Original Investigation

First-Line Aldoxorubicin vs Doxorubicin in Metastatic or Locally Advanced Unresectable Soft-Tissue Sarcoma
A Phase 2b Randomized Clinical Trial

Sant P. Chawla, MD; Zsuzsanna Papai, MD; Guzel Mukhametshina, MD; Kamalesh Sankhala, MD; Leonid Vasylyev, MD; Alexander Fedenko, MD; Kenneth Khamly, MD; Kristen Ganjoo, MD; Rajnish Nagarkar, MD; Scott Wieland, PhD; Daniel J. Levitt, MD

IMPORTANCE Standard therapy for advanced soft-tissue sarcoma has not changed substantially in decades, and patient prognosis remains poor. Aldoxorubicin, a novel albumin-binding prodrug of doxorubicin, showed clinical activity against advanced soft-tissue sarcoma in phase 1 studies.

OBJECTIVE To evaluate efficacy and safety of aldoxorubicin vs doxorubicin in patients with advanced soft-tissue sarcoma.

DESIGN, SETTING, AND PARTICIPANTS International, multicenter, phase 2b, open-label, randomized study at general community practices, private practices, or institutional practices. Between August 2012 and December 2013, 140 patients with previously untreated locally advanced, unresectable, or metastatic soft-tissue sarcoma were screened.

INTERVENTIONS Randomization (2:1) to aldoxorubicin 350 mg/m^2 (dose equivalent to doxorubicin 260 mg/m^2) or doxorubicin 75 mg/m^2, administered once every 3 weeks for up to 6 cycles.

MAIN OUTCOMES AND MEASURES Primary end point was progression-free survival. Secondary end points were 6-month progression-free survival, overall survival, tumor response rate, and safety. All efficacy end points were evaluated by independent and local review.

RESULTS A total of 126 patients were randomized, and 123 received aldoxorubicin (n = 83) or doxorubicin (n = 40). Median (range) patient age was 54.0 (21-77 years); 42 (34%) had leiomyosarcoma. By independent review, median progression-free survival was significantly improved (5.6 [95% CI, 3.0-8.1] vs 2.7 [95% CI, 1.6-4.3] months; *P* = .02) with aldoxorubicin compared with doxorubicin, as was the rate of 6-month progression-free survival (46% and 23%; *P* = .02). Median overall survival was 15.8 (95% CI, 13.0 to not available) months with aldoxorubicin and 14.3 (95% CI, 8.6-20.6) months with doxorubicin (*P* = .21). Overall tumor response rate (by Response Evaluation Criteria in Solid Tumors, version 1.1) by independent review was higher with aldoxorubicin than with doxorubicin (25% [20 patients, all partial response] vs 0%). Grade 3 or 4 neutropenia was more frequent with aldoxorubicin than with doxorubicin (24 [29%] vs 5 [12%]), but not grade 3 or 4 febrile neutropenia (12 [14%] vs 7 [18%]). No acute cardiotoxic effects were observed with either treatment, although left ventricular ejection fraction less than 50% occurred in 3 of 40 patients receiving doxorubicin.

CONCLUSIONS AND RELEVANCE Single-agent aldoxorubicin therapy showed superior efficacy over doxorubicin by prolonging progression-free survival and improving rates of 6-month progression-free survival and tumor response. Aldoxorubicin therapy exhibited manageable adverse effects, without unexpected events, and without evidence of acute cardiotoxicity. Further investigation of aldoxorubicin therapy in advanced soft-tissue sarcoma is warranted.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01514188

JAMA Oncol. doi:10.1001/jamaoncol.2015.3101
Published online September 17, 2015.

Invited Commentary

Supplemental content at jamaoncology.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Sant P. Chawla, MD, Sarcoma Oncology Center, 2811 Wilshire Blvd, Ste 414, Santa Monica, CA 90403 (santchawla@aol.com).

