 0.66; 95% CI, 0.24 to 1.83; $P = .423$). Centrally determined ETP status was known for 1,125 patients (81%), including 279 patients taken off therapy before randomization, with 92 patients having ETP or near ETP phenotype.[38] Of the 279 patients, 28 received alloHSCT (21 with ETP or near ETP [75%]) and 251 received chemotherapy alone (71 with ETP or near ETP [28%]; Fisher's exact test, $P < .001$). In multivariable analyses including ETP status, alloHSCT (n = 21) was associated with inferior DFS compared with chemotherapy (n = 792; hazard ratio, 5.86; 95% CI, 2.50 to 13.75; $P < .0001$), and ETP status did not have a statistically significant impact on DFS (hazard ratio, 0.99; 95% CI, 0.59 to 1.67; $P = .981$).

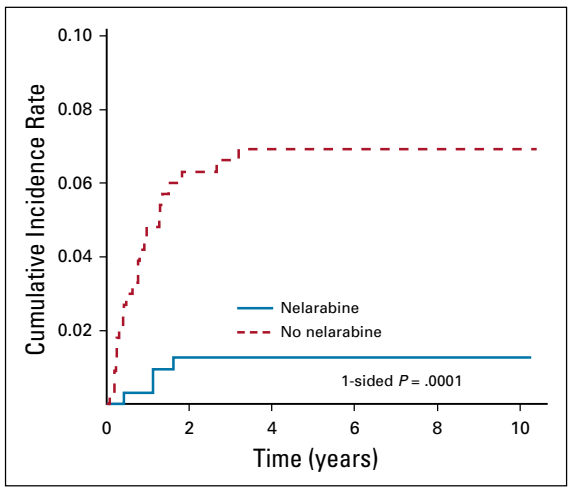

FIG 4. The 5-year cumulative incidence rates of CNS relapse (isolated and combined) in the nelarabine versus no nelarabine arms were 1.3% ± 0.63% and 6.9% ± 1.4%, respectively ($P = .0001$).

DISCUSSION

Typically, children and young adults with T-ALL have had EFS and OS rates that are inferior to patients with B-ALL.[4,5,10] In AALL0434, the 1,562 patients with T-ALL had a 5-year EFS rate of 83.7% and 5-year OS rate of 89.5%, which are superior to the outcomes in the companion COG high-risk B-ALL trial AALL0232 (5-year EFS, 75.2%; 5-year OS, 85.0%).[2] Other investigators have reported a 5-year EFS of 81.2% and 5-year OS of 86.4% in 388 patients with T-ALL in the UKALL 2003 study, 4-year EFS of 83% and 4-year OS of 89% in 97 patients with T-ALL in the DFCI 05-001 study, and 7-year EFS of

TABLE 3. Multivariable Cox Regression Analyses

Comparison Group[a]	Outcome	Covariates Included	Hazard Ratio (95% CI; Cox multivariable analyses)	*P*
Randomized cohort (± nelarabine; n = 570)	DFS	Treatment arm (nelarabine *v* no nelarabine), risk group (IR *v* HR), alloHSCT *v* chemotherapy	3.32 (1.34 to 8.23)	.009
Overall cohort with available ETP and alloHSCT status (n = 813)	DFS	ETP status (ETP or near ETP *v* no ETP), alloHSCT *v* chemotherapy	5.86 (2.50 to 13.75)	< .0001
Induction failure (n = 43)	EFS	AlloHSCT *v* chemotherapy	0.66 (0.24 to 1.83)	.423

Abbreviations: alloHSCT, allogeneic hematopoietic stem-cell transplantation; DFS, disease-free survival; EFS, event-free survival; ETP, early T precursor; HR, high risk; IR, intermediate risk.

[a]The use of alloHSCT was not a predefined study question, and results were assessed using a retrospective survey design. Because there were no recommendations for which treatments off-therapy patients should receive, those treated with chemotherapy or allogeneic transplantation are designated as having received chemotherapy or alloHSCT. Excluding patients with induction failure (n = 20), all other patients who received alloHSCT were distributed equally among the 4 treatment arms (see Fig 1, CONSORT diagram; $P = .494$).

