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ORIGINAL REPORT

Dasatinib Plus Intensive Chemotherapy in Children, Adolescents, and Young Adults With Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia: Results of Children's Oncology Group Trial AALL0622

William B. Slayton, Kirk R. Schultz, John A. Kairalla, Meenakshi Devidas, Xinlei Mi, Michael A. Pulsipher, Bill H. Chang, Charles Mullighan, Ilaria Iacobucci, Lewis B. Silverman, Michael J. Borowitz, Andrew J. Carroll, Nyla A. Heerema, Julie M. Gastier-Foster, Brent L. Wood, Sherri L. Mizrahy, Thomas Merchant, Valerie I. Brown, Lance Sieger, Marilyn J. Siegel, Elizabeth A. Raetz, Naomi J. Winick, Mignon L. Loh, William L. Carroll, and Stephen P. Hunger

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

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Corresponding author: William B. Slayton, MD, Department of Pediatrics, University of Florida, 1600 SW Archer Rd, Gainesville, FL 32610; e-mail: slaytwb@peds.ufl.edu.

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ABSTRACT

Purpose

Addition of imatinib to intensive chemotherapy improved survival for children and young adults with Philadelphia chromosome–positive acute lymphoblastic leukemia. Compared with imatinib, dasatinib has increased potency, CNS penetration, and activity against imatinib-resistant clones.

Patients and Methods

Children's Oncology Group (COG) trial AALL0622 (Bristol Myers Squibb trial CA180-204) tested safety and feasibility of adding dasatinib to intensive chemotherapy starting at induction day 15 in patients with newly diagnosed Philadelphia chromosome–positive acute lymphoblastic leukemia age 1 to 30 years. Allogeneic hematopoietic stem-cell transplantation (HSCT) was recommended for patients at high risk based on slow response and for those with a matched family donor regardless of response after at least 11 weeks of therapy. Patients at standard risk based on rapid response received chemotherapy plus dasatinib for an additional 120 weeks. Patients with overt CNS leukemia received cranial irradiation.

Results

Sixty eligible patients were enrolled. Five-year overall (OS) and event-free survival rates (± standard deviations [SD]) were 86% ± 5% and 60% ± 7% overall, 87% ± 5% and 61% ± 7% for standard-risk patients (n = 48; 19% underwent HSCT), and 89% ± 13% and 67% ± 19% for high-risk patients (n = 9; 89% underwent HSCT), respectively. Five-year cumulative incidence (± SD) of CNS relapse was 15% ± 6%. Outcomes (± SDs) were similar to those in COG AALL0031, which used the same chemotherapy with continuous imatinib: 5-year OS of 81% ± 6% versus 86% ± 5% (P = .63) and 5-year disease-free survival of 68% ± 7% versus 60% ± 7% (P = 0.31) for AALL0031 versus AALL0622, respectively. *IKZF1* deletions, present in 56% of tested patients, were associated with significantly inferior OS and event-free survival overall and in standard-risk patients.

Conclusion

Dasatinib was well tolerated with chemotherapy and provided outcomes similar to those with imatinib in COG AALL0031, where all patients received cranial irradiation. Our results support limiting HSCT to slow responders and suggest a potential role for transplantation in rapid responders with *IKZF1* deletions.

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INTRODUCTION

Survival for children with acute lymphoblastic leukemia (ALL) exceeds 85%,[1-5] and Philadelphia chromosome (Ph), t(9;22)(q34;q11.2), and *BCR-ABL1* fusion are present in 3% to 5% of children with ALL. Historically, fewer than half of children with Ph-positive ALL survived when treated with chemotherapy with or without hematopoietic stem-cell transplantation (HSCT).[6,7] Expression of the BCR-ABL1 fusion protein, a constitutively activated ABL1 tyrosine kinase, leads to transformation.[8] Secondary cytogenetic abnormalities[9,10]

ASSOCIATED CONTENT

Data Supplement
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and cooperative mutations such as *IKZF1* deletions[11-13] contribute to inferior outcomes in Ph-positive ALL.

Children's Oncology Group (COG) trial AALL0031 in Ph-positive ALL demonstrated that adding the tyrosine kinase inhibitor (TKI) imatinib to intensive chemotherapy dramatically improved survival compared with that in patients receiving chemotherapy alone.[14,15] AALL0031 patients treated with HSCT had outcomes similar to those receiving chemotherapy plus imatinib. Similarly, the EsPhALL (European Study of Postinduction Treatment of Ph-Positive ALL) group showed improved outcomes in patients receiving imatinib plus chemotherapy compared with chemotherapy alone in good-risk patients with Ph-positive ALL.[16]

Although imatinib improves survival in Ph-positive ALL, outcomes are still inferior to those in children with Ph-negative ALL. Furthermore, AALL0031 used cranial irradiation in every patient. Cranial irradiation can adversely affect learning and cognition and cause brain tumors.[17-20] The dual ABL/SRC TKI dasatinib is 300 times more potent than imatinib at blocking ABL kinase activity[21] and is active in most patients with imatinib resistance.[22,23] Dasatinib accumulates in the CNS, a sanctuary site for leukemia where penetration of imatinib is poor.[24]

We hypothesized that substituting dasatinib for imatinib and starting TKI therapy earlier (at day 15 rather than day 35) would lead to more rapid clearance of leukemia and improved survival, while abrogating the need for cranial irradiation. The objectives of the COG AALL0622 trial (Bristol Myers Squibb trial CA180-204) were to determine the feasibility and toxicity of adding dasatinib to AALL0031 chemotherapy and to determine whether dasatinib plus AALL0031-style chemotherapy would lead to 3-year event-free survival (EFS) of at least 60% in patients with good early response to therapy.