Soft-tissue sarcoma comprises a diverse group of malignant neoplasms. At diagnosis, 23% of cases are locally advanced and another 15% are metastatic.[1] First-line treatment for advanced soft-tissue sarcoma includes doxorubicin hydrochloride, alone or in combination with other chemotherapy agents (eg, ifosfamide).[2] The therapeutic benefit of doxorubicin, however, is limited by adverse effects, including mucositis, myelosuppression, and cumulative, dose-dependent cardiotoxic effects.[3-7] Although the addition of ifosfamide to doxorubicin-based regimens for soft-tissue sarcoma is standard and generally improves response rates and progression-free survival (PFS), overall survival (OS) is not improved and the incidences of grade 3 or 4 myelosuppression, febrile neutropenia, and deaths from adverse events are markedly increased.[8,9]

Aldoxorubicin (formerly INNO-206), a novel prodrug of doxorubicin, is derivatized at its C-13 keto-position with a thiol-binding, pH-sensitive linker (6-maleimidocaproic acid hydrazide).[10] On bloodstream entry, the linker rapidly and covalently binds primarily to the thiol group of cysteine-34 of endogenous albumin. The albumin-drug conjugate preferentially localizes to the tumor, and in the acidic tumor environment, the doxorubicin is released via cleavage of the acid-labile hydrazine bond between drug and carrier.[10] This novel approach to drug delivery exploits the leaky vasculature and defective lymphatic drainage (enhanced permeability and retention) characteristics of tumor tissues that promote entrapment of macromolecules within tumors, thereby increasing drug uptake and retention.[11]

Of 13 patients with soft-tissue sarcoma treated at the maximum tolerated dose of aldoxorubicin (350 mg/m^2) in a phase 1b/2 study, partial response rate was 38% and stable disease rate was 46%. Seven of the 13 patients had previously received an anthracycline.[12] Median PFS and OS for this cohort were 11.3 and 21.7 months, respectively. Myelosuppression was the most frequent adverse event with aldoxorubicin treatment.

This randomized phase 2b study compared the efficacy and safety of first-line treatment with aldoxorubicin vs doxorubicin in patients with advanced soft-tissue sarcoma.

At a Glance

- Objective was to evaluate the efficacy and safety of aldoxorubicin, an albumin-binding prodrug of doxorubicin, vs doxorubicin in patients with advanced soft-tissue sarcoma.
- Median progression-free survival was significantly improved (5.6 vs 2.7 months; *P* = .02) with aldoxorubicin as compared with doxorubicin.
- Median overall survival was 15.8 months with aldoxorubicin and 14.3 months with doxorubicin (*P* = .21).
- No acute cardiotoxic effects were observed with either treatment, although left ventricular ejection fraction less than 50% occurred in 3 patients receiving doxorubicin.

Methods

Study Design

This was a prospective, randomized, open-label, phase 2b study. Between December 21, 2012, and August 1, 2013, patients were enrolled at 31 sites in Australia, Hungary, India, Romania, Russia, Ukraine, and the United States. Patients were randomized 2:1 to receive either aldoxorubicin (350 mg/m^2; dose equivalent of 260 mg/m^2 doxorubicin) or doxorubicin (75 mg/m^2). A 2:1 randomization scheme was selected to extend safety information for aldoxorubicin; because the safety and efficacy of doxorubicin are well documented, the doxorubicin arm served to demonstrate patient responses to the drug similar to those evaluated in other studies. The protocol (Supplement 1) was approved by the institutional review board of each study site. This study was conducted in accordance with US Food and Drug Administration regulations, International Conference on Harmonisation Good Clinical Practices guidelines, the principles of the Declaration of Helsinki, and other applicable regulations and guidelines of the locale and country of each study site. Written consent was obtained from each patient by the investigator or subinvestigator before any protocol-specific tests were performed.