76.3% and 7-year OS of 81.2% in 464 patients with T-ALL in the AIEOP-BFM 2000 study.[6-9,11] Children and young adults with T-ALL treated on AALL0434 showed superior 5-year DFS with nelarabine (88%) versus without nelarabine (82%). The best results were obtained among patients who were randomly assigned to receive nelarabine plus C-MTX. The addition of nelarabine to the HDMTX regimen also improved DFS compared with HDMTX alone and decreased CNS relapse in both patients with and without CNS disease at diagnosis. Remarkably, there was only one isolated CNS relapse and four total relapses involving the CNS among the 323 patients randomly assigned to nelarabine versus 14 isolated CNS relapses and 23 total relapses involving CNS among the 336 patients randomly assigned to not receive nelarabine. We did not observe a difference in OS between the nelarabine and no nelarabine arms, although the OS for patients with HR T-ALL trended toward statistical significance.

Unlike in other studies, the nelarabine DFS advantage was not restricted by age or race.[7,9-11] The UKALL 2003 study showed improvement in T-ALL survival using dexamethasone instead of prednisone, but only for patients younger than age 10 years, and the AIEOP-BFM 2000 trial showed improvement in T-ALL survival using dexamethasone only for those who were prednisone good responders.[3,7,9] The lack of age restriction on DFS is particularly important and novel because T-ALL tends to affect older children and approximately 25% of adults with ALL, but survival for older children and young adults was equivalent to that of younger patients on AALL0434.[3,7,39]

The improvement in outcome may be explained by the activity of nelarabine in patients with higher-risk disease (high MRD and IF) and enhanced CNS prophylaxis. Higher postinduction MRD (≥ 0.1%) was highly prognostic on AALL0434, but patients with high MRD who received nelarabine had a 5-year DFS rate of 83.5%, compared with 73.4% for those who did not receive nelarabine. The excellent outcome for older patients might also be affected by this because older patients had increased higher-risk features. Nelarabine has good penetration into the CNS,[23] and T-ALL has a higher likelihood of CNS relapse as compared with B-ALL. The incidence of CNS relapse was significantly lower for patients assigned to the nelarabine arms ($P = .0001$), even though all patients received CRT. The decrease in incidence of CNS relapse was seen both in patients who were CNS3 at diagnosis and those who were not. The advantage in CNS protection did not come at the cost of increased toxicity. This study and COG AALL00P2 showed that nelarabine was not associated with an overall increased risk of neurotoxicity in newly diagnosed patients, although there were rare serious neurotoxicities (three of 366 patients; 0.8%), similar to those described for patients with heavily pretreated relapsed T-ALL.[22-26] Notably, two of the three patients with severe neurotoxicity had induction failure and developed fatal neurotoxicity during consolidation. Although AALL0434 did not address whether nelarabine would improve outcome in patients treated without CRT, the significant CNS-protective effect of nelarabine supports its use in future clinical trials.

Patients with T-ALL and IF typically die of disease, but the 5-year EFS was 53% for such patients in AALL0434. A study from 14 cooperative study groups in the United States and the European Union found that patients with postinduction M3 marrow had a 10-year EFS of only 19%.[40] Approximately 4% of AALL0434 participants received alloHSCT, including approximately half of patients with IF. There was no EFS advantage for patients with IF who subsequently received alloHSCT even when standard risk factors were taken into consideration in a multivariable analysis. However, we do not have information regarding whether there were other clinical factors that resulted in the patient undergoing HSCT. Schrappe et al[40] reported that patients who received chemotherapy alone for IF had a 10-year EFS of 26%, whereas those who received matched alloHSCT or other donor types had 10-year EFS rates of 40% and 45%, respectively. Given the excellent results for patients who received C-MTX with nelarabine in AALL0434, this regimen deserves consideration for patients with IF.

In summary, the addition of nelarabine decreased CNS relapses and improved overall DFS, especially for patients with higher-risk disease, independent of age or race.

Although many centers have used alloHSCT in first CR for HR T-ALL, this study showed a survival advantage for chemotherapy alone for patients with IR, HR, and IF. Patients with relapsed T-ALL have dismal survival with salvage therapy, and unlike B-ALL, there are no excellent salvage options such as chimeric antigen receptor T-cell immunotherapy, supporting the use of nelarabine in patients with newly diagnosed disease.

