Title

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Journal

Journal of Clinical Oncology, 41(31)

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Publication Date

2023-11-01

DOI

10.1200/JCO.23.00045

Peer reviewed

Outcomes After Preoperative Chemoradiation With or Without Pazopanib in Non-Rhabdomyosarcoma Soft Tissue Sarcoma: A Report From Children's Oncology Group and NRG Oncology

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DOI https://doi.org/10.1200/JCO.23.00045

ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

ARST1321 was a phase II study designed to compare the near complete pathologic response rate after preoperative chemoradiation with/without pazopanib in children and adults with intermediate-/high-risk chemotherapy-sensitive body wall/extremity non-Rhabdomyosarcoma Soft Tissue Sarcoma (ClinicalTrials.gov identifier: NCT02180867). Enrollment was stopped early following a predetermined interim analysis that found the rate of near complete pathologic response to be significantly greater with the addition of pazopanib. As a planned secondary aim of the study, the outcome data for this cohort were analyzed. Eight-five eligible patients were randomly assigned to receive (regimen A) or not receive (regimen B) pazopanib in combination with ifosfamide and doxorubicin + preoperative radiotherapy followed by primary resection at week 13 and then further chemotherapy at week 25. As of December 31, 2021, at a median survivor follow-up of 3.3 years (range, 0.1-5.8 years), the 3-year event-free survival for all patients in the intent-to-treat analysis was 52.5% (95% CI, 34.8 to 70.2) for regimen A and 50.6% (95% CI, 32 to 69.2) for regimen B (P = .8677, log-rank test); the 3-year overall survival was 75.7% (95% CI, 59.7 to 91.7) for regimen A and 65.4% (95% CI, 48.1 to 82.7) for regimen B (P = .1919, log-rank test). Although the rate of near complete pathologic response was significantly greater with the addition of pazopanib, outcomes were not statistically significantly different between the two regimens.

ACCOMPANYING CONTENT

Data Supplement

Protocol

Accepted June 27, 2023

Published July 31, 2023

J Clin Oncol 41:4842-4848

View Online Article

INTRODUCTION

Pazopanib is a multitargeted tyrosine kinase inhibitor with activity in advanced soft tissue sarcoma. ARST1321 was a phase II study designed to compare the near complete pathologic response rate (≥90% necrosis) after preoperative chemoradiation with or without pazopanib in children and adults with large, unresected, intermediate- or high-grade body wall/extremity soft tissue sarcoma (ClinicalTrials.gov identifier: NCT02180867). Enrollment was stopped early after a predetermined interim analysis that found the rate of near complete pathologic response to be significantly greater with the addition of pazopanib.[1] We now report the 3-year survival outcomes as part of a planned secondary analysis of the study, along with updated toxicity data.

METHODS

Study Design

Details of the study design of ARST1321 have been published previously.[1] After a dose-finding phase, patients were randomly assigned 1:1, stratified by age (younger than 18 years *v* 18 years and older), and localized versus metastatic disease, and synovial sarcoma versus other histology, to receive (regimen A) or not receive (regimen B) pazopanib (younger than 18 years: 350 mg/m² once daily; 18 years and older: 600 mg once daily) in combination with ifosfamide (2.5 g/m² once daily for 3 days) and doxorubicin (37.5 mg/m² once daily for 2 days) + 45 Gy preoperative radiation therapy followed by primary resection at week 13 and then further