Patients

Patients were enrolled by the investigator at the clinical site. Eligible patients were 15 to 80 years of age (US sites) or 18 to 80 years of age (non-US sites) and had locally advanced, unresectable, and/or metastatic soft-tissue sarcoma of intermediate or high grade, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, life expectancy greater than 12 weeks (determined by investigator judgement), and disease measurable by Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1).[13] Prior adjuvant or neoadjuvant chemotherapy (including doxorubicin) was allowed if no tumor recurred for at least 12 months since the last measurement. Patients were excluded if they had prior chemotherapy for advanced disease, prior treatment with doxorubicin or pegylated liposomal doxorubicin of more than 3 cycles or greater than 225 mg/m^2 cumulative dose, palliative surgery or radiation treatment less than 4 weeks before randomization, or exposure to any investigational agent within 30 days of randomization. Patients with evidence or diagnosis of alveolar soft part sarcoma, chondrosarcoma, rhabdomyosarcoma, osteosarcoma, gastrointestinal stromal tumor, dermatofibrosarcoma, Ewing sarcoma, Kaposi sarcoma, mixed mesodermal tumor, clear-cell sarcomas, or unresectable low-grade liposarcomas were excluded, as were patients with ongoing infection, or with either current or past history of clinically significant cardiac events. Race and ethnicity information, based on the participant's assessment, was recorded to determine whether bias existed in these areas that might explain differences in either efficacy or safety between the 2 arms of the study.

Interventions

Patients received aldoxorubicin 350 mg/m^2 or doxorubicin 75 mg/m^2 administered as a 30-minute intravenous infusion on day 1 of each 21-day cycle, for up to 6 cycles. Two additional cycles of treatment were permitted with approval. Supportive care, including administration of antibiotics, blood components, antiemetics, prophylactic colony-stimulating factor, and

erythropoietin was permitted, at investigator discretion. Localized radiotherapy (with approval) was permitted.

Outcomes

The primary end point was PFS, defined as the interval between the date of randomization and the date of documented objective tumor progression or death by any cause, whichever occurred first. Secondary end points included PFS at 6 months, tumor response, and OS (defined as the interval between the date of randomization and the date of death by any cause). Tumor size was measured by computed tomography or magnetic resonance imaging every 6 weeks and as clinically indicated. Tumor response was assessed using RECIST 1.1, based on measurement of both target and nontarget lesions. Progression-free survival and tumor response end points were assessed both by local investigators and by a central independent laboratory (formerly CoreLab Partners, Inc; Princeton, New Jersey; currently BioClinica, Inc; Newtown, Pennsylvania) that received imaging scans with no patient identifiers, clinical information, or treatment assignment information. The OS end point was assessed by local investigators only. Event-driven end points were recorded in days and converted to months by dividing by 30.4 days/mo. Treatment safety, including incidence and severity of adverse events, was fully evaluated by National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Cardiac safety was assessed by electrocardiography at the end of every cycle. Echocardiography or multigated acquisition scan was performed at the end of cycles 2, 4, and 6, at the end of treatment, and during the follow-up period (at 2 months following the end of treatment, then every 3 months thereafter until disease progression or until another therapy was started).

Sample Size

Power calculations and sample size were calculated on the basis of the primary end point (PFS).[14(pp254-264)] Published data show that the PFS (or time to progression, in some cases) in this population treated with single-agent doxorubicin is approximately 4.4 months by investigator assessment.[8,15-18] On the basis of the use of a 2-sided log-rank test at an $\alpha = .05$ level of significance, a total of 89 events would be required for at least 83% power to detect a PFS of 8.5 months for aldoxorubicin if 105 patients were entered in the study. Assuming a 15-month accrual period and 12-month follow-up, dropout rates of 20% for each treatment arm at the end of the study (month 27), and that dropouts follow the exponential distribution, 70 and 35 patients would be needed in the aldoxorubicin and doxorubicin arms, respectively, to achieve a total of 89 events, using a randomization ratio of 2:1::aldoxorubicin:doxorubicin. As a result of study site interest and increased screening, enrollment was allowed to increase to 126 randomized participants with 123 treated participants eligible for evaluation.