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CLINICAL TRIAL INFORMATION

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

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Children's Oncology Group AALL0434: A Phase III Randomized Clinical Trial Testing Nelarabine in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia

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APPENDIX

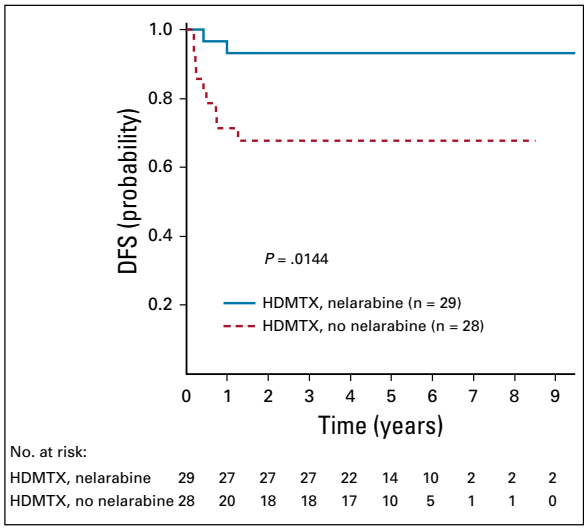

FIG A1. Disease-free survival (DFS) for patients with CNS3 randomly assigned to high-dose methotrexate with leucovorin rescue (HDMTX) with or without nelarabine; 5-year DFS rates were 93.1% ± 6.5% for HDMTX with nelarabine and 67.9% ± 12.2% for HDMTX without nelarabine (P = .014).

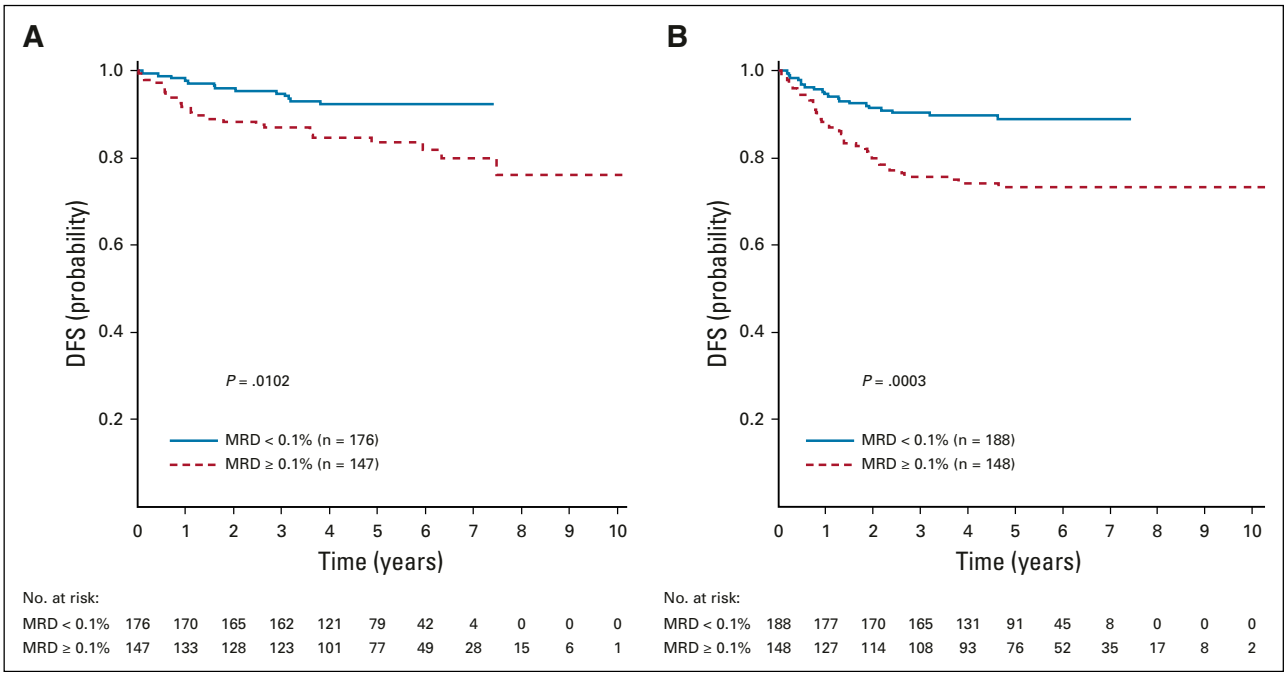

FIG A2. Disease-free survival (DFS) by day 29 minimal residual disease (MRD) status. (A) Five-year DFS rates in the nelarabine group were 92.3% ± 2.9% in those with MRD < 0.1% and 83.5% ± 3.9% for those with MRD ≥ 0.1% ($P = .0102$). (B) Five-year DFS rates in the no nelarabine group were 89.0% ± 3.1% in those with MRD < 0.1% and 73.4% ± 4.3% in those with MRD ≥ 0.1% ($P = .0003$).