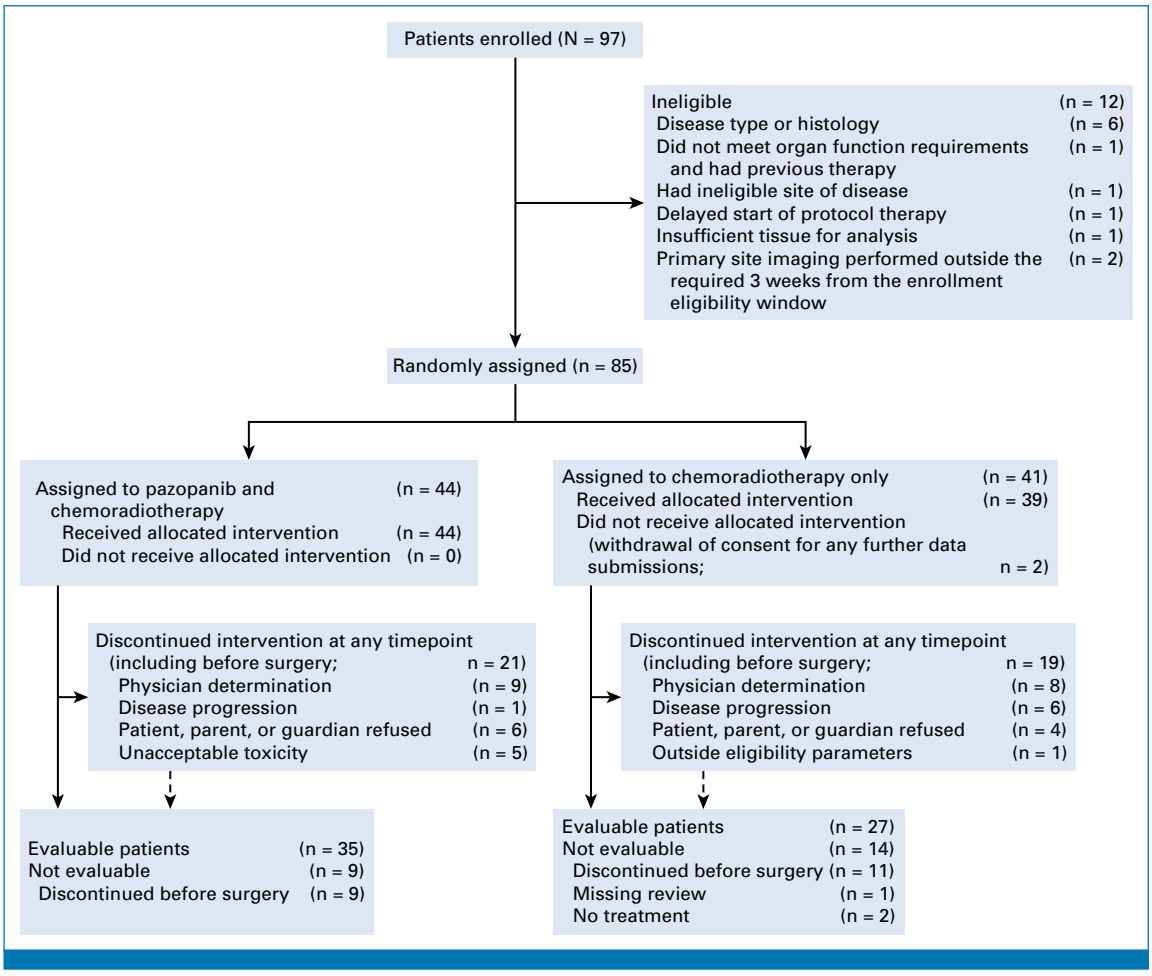

FIG 1. CONSORT diagram.

chemotherapy at week 25 (cumulative doses: ifosfamide 45 g/m^2 and doxorubicin 375 mg/m^2). The trial was approved by the Pediatric Central Institutional Review Board of the National Cancer Institute and by the institutional review boards of each participating institution, as required. Informed consent from the patient or the parent or guardian and patient assent as appropriate was obtained before enrollment.

End Points

Event-free survival (EFS) was defined as the time from study enrollment to first progression/recurrence, a secondary cancer, or death from any cause. Overall survival (OS) was defined as time from study enrollment to death from any cause. Survival was estimated by the Kaplan-Meier method, and the Peto-Peto method was used to estimate the SE of the Kaplan-Meier estimate. The data cutoff for this report was December 31, 2021. The OS and EFS distributions were compared by demographics and patient history using the log-rank test. All variables with a P value of <.1 were subsequently included in the multivariable Cox regression model. The proportional hazards assumption was assessed for all significant univariate variables. A P value of <.05 was considered statistically significant. A subgroup analysis was also performed with the estimated difference in 3-year OS and EFS between the two regimen arms and the 95% CI. Descriptive analyses were planned for EFS and OS as a secondary aim of the study (estimate survival and SE). The comparison of EFS and OS by patient characteristics and clinical history, subgroup, univariate, and multivariable analyses are ad hoc analyses and were not included within the study protocol as planned analyses.

RESULTS

Baseline Demographics and Patient History

From July 7, 2014, to October 1, 2018, 85 eligible patients were enrolled and randomly assigned. Figure 1 shows the CONSORT diagram for this study. Baseline demographics are presented in Table 1. When comparing the baseline characteristics of the subset of patients with evaluable pathologic response with those who did not have evaluable pathologic response, no differences were found between the two groups (Data Supplement, Table S1 [online only]).