PATIENTS AND METHODS

Patients

AALL0622 enrolled patients age 1 to 30 years with Ph-positive ALL from July 14, 2008, through February 3, 2012. This study was approved by the National Cancer Institute and the institutional review boards of COG and Dana-Farber Cancer Institute member institutions. Informed consent and assent were obtained in accordance with federal guidelines. Dasatinib was supplied by the National Cancer Institute. Inclusion and exclusion criteria were similar to those in AALL0031 except for the inclusion of young adults age 22 to 30 years (Data Supplement).

Risk Stratification

Minimal residual disease (MRD) was assessed by flow cytometry at one of two central reference laboratories at end of induction and after two consolidation cycles.[25] Patients were stratified as high risk (HR) if end-of-induction MRD levels were $\geq$ 1% and/or MRD level was $\geq$ 0.01% at end of consolidation 2; the remaining patients were standard risk (SR). Allogeneic HSCT was recommended after at least 11 weeks of therapy for HR patients and for SR patients with a matched family donor. The remaining SR patients received chemotherapy plus dasatinib for an additional 120 weeks. Patients who underwent HSCT came off protocol-directed therapy at the time of HSCT. The AALL0622 chemotherapy plan was the same as that used in COG AALL0031,[14] with minor modifications (Data Supplement). Only patients with overt CNS leukemia received 18-Gy cranial irradiation.

Dasatinib Therapy

In cohort 1, dasatinib 60 mg/m^2 once daily was administered starting on induction day 15 for 2 weeks of each 3- to 4-week treatment block (discontinuous dasatinib; Data Supplement). By study design, patients continued to be enrolled in cohort 1 until six completed the first intensification block (week 23). If five of six patients completed therapy through week 23 without dose-limiting toxicity (Data Supplement), then patients would be enrolled in cohort 2 and receive dasatinib 60 mg/m^2 per day continuously throughout therapy starting at induction day 15. Dasatinib was not recommended after HSCT, and data were not collected regarding whether patients received TKI post-HSCT or after completion of chemotherapy.

IKZF1 Deletion Analysis

IKZF1 deletions were assessed using the Illumina 2.5 Exome Array (San Diego, CA) as previously described.[26]

Statistical Analysis

Data are current as of December 2016. EFS and overall survival (OS) were calculated based on the date of study enrollment to date of first event or last follow-up. Events included induction failure, relapse at any site, second malignancy, or death. Patients for whom induction did not fail were censored as of the date of last contact. Cumulative incidence rates (CIRs) were estimated using the method of Fine and Gray.[27] Survival curves were constructed using the Kaplan-Meier life table method,[28] with standard errors computed using the method of Peto and Peto.[29] Log-rank tests were used to compare survival curves between groups.[30] Fisher's exact and two-sample χ^2 tests across available categories were used in analyses involving proportions (remission and MRD-positive rates). A two-sided Wilcoxon rank sum test was used to compare times to event for those receiving HSCT or chemotherapy alone. Differences with P values $\leq$ .05 were considered significant.

RESULTS

Patient Characteristics

Sixty-three patients from 47 institutions were enrolled from July 2008 to February 2012 (Data Supplement). Patient characteristics are summarized in Table 1. Two patients were ineligible because they had chronic myeloid leukemia in lymphoid blast crisis. One patient was ineligible because an ECG was not performed before enrollment.

Of 60 eligible patients, 34 completed protocol therapy, which consisted of seven intensive blocks and 10 maintenance blocks of chemotherapy plus dasatinib. Of the patients who did not complete protocol therapy, 19 underwent HSCT; four discontinued protocol therapy for posterior reversible encephalopathy syndrome, poor patient compliance, leukoencephalopathy, or prolonged corrected QT interval, and three experienced events during therapy. The remaining events were relapses that occurred after patients completed therapy or went off protocol for HSCT. Patients were observed for outcome data until they went off study for reasons such as death, loss to follow-up, withdrawal of consent, or enrollment in another study with therapeutic intent after being in follow-up.

Thirty-nine patients were assigned discontinuous dasatinib (cohort 1), and 21 were assigned continuous dasatinib (cohort 2). Four had T-cell immunophenotype, and 56 had B-cell immunophenotype. Table 2 summarizes outcomes and events by risk group.

Summary of Toxicities

The combination of dasatinib plus intensive chemotherapy was found to be safe and feasible. A summary of the toxicities is

Table 1. Patient Characteristics

Characteristic	No. (%) of Eligible Enrollees (N = 60)
Age at diagnosis, years	
Mean	10.2
Range	1.5-27.6
Sex	
Male	40
Female	20
Median WBC count, $\times 10^3/\mu L$	29.2
WBC $\geq$ 50,000 $\times 10^3/\mu L$	25 (42)
Induction failure	0 (0)
CNS2 at diagnosis	7 (12)
CNS3 at diagnosis	4 (7)
Testicular disease at diagnosis	0 (0)*
IKZF1/Ikaros deletions	25 (57)†
HSCT, related sibling	11 (18)
HSCT, matched unrelated donor	8 (13)
T-cell phenotype	4 (7)
Age > 21 years‡	3 (5)

Abbreviation: HSCT, hematopoietic stem-cell transplantation.
*Percentage of male patients.
†Percentage of known deletions.
‡Adult patients.

provided in the Data Supplement. Importantly, no deaths resulting from toxicity occurred in this study.