Randomization

A random allocation sequence was generated by INC Research. After providing informed consent, patients were assigned a unique identification number. The investigator accessed an interactive, integrated voice/web response system (IXRS, Almac Group) and the patient was randomly assigned to a treatment arm. Patients in each treatment arm were stratified by baseline ECOG performance status (0 or 1 vs 2) and by prior chemotherapy status (adjuvant or neoadjuvant chemotherapy vs none). The study was open label; treatments were not blinded to patients or investigators but only to independent reviewers at the central laboratory.

Statistical Analyses

Efficacy was assessed in patients who received at least 1 dose of study drug and had at least 1 postbaseline tumor measurement, thus a modified intent-to-treat population. The primary efficacy end point was analyzed using a log-rank test stratified by the initial performance status and participants who had received prior chemotherapy. For the primary treatment comparison, the treatment effect was statistically significant if the 2-sided log rank $P < .05$. Safety was assessed in patients who received any amount of study drug. Continuous variables were summarized by mean (standard deviation) or median (range). Frequency tables were used to summarize categorical variables. Logistic regression analysis was used to assess the potential effects of patient characteristics on response and toxicity rates. The distributions of time-to-event end points (eg, PFS and OS) were estimated using the Kaplan-Meier method. Comparison of time-to-event end points by important subgroups of participants was made using the log-rank test. Cox (proportional hazards) regression analysis was used to evaluate multivariable predictive models of time-to-event outcomes.

Results

Patients

A total of 140 patients were screened, 126 patients were randomized to aldoxorubicin (n = 86) or doxorubicin (n = 40), and 123 patients were treated (**Figure 1**). The distribution of patients by country is shown in eTable 1 in Supplement 2. Three patients randomized to aldoxorubicin did not receive treatment because each withdrew consent before receiving the first dose. Median (range) follow-up was 13 (<1 to 31) months in each treatment group. As of data cutoff date (December 15, 2014), 39 (47%) and 26 (65%) of the aldoxorubicin and doxorubicin cohorts, respectively, had died, 30 (36%) and 7 (18%) remained in follow-up for survival, and 14 (17%) and 7 (18%) had terminated the study. Early terminations due to events other than disease progression were uncommon and similar in both groups.

Overall, baseline patient demographic characteristics were similar between treatment groups (**Table 1**). The most common histopathologic subtype was leiomyosarcoma (42 [34%]). The 2 groups were otherwise balanced in the distribution of soft-tissue sarcoma subtypes. Per protocol, all patients had tumors of intermediate to high grade. Thirteen (11%) patients had prior adjuvant or neoadjuvant chemotherapy; of these, 7 (54%) had received doxorubicin.

Progression-Free and Overall Survival

Median PFS by investigator assessment was 8.3 (95% CI, 6.4-9.7) months for the aldoxorubicin group and 4.6 (95% CI, 2.7-