TABLE A1. Two-Stage Consenting Process and Details of Therapies

Drug	Dose	Schedule
First stage consent: induction, all arms		
IT cytarabine	Age adjusted[a]	At diagnostic lumber puncture or day 1
Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 22
Prednisone	30 mg/m^2/dose twice a day	Days 1-28
Daunorubicin	25 mg/m^2	Days 1, 8, 15, 22
Pegaspargase	2,500 units/m^2	Day 4, 5, or 6
IT-MTX	Age adjusted[a]	Days 8, 29 (CNS3: + days 15, 22)
Second stage consent: risk stratification and postinduction randomization to arm A, B, C, or D		
Consolidation[b]		
Courses without nelarabine (arms A and C)		
Cyclophosphamide	1,000 mg/m^2	Days 1, 29
Cytarabine	75 mg/m^2	Days 1-4, 8-11, 29-32, 36-39
Mercaptopurine	60 mg/m^2	Days 1-14, 29-42
Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 15, 22, 43, 50
Pegaspargase	2,500 units/m^2	Days 15, 43
IT-MTX	Age adjusted[a]	Days 8, 15, 22, 29 (high risk); days 1, 8 (CNS3); days 1, 8, 15, 22 (all others)
CRT[c]	12 Gy (18 Gy for CNS3)	Start on day 15
Testicular radiotherapy[d]	24 Gy (persistent disease only)	Completed before day 15
Courses with nelarabine (arms B and D)		
Cyclophosphamide	1,000 mg/m^2	Days 8, 50
Cytarabine	75 mg/m^2	Days 8-11, 15-18, 50-53, 57-60
Mercaptopurine	60 mg/m^2	Days 8-21, 50-63
Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 22, 29, 64, 71
Pegaspargase	2,500 units/m^2	Days 22, 64
IT-MTX	Age adjusted[a]	Days 15, 22, 57, 64 (omit day 22 for CNS3)
CRT[c]	12 Gy (18 Gy for CNS3)	Start on day 22
Testicular radiotherapy[d]	24 Gy (persistent disease only)	Completed before day 15
Nelarabine	650 mg/m^2	Days 1-5, 43-47
Interim maintenance		
C-MTX (arms A and B)		
Vincristine	1.5 mg/m^2 (2 mg maximum)	Every 10 days × 5 doses on days 1, 11, 21, 31, 41
IV-MTX[e]	100 mg/m^2	Every 10 days × 5 doses on days 1, 11, 21, 31, 41
Pegaspargase	2,500 units/m^2	Days 2, 22
IT-MTX	Age adjusted[a]	Days 1, 31
HDMTX (arms C and D)		
Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 15, 29, 43
IV-MTX	5,000 mg/m^2	Days 1, 15, 29, 43

(continued on following page)

TABLE A1. Two-Stage Consenting Process and Details of Therapies (continued)