Impact of Adding TKI Mid-Induction on Early Response Rates

AALL0622 introduced dasatinib on induction day 15, compared with imatinib therapy initiated on day 1 of consolidation 1 in AALL0031. End-of-induction (day 29) complete remission rate was 98% (n = 59) in AALL0622 compared with 89% (n = 91) in AALL0031 (P = .01; Table 3). Furthermore, 59% of AALL0622 versus 25% of AALL0031 patients had MRD < 0.01% at end of induction (P < .001; Table 3). Despite two thirds of AALL0622 patients being treated with discontinuous dasatinib, 89% of AALL0622 patients (n = 57) had MRD < 0.01% at end of consolidation 2 versus 71% treated with continuous imatinib in AALL0031 (n = 48; P = .03; Table 3).

Table 2. Type of Event by Event Time

Event	SR Patients (n = 48)		HR Patients (n = 9)		Not Risk Assigned (n = 3)	
	< 2 Years	≥ 2 Years	< 2 Years	≥ 2 Years	< 2 Years	≥ 2 Years
Relapse, marrow	3	9	2	0	1	0
Relapse, marrow/CNS	0	2	0	0	0	0
Relapse, CNS	1	3	0	0	0	0
Relapse, axilla	0	0	0	0	0	1
SMN	1	0	0	0	0	0
Death as first event	0	1	1	0	0	0
Total	5	15	3	0	1	1

Abbreviations: EFS, event-free survival; HR, high risk; SMN, secondary malignant neoplasm; SR, standard risk.

Table 3. Remission and MRD Status

Status	No. (%) AALL0031	No. (%) AALL0622
End induction marrow status* (P = .01)		
M1	81 (89)	58 (98)
M2	1 (1)	1 (2)
M3	9 (10)	0
End induction MRD (P < .001), %		
< 0.01	19 (25)	34 (59)
0.01-0.099	10 (13)	10 (17)
0.1-0.99	13 (17)	8 (14)
≥ 1	35 (45)	6 (10)
End consolidation MRD (P = .03), %		
< 0.01	34 (71)	51 (89)
0.01-0.099	6 (13)	5 (9)
0.1-0.99	4 (8)	1 (2)
≥ 1	4 (8)	0

Abbreviation: MRD, minimal residual disease.
*M1, < 5% lymphoblasts; M2, 5% to 25% lymphoblasts; M3, > 25% lymphoblasts.

Impact of Dasatinib on EFS and OS

The primary outcome end point of AALL0622 was achievement of 3-year EFS ≥ 60% among SR patients. Three-year EFS (± standard deviation [SD]) in SR patients was 84.6% ± 5.7%. Because relapses continued after 3 years, we continued to observe patients to report 5-year outcomes. For the 60 evaluable patients, 5-year OS and EFS rates (± SDs) were 86% ± 5% and 60% ± 7%, respectively (Figs 1A and 1B). SR patients (n = 48; 19% underwent HSCT in first complete remission [CR1]) had 5-year OS and EFS rates (± SDs) of 87% ± 5% and 61% ± 7%, respectively, and HR patients (n = 9; 89% underwent HSCT in CR1) had 5-year OS and EFS rates (± SDs) of 89% ± 13% and 67% ± 19%, respectively (Figs 1C and 1D). Table 2 summarizes events and whether they occurred early (< 2 years) or late (> 2 years).

Among 60 patients, four (6.7%) had CNS3 status at diagnosis. Despite the addition of dasatinib and substantial CNS-directed chemotherapy, non-HSCT and non-CNS3 patients in AALL0622 had a trend toward increased 5-year CIR (± SD) of isolated or combined CNS relapse of 15.4% ± 5.9% (n = six of 40), compared with 6.6% ± 4.6% (n = two of 31; P = .30) in those treated with continuous imatinib and 12-Gy cranial irradiation in AALL0031.[14,15] Three CNS relapses occurred in each cohort of AALL0622. All CNS relapses occurred in SR patients receiving chemotherapy plus dasatinib. No patient undergoing transplantation, most of whom received CNS irradiation as part of their conditioning, experienced CNS relapse. No AALL0622 patients had testicular leukemia at diagnosis or relapse. Five-year CIR (± SD) for isolated marrow relapse was similar between the two trials (18.0% ± 6.3% in AALL0622 and 23.7% ± 8.0% in AALL0031; P = .97).

There was no difference in OS or disease-free survival between patients receiving imatinib in AALL0031 (cohorts 4 and 5, including patients undergoing HSCT; n = 54) and AALL0622 (cohorts 1 and 2, including those undergoing HSCT; n = 60). Five-year OS (± SD) was 81% ± 6% for AALL0031 versus 86% ± 5% for AALL0622 (P = .63); 5-year disease-free survival (± SD) was 68% ± 7% for AALL0031 versus 60% ± 7% in AALL0622 (P = .31;