TABLE 1. Patient Demographics and Disease Characteristics

Characteristic	Total	Regimen A[a] (n = 44)	Regimen B[b] (n = 41)	*P*
Age, years				
Median (range)	22.1 (5.7-73.5)	22.0 (5.7-71.3)	22.1 (7.3-73.5)	
Younger than 18	30 (35.3)	14 (31.8)	16 (39.0)	.4872[c]
18 and older	55 (64.7)	30 (68.2)	25 (61.0)	
Sex, No. (%)				
Male	42 (49.4)	16 (36.4)	26 (63.4)	.0127[c]
Female	43 (50.6)	28 (63.6)	15 (36.6)	
Tumor size, cm, median (IQR)	10.6 (8.5-15.4)	11.2 (8.6-15.1)	10.2 (8.4-15.7)	
Primary site, No. (%)				
Extremity	73 (85.9)	39 (88.6)	34 (82.9)	.6217[c]
Trunk	11 (12.9)	5 (11.4)	6 (14.6)	
Unknown	1 (1.2)	0 (0.0)	1 (2.4)	
T stage, No. (%)				
T2a	13 (15.3)	6 (13.6)	7 (17.1)	.0686[d]
T2b	62 (72.9)	30 (68.2)	32 (78.0)	
Tx	9 (10.6)	8 (18.2)	1 (2.4)	
Unknown	1 (1.2)	0 (0.0)	1 (2.4)	
N stage, No. (%)				
N0	58 (68.2)	28 (63.6)	30 (73.2)	.3291[c]
N1	11 (12.9)	8 (18.2)	3 (7.3)	
Nx	15 (17.6)	8 (18.2)	7 (17.1)	
Unknown	1 (1.2)	0 (0.0)	1 (2.4)	
Metastases, No. (%)				
None	63 (74.1)	32 (72.7)	31 (75.6)	>.999[d]
Lung only	13 (15.3)	7 (15.9)	6 (14.6)	
Others	9 (10.6)	5 (11.4)	4 (9.8)	
Histology, No. (%)				
Synovial sarcoma	45 (52.9)	24 (54.5)	21 (51.2)	.7669[d]
Undifferentiated pleomorphic sarcoma	19 (22.4)	9 (20.5)	10 (24.4)	
Liposarcoma	6 (7.1)	4 (9.1)	2 (4.9)	
Undifferentiated sarcoma NOS	6 (7.1)	3 (6.8)	3 (7.3)	
Leiomyosarcoma	4 (4.7)	3 (6.8)	1 (2.4)	
Embryonal sarcoma (undifferentiated sarcoma) of the liver	4 (4.7)	1 (2.3)	3 (7.3)	
Mesenchymal chondrosarcoma	1 (1.2)	0 (0.0)	1 (2.4)	

[a]Regimen A = chemoradiation + pazopanib.
[b]Regimen B = chemoradiation.
[c]Chi-square *P* value.
[d]Fisher's exact *P* value.

EFS and OS

At a median survivor follow-up of 3.3 years (range, 0.1-5.8 years), the 3-year EFS for all patients in the intent-to-treat analysis was 52.5% (95% CI, 34.8 to 70.2) for regimen A and 50.6% (95% CI, 32 to 69.2) for regimen B. There was no statistically significant difference in the distribution of EFS between regimens A and B ($P = .8677$, log-rank test; Fig 2A). The 3-year OS was 75.7% (95% CI, 59.7 to 91.7) for regimen A and 65.4% (95% CI, 48.1 to 82.7) for regimen B. There was no statistically significant difference in the distribution of OS between regimens A and B ($P = .1919$, log-rank test; Fig 2B). There were more deaths as a result of disease on regimen B (Data Supplement, Table S2), and more patients on regimen B were removed from the protocol/study for physician determination and because of secondary to progressive disease before the Week 13 timepoint (Data Supplement, Table S3).

Univariate, Multivariate, and Subgroup Analyses

When combining all patients on regimens A and B, age ≥18 years, male sex, metastatic disease status, and N1