Figure 1. Flow of Study Patient Disposition

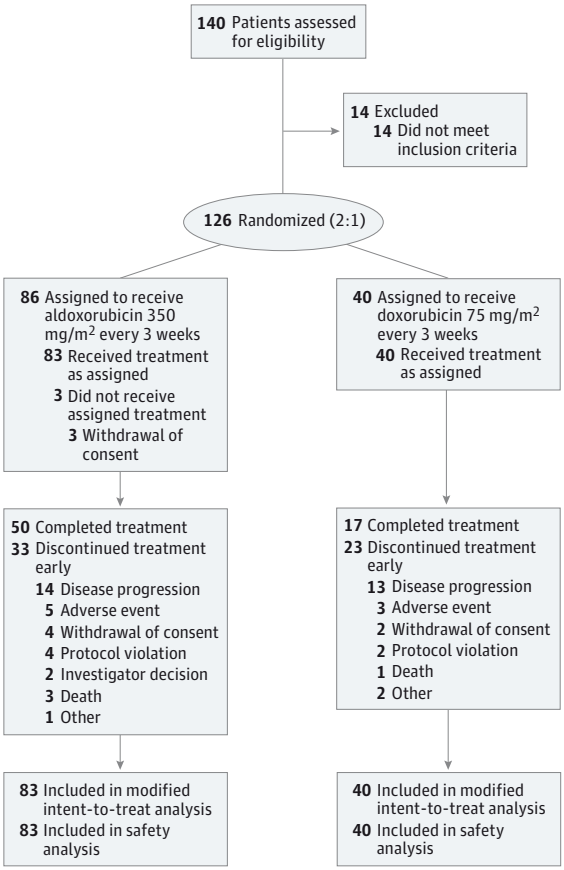


Table 1. Baseline Patient Demographic and Disease Characteristics

Parameter	Aldoxorubicin Group (n = 83)	Doxorubicin Group (n = 40)	All Patients (N = 123)
Age, median (range), y	54.0 (21-77)	54.0 (23-77)	54.0 (21-77)
Male/Female sex, No. (%)	38/45 (46/54)	18/22 (45/55)	56/67 (46/54)
Ethnic origin, No. (%)			
White	61 (73)	32 (80)	93 (76)
Asian	16 (19)	6 (15)	22 (18)
Black	1 (1)	1 (2)	2 (2)
Native Hawaiian or other Pacific Islander	0	1 (2)	1 (1)
Other	5 (6)	0	5 (4)
Eastern Cooperative Oncology Group performance status, No. (%)			
0-1	80 (96)	37 (92)	117 (95)
2	3 (4)	3 (8)	6 (5)
Tumor histopathologic subtype, No. (%)			
Leiomyosarcoma	28 (34)	14 (35)	42 (34)
Liposarcoma	13 (16)	6 (15)	19 (15)
Fibrosarcoma	12 (14)	4 (10)	16 (13)
Synovial sarcoma	5 (6)	4 (10)	9 (7)
Other[a]	25 (30)	12 (30)	37 (30)
Prior adjuvant or neoadjuvant chemotherapy, No. (%)			
Yes	8 (10)	5 (12)	13 (11)
No	75 (90)	35 (88)	110 (89)

[a] Includes angiosarcoma, malignant fibrous histiocytoma, nerve sheath sarcoma, spindle sarcoma, undifferentiated high-grade sarcoma not otherwise specified, and other types not falling under these categories.

5.9) months for the doxorubicin group ($P < .001$) (**Figure 2**A). Corresponding median PFS by independent assessment was 5.6 (95% CI, 3.0-8.1) and 2.7 (95% CI, 1.6-4.3) months, respectively ($P = .02$) (Figure 2B). Rates of PFS at 6 months by investigator assessment were 68% for the aldoxorubicin group and 33% for the doxorubicin group ($P < .001$). Corresponding rates of PFS at 6 months by independent assessment were 46% and 23%, respectively ($P = .02$).

By investigator assessment, median OS was 15.8 (95% CI, 13.0 to not available) months for the aldoxorubicin group and 14.3 (95% CI, 8.6-20.6) months for the doxorubicin group ($P = .21$; hazard ratio, 0.73 [95% CI, 0.44-1.20]) (Figure 2C). Considering patients in the aldoxorubicin (n = 75) and doxorubicin (n = 35) arms with no prior adjuvant or neoadjuvant chemotherapy for soft-tissue sarcoma, median OS was 15.8 (95% CI, 13.0 to not available) months with aldoxorubicin and 13.8 (95% CI, 8.6-19.8) months with doxorubicin ($P = .14$).