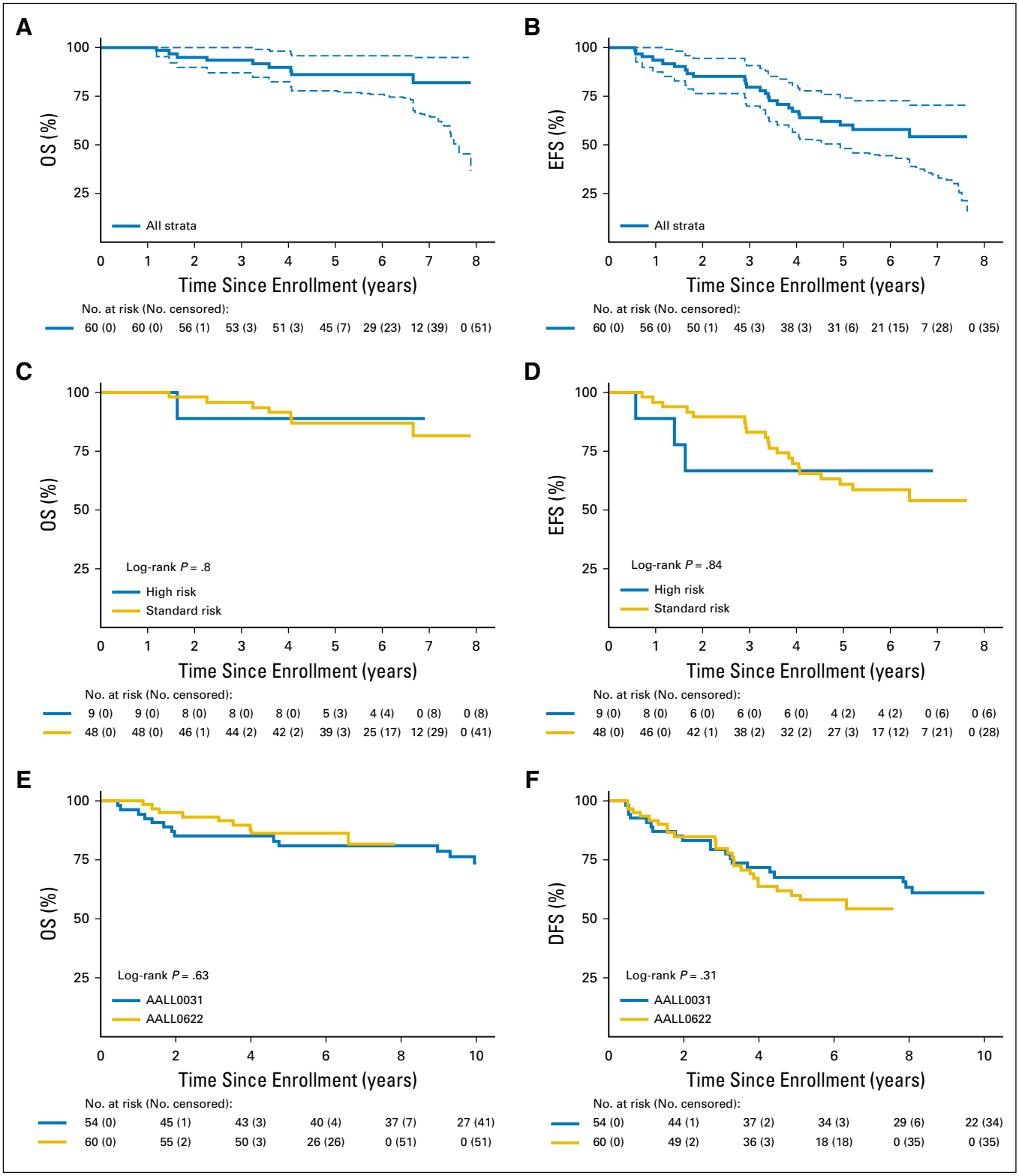

Fig 1. Long-term survival in AALL0622. (A) Overall survival (OS) and (B) Event-free survival (EFS) in whole cohort. (C) OS and (D) EFS by risk group. (E) OS and (F) disease-free survival (DFS) comparison between AALL0031 and AALL0622.

Figs 1E and 1F). Outcomes remained similar between the two trials when analyses were limited to patients age ≤ 21 years. Of the four patients with T-cell ALL, three were SR and one was not assigned to a risk group (HSCT). Two experienced events; one SR patient had a CNS relapse, and the patient not assigned to a risk group had a relapse involving lymph nodes.

Impact of HSCT

AALL0622 recommended HSCT for patients with a matched sibling donor or with high-risk features based on MRD. Nineteen patients underwent HSCT, including eight HR (42%), nine SR (47%, six who had sibling donors), and two non–risk assigned patients (11%) because of lack of MRD data. Four patients did not undergo transplantation according to protocol guidelines; three SR patients underwent unrelated HSCT, and one patient underwent HSCT in maintenance rather than after consolidation 2. Transplantation-preparative regimens and supportive care were provided at the discretion of the local centers.

Outcomes for patients receiving HSCT and chemotherapy alone are compared in Figure 2. There were a total of 48 patients deemed SR based on response, nine of whom underwent HSCT based on the presence of a matched sibling donor (n = 6) or physician or patient choice (n = 3). Among the remaining 39 SR patients, 33 completed protocol therapy in CR1 (dropouts, n = 3; relapses, n = 2; and secondary malignant neoplasm during therapy, n = 1). Of these 33 patients, 13 subsequently relapsed (and another died as a result of unrelated cause).