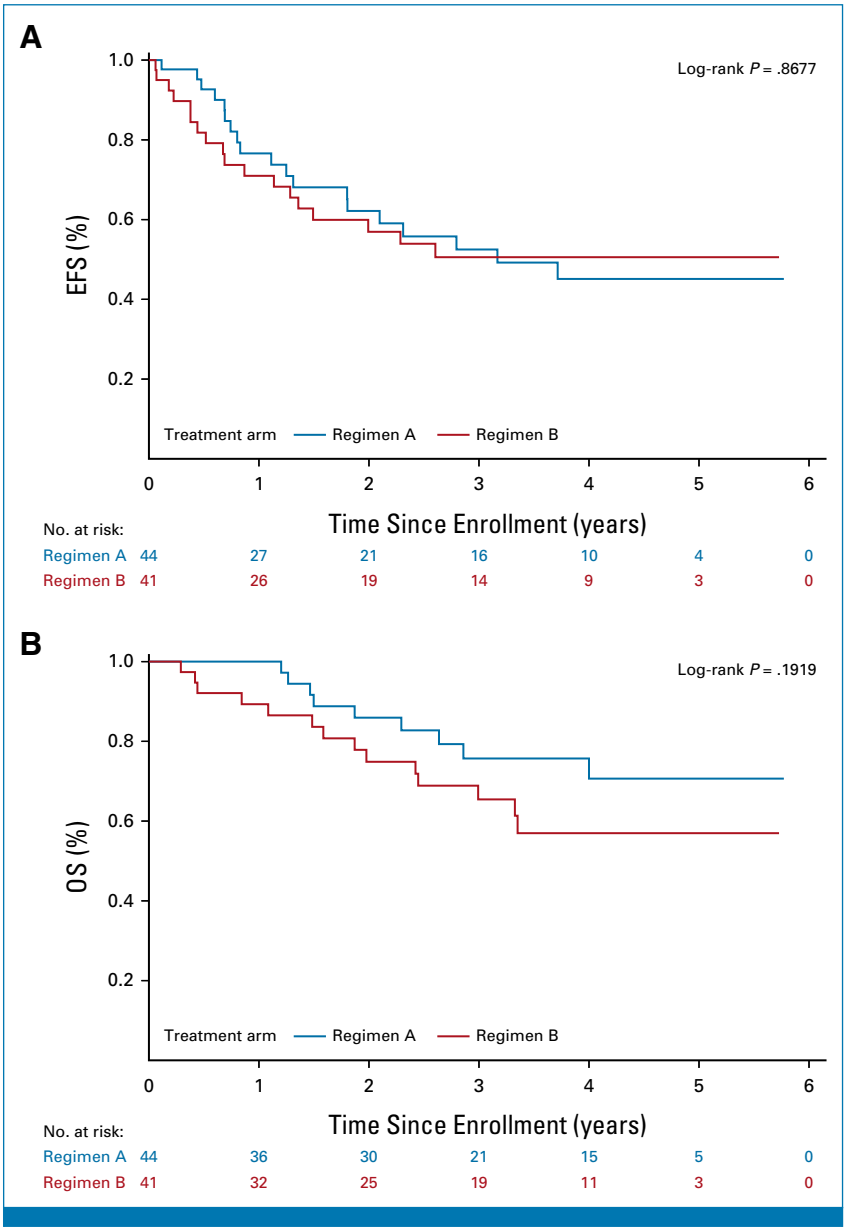

FIG 2. Outcome analyses (intent-to-treat population) showing Kaplan-Meier estimate of (A) 3-year EFS and (B) 3-year OS for regimens A (pazopanib) and B (no pazopanib). EFS, event-free survival; OS, overall survival.

status were significantly associated with inferior EFS on univariate analysis (Data Supplement, Table S4). Only metastatic status and N1 status were associated with statistically significant inferior OS. On multivariate analysis, male sex and metastatic disease status were statistically significant for inferior EFS and male sex was the only variable significantly associated with inferior OS (Data Supplement, Table S5). There were no patient subgroups in which the difference between regimen A and regimen B was statistically significant for either EFS or OS (Data Supplement, Tables S6 and S7).

Safety

The incidence of adverse events was greater with the addition of pazopanib, particularly during the induction and consolidation phases (Data Supplement, Table S8). The most common toxicities in both groups were febrile neutropenia and myelotoxicity. Although there was a higher incidence of myelotoxicity in patients 18 years and older during the induction phase, the frequency of febrile neutropenia was similar to that of the younger age group (Data Supplement, Table S9). There was a higher incidence of wound complications for patients receiving pazopanib.