Drug	Dose	Schedule
Leucovorin	15 mg/m^2	42, 48, 54 hours after IV-MTX
Mercaptopurine (oral)	25 mg/m^2	Days 1-56
IT-MTX	Age adjusted[a]	Day 1, 29
Delayed intensification		
Without nelarabine (arms A and C)		
Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 43, 50
Pegaspargase	2,500 units/m^2/dose	Day 4 or 5 or 6 and 43
Dexamethasone	5 mg/m^2/dose twice a day	Days 1-7, 15-21
Doxorubicin	25 mg/m^2/d	Days 1, 8, 15
Cytarabine	75 mg/m^2/d	Days 29-32, 36-39
Cyclophosphamide	1,000 mg/m^2	Day 29
Thioguanine	60 mg/m^2/d	Days 29-42 (omit for patients receiving CRT)
IT-MTX	Age adjusted[a]	Days 1, 29, 36
CRT[c]	12 Gy (18 Gy for CNS3)	Start on day 50 (arm C)
With nelarabine (arms B and D)		
Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 50
Pegaspargase	2,500 units/m^2/dose	Days 4 or 5 or 6 and 50
Dexamethasone	5 mg/m^2/dose twice a day	Days 1-7, 15-21
Doxorubicin	25 mg/m^2/d	Days 1, 8, 15
Cytarabine	75 mg/m^2/d	Days 36-39, 43-46
Cyclophosphamide	1,000 mg/m^2	Day 36
Thioguanine	60 mg/m^2/d	Days 36-49 (omit for patients receiving CRT)
IT-MTX	Age adjusted[a]	Days 1, 36, 43
CRT[c]	12 Gy (18 Gy for CNS3)	Start on day 50 (arm D)
Nelarabine	650 mg/m^2	Days 29-33
Maintenance[f]		
Without nelarabine (arms A and C)		
Vincristine	1.5 mg/m^2 (2 mg max)	Days 1, 29, 57
Prednisone	20 mg/m^2/dose twice a day	Days 1-5, 29-33, 57-61
Mercaptopurine (oral)	75 mg/m^2/d	Daily/days 1-84
Methotrexate (oral)	20 mg/m^2/dose	Weekly (omit on day 29 for LR T-ALL and SR T-LLy)
IT-MTX	Age adjusted[a]	Day 1 (and day 29 first 4 cycles; low-risk patients only)
With nelarabine (arms B and D)		
Vincristine	1.5 mg/m^2 (2 mg max)	Days 1, 57

(continued on following page)

TABLE A1. Two-Stage Consenting Process and Details of Therapies (continued)

Drug	Dose	Schedule
Prednisone	20 mg/m^2/dose twice a day	Days 1-5, 57-61
Mercaptopurine (oral)	75 mg/m^2/d	Days 1-28, 36-84
Methotrexate (oral)	20 mg/m^2/dose	Days 8, 15, 22, 36, 43, 50, 57, 64, 71, 78/weekly; omitted while taking nelarabine
IT-MTX	Age adjusted[a]	Day 1
Nelarabine	650 mg/m^2	Days 29-33 (first 3 cycles)

NOTE. Treatment arms were as follows: arm A, C-MTX; arm B, C-MTX plus nelarabine; arm C, HDMTX; and arm D, HDMTX plus nelarabine.

Abbreviations: C-MTX, escalating-dose methotrexate without leucovorin rescue plus pegaspargase; CRT, cranial radiotherapy; HDMTX, high-dose methotrexate with leucovorin rescue; IT, intrathecal; IT-MTX, intrathecal methotrexate; IV-MTX, intravenous methotrexate.

[a]IT cytarabine: 1-1.99 years, 30 mg; 2-2.99 years, 50 mg; ≥ 3 years, 70 mg. IT-MTX: 1-1.99 years, 8 mg; 2-2.99 years, 10 mg; 3-8.99 years, 12 mg; ≥ 9 years, 15 mg.

[b]In case of induction failure (M3 at day 29), begin arm D consolidation as soon as possible.

[c]Cranial radiation therapy: CNS1 or CNS2: 1.5 Gy/d over 8 fractions; CNS3: 1.8 Gy/d in 10 fractions for intermediate-risk and high-risk participants only. IT therapy is not held during the concomitant administration of CRT.

[d]Testicular radiation therapy: For biopsy-proven, persistent disease only: 2 Gy/d in 12 fractions.

[e]IV-MTX: 100 mg/m^2 (dose escalated by 50 mg/m^2 every 10 days for a total of 5 doses, adjusted for toxicity).

[f]Total duration of treatment from start of interim maintenance: female T-cell acute lymphoblastic leukemia, 2 years; male T-cell acute lymphoblastic leukemia, 3 years.

TABLE A2. Risk Assignment Algorithm

Criteria for Risk Assignment	Low Risk (n = 109; 9.2%)	Intermediate Risk (n = 808; 68.0%)	High Risk (n = 229; 19.2%)	Induction Failure (n = 43; 3.6%)
Pretreatment corticosteroids	No	Allowed	Allowed	Allowed
NCI Risk[a]	Standard	Any	Any	Any
CNS status[b]	CNS1	Any	any	Any
Testes involvement	Negative	Any	any	Any
Induction-related marrow responses				
Day 15 (M1, M2 or M3)[c]	RER	Any	Any	Any
Day 29 morphology and MRD	M1 and < 0.1%	M1 and 0.1% to < 1.0%	M2 or ≥ 1.0%	M3

Abbreviations: HPF, high-power field; MRD, minimal residual disease; NCI, National Cancer Institute; RER, rapid early responder.