OS and EFS rates were similar in patients receiving chemotherapy plus dasatinib and chemotherapy plus dasatinib before HSCT (5-year OS [± SD], 88% ± 5% *v* 83% ± 10%; $P = .71$ and EFS, 60% ± 8% *v* 61% ± 13%; $P = .84$). Importantly, nearly half of the patients undergoing HSCT were HR based on MRD (n = 8 of 19). However, 5-year EFS (± SD) was 63% ± 19% (n = 8) in HR and 76% ± 17% (n = 9) in SR patients who received HSCT, compared with 59% ± 8% (n = 39) in SR patients receiving chemotherapy plus dasatinib, although these analyses were hindered by small patient numbers. Only one HR patient received dasatinib plus chemotherapy, and this patient remained in CR1. Events occurred significantly earlier in patients undergoing HSCT versus those receiving chemotherapy, with median time to first event of 506 versus 1,275 days, respectively ($P = .002$).

Impact of IKZF1 *Deletions on Outcome*

We analyzed diagnostic specimens from 44 patients who had adequate banked material for the presence of *IKZF1* deletions. An *IKZF1* deletion was present in 56.8% of tested AALL0622 patients (n = 25 of 44) and was associated with significantly inferior outcomes (5-year OS [± SD], 80% ± 8% *v* 100%; $P = .04$ and EFS [± SD], 52% ± 10% *v* 82% ± 10%; $P = .04$, respectively; Figs 3A and 3B). Among the SR patients, 58.8% (20 of 34) had *IKZF1* deletions, which were associated with inferior OS and EFS (5-year OS [± SD], 80% ± 9% *v* 100%; $P = .07$ and EFS [± SD], 50% ± 11% *v* 83% ± 13%; $P = .04$; Figs 3C and 3D). Half (four of eight) of tested HR patients had *IKZF1* deletions, which were not predictive of outcome, with 5-year OS of 100% for both groups and 5-year EFS (± SD) of 75% ± 22% for those with deletions and 75% ± 38% for those without deletions.

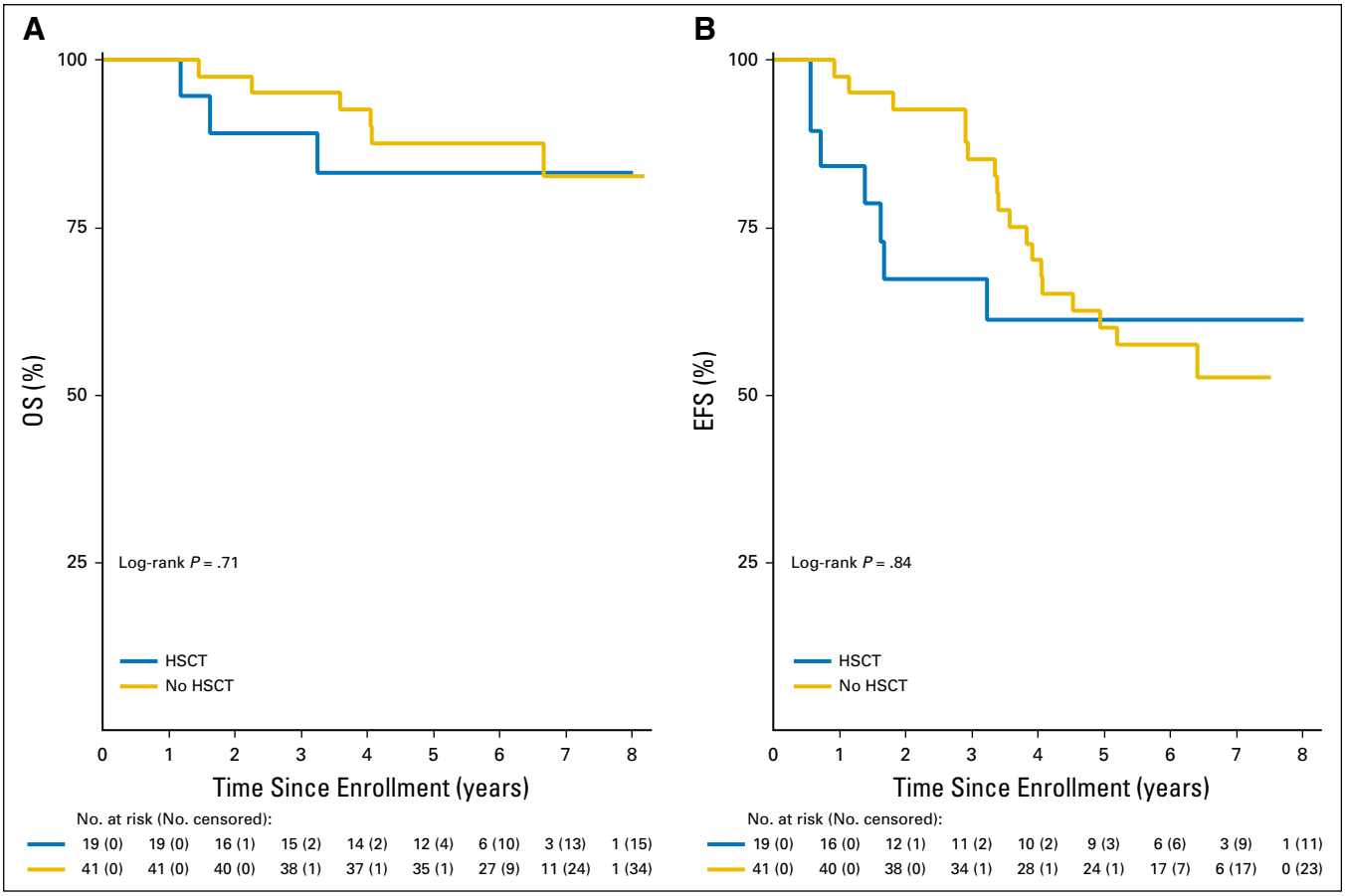

Fig 2. Outcomes comparing patients who underwent and did not undergo bone marrow transplantation: (A) Overall survival (OS) and (B) event-free survival (EFS).