DISCUSSION

Although the rate of near complete pathologic response was significantly greater with the addition of pazopanib to preoperative chemoradiation at the time of the predetermined statistical landmark in children and adults with intermediate-/high-risk body wall/extremity soft tissue sarcoma and led to early study closure, acknowledging trial design and patient sample size limitations, no statistically significant differences in EFS and OS were observed between the two regimens. At the time this study was designed, there was evidence to suggest that pathologic response may be a reliable predictor of outcome in soft tissue sarcoma for a similarly treated population of patients.[2-4] Subsequent analyses have largely demonstrated supportive findings.[5,6]

However, in a more recent publication involving children and young adults with synovial sarcoma treated with nearly identical neoadjuvant chemoradiotherapy backbone therapy as in our study, patients with ≥90% tumor necrosis had statistically marginally worse outcomes when compared with patients with <90% tumor necrosis (EFS 37.5% *v* 61.6%, $P = .072$; OS 47.4% *v* 68.5, $P = .0998$).[7] Another recently conducted single-institution study of adults with extremity and trunk soft tissue sarcoma treated with neoadjuvant therapy similarly found that necrosis predicted worse outcome and positively correlated with size and grade.[8] An explanation for the discordant findings among these various studies is unclear. In an attempt to identify subsets of patients who may benefit from the addition of pazopanib, we were unable to find any variables that predicted outcome when comparing the two regimens.

An important limitation of this analysis is that our study was not designed to detect a difference in outcome between the two chemoradiotherapy study arms. Although the OS curves did not reach statistical significance, they are nonoverlapping; thus, it is possible that a difference in outcome was present, but the study was inadequately powered to detect it. We were unable to better understand the discrepancy observed between EFS and OS outcomes. It could have simply been due to the small number of patients in this analysis and the fact that a larger number would have detected a difference. Furthermore, the difference might have been due to factors that we are currently not aware of or unable to evaluate on the basis of the limitations of our data collection forms. Other sarcoma studies with outcome as primary end points have demonstrated statistically significant improvements in OS in the absence of similar corresponding findings in EFS.[9,10]

In the pivotal phase III randomized trial of pazopanib in adults with advanced (progressive and metastatic disease after at least one anthracycline-containing regimen) soft tissue sarcoma that led to Food and Drug Administration approval for single-agent use (PALETTE), an improvement in progression-free survival was demonstrated.[11] When comparing our study results with PALETTE, there is a suggestion that the timing and manner of pazopanib incorporation may be important. Specifically, pazopanib may be best reserved for the relapse setting and/or combined with a different chemotherapy regimen since its upfront incorporation and concurrent use with ifosfamide and doxorubicin did not provide similar benefit.[12] There may be a role for TKIs as maintenance therapy in soft tissue sarcoma, particularly for those at highest risk for relapse.[13] In addition, although adverse events observed in our trial were mostly expected and manageable, patients receiving pazopanib did experience increased toxicities, which need to be considered in designing future studies and balanced with the overall goals of therapy.

Ultimately, it is possible that pathologic necrosis may not be an accurate measure of treatment response. Instead, it may simply reflect an inherently more aggressive tumor biology. The identification of predictive and reproducible biomarkers of response and outcome is needed for soft tissue sarcoma, particularly at earlier therapy timepoints. Less invasive diagnostic techniques such as fluorodeoxyglucose positron emission tomography and circulating tumor DNA are particularly appealing and are actively being evaluated in this setting.[14,15] Within the statistical limitations of our analysis, however, pathologic response cannot be considered a surrogate marker of response and predictor of outcome in pediatric and adult patients with extremity and trunk soft tissue sarcoma treated with neoadjuvant chemoradiotherapy and pazopanib.

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PRIOR PRESENTATION

Presented in part at the ASCO annual meeting, Chicago, IL, June 3-7, 2022.

SUPPORT

National Clinical Trials Network Operations Center Grant U10CA180886; National Clinical Trials Network Statistics & Data Center Grant U10CA180899; National Cancer Institute IROC Operations Grant CA180803; St Baldrick's Foundation; and Seattle Children's Foundation, from Kat's Crew Guild through the Sarcoma Research Fund.

CLINICAL TRIAL INFORMATION

NCT02180867

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.23.00045.

DATA SHARING STATEMENT

An individual level deidentified data set containing the variables analyzed in this paper can be expected to be available upon request. Requests for access to Children's Oncology Group (COG) protocol research data should be sent to datarequest@childrensoncologygroup.org. Data are available to researchers whose proposed analysis is found by COG to be feasible and of scientific merit and who agree to the terms and conditions of use. In addition, release of data collected in a clinical trial conducted under a binding collaborative agreement between COG or the National Cancer Institute Cancer Therapy Evaluation Program and a pharmaceutical or biotechnology company must comply with the data sharing terms of the binding collaborative and contractual agreement and must receive the proper approvals. The study protocol is provided in the Data Supplement.

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ACKNOWLEDGMENT

We gratefully acknowledge all the patients and their families, care providers, and research personnel who participated in this study, and a special thank you to the staff at the Operations Center of the Children's Oncology Group for all their assistance in shepherding this study from inception to completion.

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No other potential conflicts of interest were reported.