[a]NCI standard risk: age 1-10 years, WBC < 50,000 cells/μL; NCI high risk: age ≥ 10 years or WBC ≥ 50,000 cells/μL.

[b]CNS1: total nucleated cells < 5/HPF with no blasts; CNS2: total nucleated cells < 5/HPF with blasts identified by light microscopy; CN3: total nucleated cells ≥ 5/HPF with blasts identified. RBC contamination adjusted per the Steinherz-Bleyer algorithm.

[c]Marrow response by day 15 of induction: RER, M1; slow early responder, M2/M3. M1, < 5% blasts; M2, 6%-25% blasts; M3, > 25% blasts.

TABLE A3. Reasons for Study Ineligibility of Patients With T-Cell Acute Lymphoblastic Leukemia

Reason	No. of Patients (n = 33)
Disease type/histology	8
Prior therapy	2
Stage, extent of disease[a]	3
Timing of start of protocol therapy	13
Other, specify[b]	7

[a]CNS status not determined before start of therapy.

[b]Inadequate consent (n = 3), used cytogenetics laboratory not approved by the Children's Oncology Group (n = 4).

TABLE A4. Reason for Receiving Off-Protocol Therapy at the End of Induction

Reason	No. of Patients (n = 373)
Refusal of further protocol therapy by patient, parent, or guardian	218
Physician determined it was in the patient's best interest	60
Adverse event or complication	18
Identified as Philadelphia chromosome positive	9
Death	6
Allogeneic hematopoietic stem-cell transplantation	32
Other[a]	10
Inevaluable for postinduction therapy[b]	20

[a]Other reasons include the following: transferred to another non–Children's Oncology Group institution and could not continue on study (n = 4), temporary closure of postinduction randomization (n = 3), protocol deviation (n = 2), and drug shortage (n = 1).

[b]Inadequate consent for postinduction therapy (n = 2), incomplete data for end of induction risk assignment (n = 13), started therapy before randomization (n = 3), or ineligible for nelarabine randomization because of history of neurologic issues (n = 2).

TABLE A5. SMN Types by Arm for Nelarabine Randomized Cohort

	No. of Patients (n = 659)			
SMN Type	**Arm A (C-MTX)**	**Arm B (C-MTX+Nel)**	**Arm C (HDMTX)**	**Arm D (HDMTX+Nel)**
Ewing sarcoma	1	0	0	0
AML	2	0	1	0
Mucoepidermoid carcinoma	0	2	0	0
Malignant melanoma	0	1	0	0
Langerhans cell histiocytosis	0	1	0	0
Myelodysplastic syndrome	0	1	0	0
Malignant histiocytosis histiocytic medullary reticulosis	0	0	1	0
Lymphoproliferative disease	0	0	0	1
Malignant lymphoma	0	0	0	1
Total	3	5	2	2

Abbreviations: AML, acute myeloid leukemia; C-MTX, escalating-dose methotrexate without leucovorin rescue plus pegaspargase; HDMTX, high-dose methotrexate with leucovorin rescue; Nel, nelarabine; SMN, second malignant neoplasm.

TABLE A6. Target Central Neurotoxicities in the Nelarabine Randomized Cohort

	No. of Patients (n = 659; %)				
Central Neurotoxicity	**Grade 3**	**Grade 4**	**Grade 5**	**Grades 3-5**	***P***
Nelarabine (n = 323)	7 (2.2)	3 (0.9)	1 (0.3)	11 (3.4)	.298
No nelarabine (n = 336)	7 (2.1)	0	0	7 (2.1)	

TABLE A7. Targeted Peripheral Neurotoxicities in the Nelarabine Randomized Cohort

	No. of Patients (n = 659; %)			
Neuropathy	**Grade 3**	**Grade 4**	**Grades 3-4**	***P***
Peripheral motor neuropathy				.223
Nelarabine	25 (7.7)	1 (0.3)	26 (8.0)	
No nelarabine	17 (5.1)	2 (0.6)	19 (5.7)	
Peripheral sensory neuropathy				.664
Nelarabine	28 (8.7)	1 (0.3)	29 (9.0)	
No nelarabine	26 (7.7)	1 (0.3)	27 (8.0)	