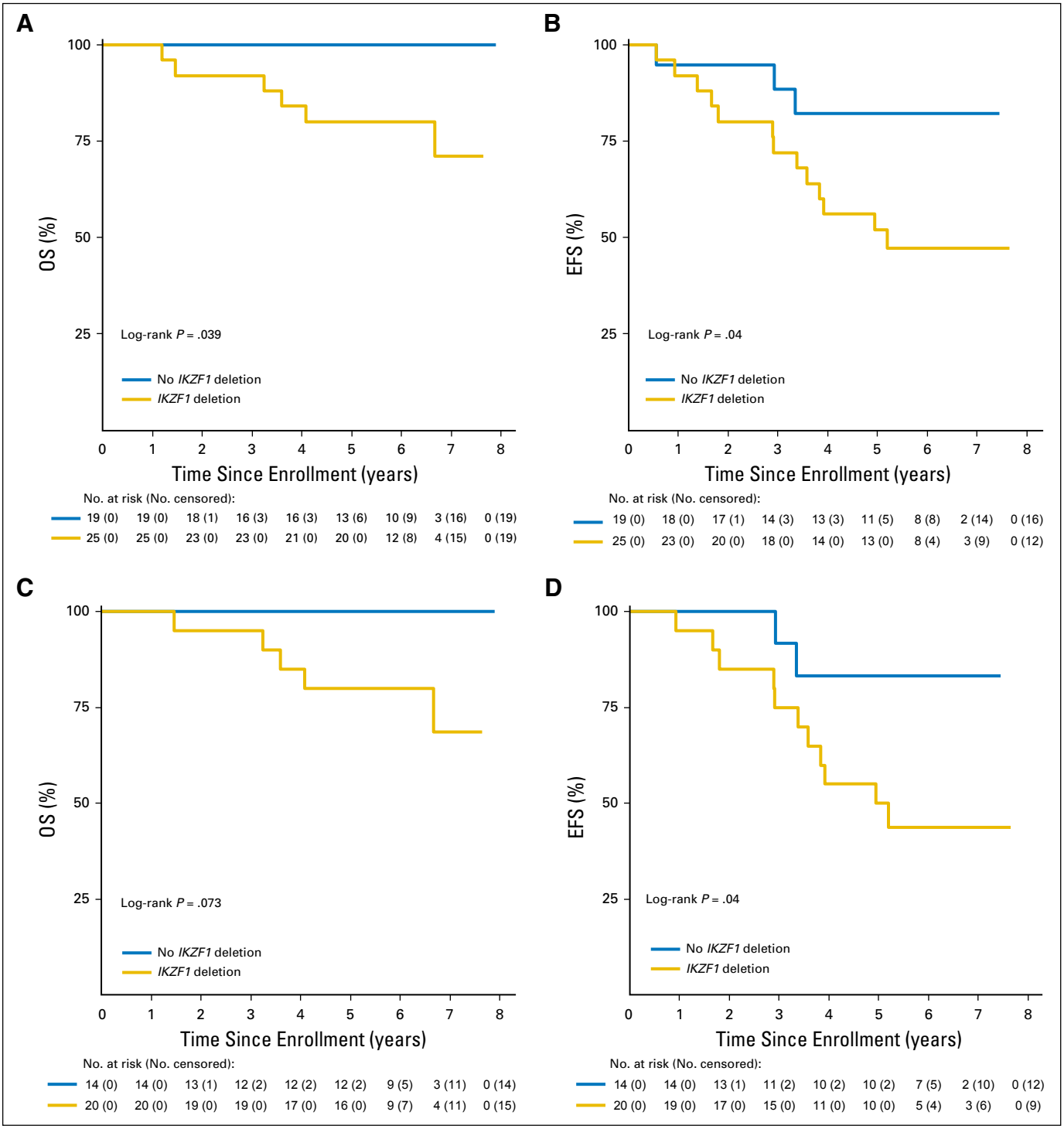

Fig 3. Outcomes based on presence or absence of an Ikaros deletion. (A) Overall survival (OS) and (B) event-free survival (EFS) in whole cohort based on presence of *IKZF1* deletion. (C) OS and (D) EFS in standard-risk patients based on presence of *IKZF1* deletion.

DISCUSSION

AALL0622, the first pediatric cooperative group study to our knowledge of using dasatinib in Ph-positive ALL, met its primary safety and efficacy aims. Two additional pediatric cooperative group Ph-positive ALL trials, COG AALL0031[14,15] and the EsPhALL trial,[16] used imatinib as the TKI. All three trials had small patient numbers, the largest being EsPhALL with 178 participants.[16] Given the limitations of small size, the outcomes in these three trials were similar. EFS rates were 60% for AALL0622 (5 years), 61.9% for EsPhALL (4 years),[16] and 58% overall for AALL0031 (5 years).[15] For AALL0031

cohort 5, which used continuous imatinib, 5-year EFS was 63% for those undergoing unrelated-donor HSCT, 64% for those undergoing related-donor HSCT, and 71% for those receiving chemotherapy alone. Overall survival rates for these trials were 86% for AALL0622 (5 years), 72.1% for EsPhALL (4 years),[16] and 70% for AALL0031 overall (5 years).[15] The apparent better OS rate in AALL0622 may reflect that only approximately one third of patients underwent HSCT in first remission, compared with 80% in the EsPhALL trial. It is notable that 5-year OS rate in AALL0622 approaches that of all children with ALL treated in COG trials from 2000 to 2005 (90%).[2] However, the 4- and 5-year EFS rates of approximately 60% in these three Ph-positive ALL trials are much lower than the expected approximately 85% EFS rate for unselected patients with ALL.[31,32] The discussion will focus on ways to potentially improve EFS rates for children with Ph-positive ALL.

In AALL0622, early responses to dasatinib plus chemotherapy based on MRD by flow cytometry were impressive. The improved induction success rate and reduced rate of detectable MRD at the end of consolidation may reflect in part the addition of TKI earlier in treatment in AALL0622 compared with AALL0031 (week 3 *v* 5, respectively). Detection of MRD at the end of induction is usually a powerful predictor of relapse in children with ALL.[25,33-37] However, improved early response did not translate to improved EFS. Why did the improved early response not lead to better outcomes in AALL0622 versus AALL0031 or EsPhALL? Most patients in AALL0622 received dasatinib discontinuously. Continuous rather than discontinuous imatinib exposure led to better outcomes in AALL0031. However, AALL0622 was closed before we could fully test the effect of providing dasatinib continuously. A second possibility that could explain the lack of improvement is the reduction from 9 to 7 high-dose methotrexate doses. We consider this to be less likely, because this is almost double the number of high methotrexate doses used in other pediatric trials that have had better leukemia control and much lower CNS relapse rates.[38,39]

Our study posited that dasatinib would replace CNS irradiation to prevent CNS relapse. However, the cumulative incidence of isolated and combined CNS relapses for patients treated without radiotherapy in AALL0622 was surprisingly high at 15%, compared with 6% in AALL0031, where all patients received radiotherapy. Most patients in the original EsPhALL cohort underwent HSCT, and so these data cannot be compared easily. Results from the recently completed COG AALL1122 trial will more definitively explore the consequence of eliminating radiotherapy in CNS relapse in a larger cohort of children with Ph-positive ALL treated with dasatinib.

AALL0622 used HSCT to control resistant leukemia in HR (MRD-positive) patients but also recommended transplantation in SR patients with sibling donors. Five-year OS in SR patients, most of whom did not undergo transplantation, was 87%, suggesting that if relapse occurred, salvage by HSCT in second remission may have been possible in many of these patients. Thus, the results of our trial suggest that HSCT may not be necessary in SR patients, and the availability of a sibling donor should not be considered an indication for HSCT. For HR patients, HSCT was associated with OS and EFS comparable to SR patients, suggesting that HSCT abrogated the adverse prognostic significance of high MRD in these patients.

We made no recommendations regarding clearing MRD before HSCT in this study. At the time this study was conducted, it was not known that MRD levels before HSCT significantly predicted outcomes in ALL.[40-43] Although patients undergoing HSCT received dasatinib for only 6 to 10 weeks before transplantation, additional TKI exposure pre- or post-HSCT may not improve outcomes in patients with suboptimal early responses. Immuotherapy such as blinotumomab[44,45] or rapid reduction of immunosuppression post-transplantation[42] could improve outcomes in HR patients.

Our data support measuring *IKZF1* deletions to identify HR patients. Patients harboring *IKZF1* deletions had significantly inferior outcomes. Conversely, those with wild-type *IKZF1* had 5-year OS of 100%. These data are consistent with other studies showing that *IKZF1* deletion confers poor prognosis in Ph-positive ALL.[12,13] Furthermore, *IKZF1* deletions were associated with a higher risk of relapse in patients who were SR based on MRD. Additional data from more recent trials in which fewer patients received HSCT will be necessary to see if this is a consistent finding that merits a change in risk stratification.

AALL0622 compared outcomes with historical controls. AALL0622 closed early to open COG AALL1122 (ClinicalTrials.gov identifier: NCT01460160), using dasatinib with EsPhALL chemotherapy backbone, leading to a smaller number of patients enrolled in cohort 2 than planned.

In conclusion, AALL0622 established that dasatinib was well tolerated with intensive chemotherapy. The addition of dasatinib during induction led to better early response rates but not improved EFS relative to AALL0031, in part because of increased CNS relapse. We cannot yet conclude that the current dasatinib plus chemotherapy combination is better than imatinib plus chemotherapy, but results using dasatinib were at least similar to those of AALL0031 using imatinib. The favorable 5-year OS of 88% in patients receiving chemotherapy plus dasatinib without HSCT demonstrates that most children with Ph-positive ALL should not undergo transplantation in first remission. Our study suggests that screening for *IKZF1* deletions might be added to assessment of early response rates to identify low-risk Ph-positive patients who do not need transplantation and high-risk Ph-positive patients who may be suitable candidates for HSCT and/or alternative therapies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: William B. Slayton, Kirk R. Schultz, John A. Kairalla, Meenakshi Devidas, Michael A. Pulsipher, Bill H. Chang, Michael J. Borowitz, Sherri L. Mizrahy, Thomas Merchant, Lance Sieger, Marilyn J. Siegel, Elizabeth A. Raetz, Naomi J. Winick, Mignon L. Loh, William L. Carroll, Stephen P. Hunger

Provision of study materials or patients: William B. Slayton, Valerie I. Brown

Collection and assembly of data: William B. Slayton, John A. Kairalla, Meenakshi Devidas, Charles Mullighan, Ilaria Iacobucci, Lewis B. Silverman, Michael J. Borowitz, Andrew J. Carroll, Nyla A. Heerema, Julie M. Gastier-Foster, Brent L. Wood

Data analysis and interpretation: William B. Slayton, Kirk R. Schultz, Meenakshi Devidas, Xinlei Mi, Charles Mullighan, Lewis B. Silverman, Michael J. Borowitz, Valerie I. Brown, Stephen P. Hunger

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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Affiliations

William B. Slayton, **John A. Kairalla**, **Meenakshi Devidas**, **Xinlei Mi**, and **Sherri L. Mizrahy**, University of Florida, Gainesville, FL; **Kirk R. Schultz**, BC Children's Research Institute, University of British Columbia, Vancouver, British Columbia, Canada; **Michael A. Pulsipher**, Children's Hospital of Los Angeles, Los Angeles; **Lance Sieger**, University of California Los Angles–Harbor, Torrance; **Mignon L. Loh**, University of California San Francisco, San Francisco, CA; **Bill H. Chang**, Oregon Health and Science University, Portland, OR; **Charles Mullighan**, **Ilaria Iacobucci**, and **Thomas Merchant**, St Jude's Research Hospital, Memphis, TN; **Lewis B. Silverman**,

Dana-Farber Cancer Institute, Boston, MA; **Michael J. Borowitz**, Johns Hopkins University, Baltimore, MD; **Andrew J. Carroll**, University of Alabama at Birmingham, Birmingham, AL; **Nyla A. Heerema**, Ohio State University; **Julie M. Gastier-Foster**, Nationwide Children's Hospital, Columbus, OH; **Brent L. Wood**, University of Washington Seattle, Seattle, WA; **Valerie I. Brown**, Penn State Health Children's Hospital, Hershey; **Stephen P. Hunger**, Children's Hospital of Philadelphia, Philadelphia, PA; **Marilyn J. Siegel**, Washington University School of Medicine, St Louis, MO; **Elizabeth A. Raetz**, University of Utah, Salt Lake City, UT; **Naomi J. Winick**, University of Texas Southwestern Medical Center, Dallas, TX; and **William L. Carroll**, New York University Langone Health Center, New York, NY.

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William B. Slayton
No relationship to disclose

Kirk R. Schultz
Honoraria: Jazz Pharmaceuticals, Janssen Oncology
Consulting or Advisory Role: Juno Therapeutics, Mesoblast
Travel, Accommodations, Expenses: Jazz Pharmaceuticals, Janssen Oncology

John A. Kairalla
Stock or Other Ownership: Johnson & Johnson, Sophiris Bio

Meenakshi Devidas
Honoraria: Pfizer, Novartis, PSI CRO

Xinlei Mi
No relationship to disclose

Michael A. Pulsipher
Consulting or Advisory Role: Novartis, Jazz Pharmaceuticals
Speakers' Bureau: Novartis
Research Funding: Adaptive Biotechnologies
Travel, Accommodations, Expenses: Medac, Amgen

Bill H. Chang
No relationship to disclose

Charles Mullighan
Honoraria: Amgen
Consulting or Advisory Role: TRM Oncology
Speakers' Bureau: Amgen
Research Funding: Loxo Oncology
Travel, Accommodations, Expenses: Amgen

Ilaria Iacobucci
No relationship to disclose

Lewis B. Silverman
No relationship to disclose

Michael J. Borowitz
Honoraria: Beckman Coulter
Consulting or Advisory Role: HTG Molecular Diagnostics
Research Funding: Becton Dickinson, Bristol-Myers Squibb

Andrew J. Carroll
No relationship to disclose

Nyla A. Heerema
No relationship to disclose

Julie M. Gastier-Foster
Research Funding: Bristol-Myers Squibb (Inst), Incyte (Inst)

Brent L. Wood
Honoraria: Seattle Genetics, Amgen
Consulting or Advisory Role: Spectrum Pharmaceuticals
Research Funding: Seattle Genetics (Inst), Amgen (Inst), Juno Therapeutics (Inst), BiolineRx (Inst), Coronado Biosciences (Inst), JW Pharmaceutical (Inst), MedImmune (Inst), Stemline Therapeutics (Inst)
Travel, Accommodations, Expenses: Amgen

Sherri L. Mizrahy
No relationship to disclose

Thomas Merchant
Travel, Accommodations, Expenses: Philips Healthcare

Valerie I. Brown
No relationship to disclose

Lance Sieger
Stock or Other Ownership: Amgen, Merck, Pfizer, Celgene

Marilyn J. Siegel
Honoraria: Siemens Healthcare Diagnostics
Consulting or Advisory Role: General Electric Healthcare (I)
Speakers' Bureau: Siemens Healthcare Diagnostics
Travel, Accommodations, Expenses: Siemens Healthcare Diagnostics

Elizabeth A. Raetz
No relationship to disclose

Naomi J. Winick
No relationship to disclose

Mignon L. Loh
No relationship to disclose

William L. Carroll
No relationship to disclose

Stephen P. Hunger
Stock or Other Ownership: Amgen, Merck (I), Amgen (I), Pfizer (I)
Honoraria: Jazz Pharmaceuticals, Spectrum Pharmaceuticals, Erytech Pharma
Consulting or Advisory Role: Novartis