Tumor Response

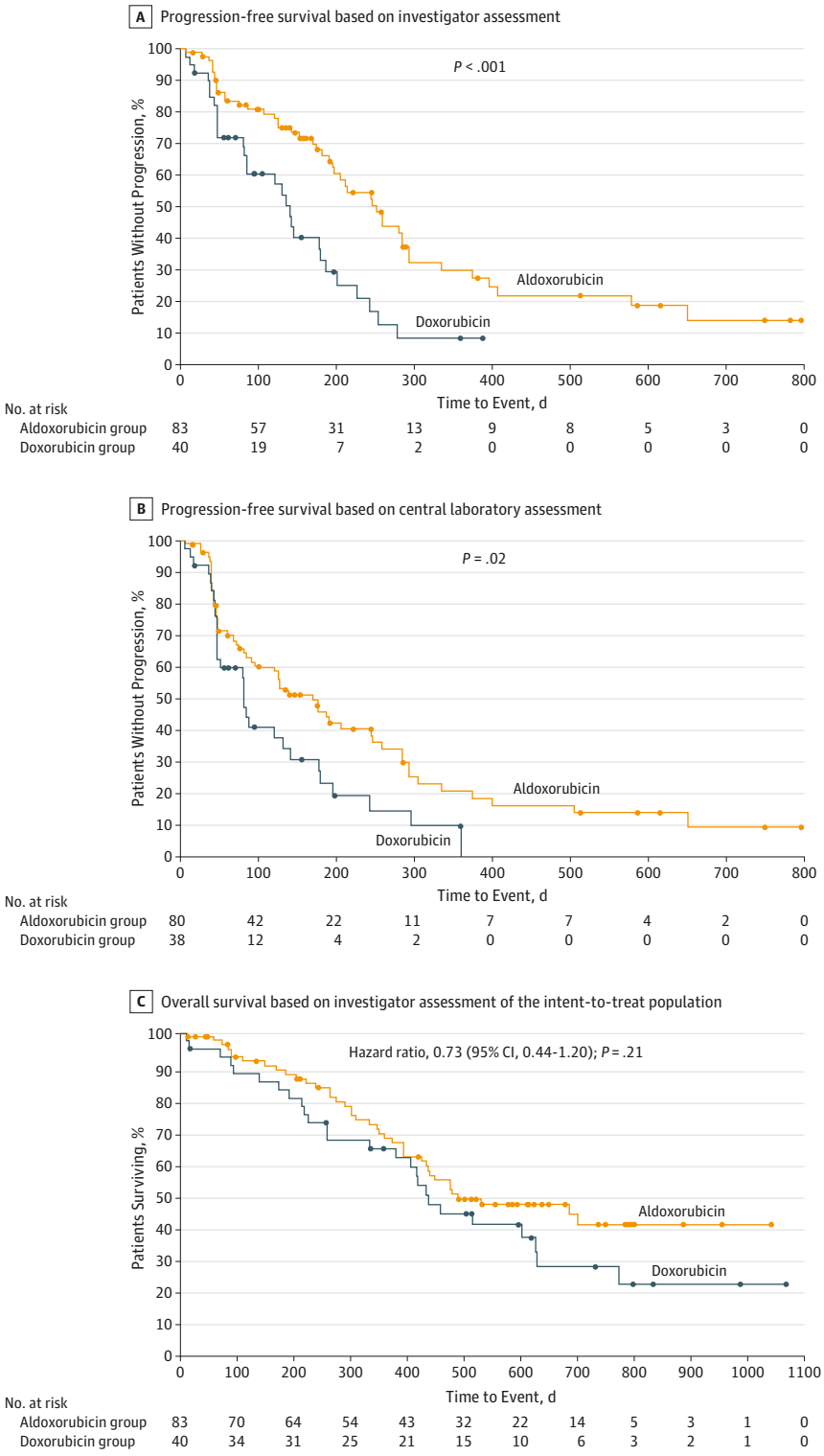
Using RECIST 1.1 criteria, overall response rates by investigator assessment were 23% (19 patients) with aldoxorubicin (including 2% [2 patients] complete response) and 5% (2 patients) with doxorubicin (no complete response) (**Table 2**). Disease control rates were 77% (64 patients) with aldoxorubicin and 68% (27 patients) with doxorubicin. Corresponding overall response rates by independent assessment were 25% (20 patients, all partial response) and 0, respectively (Table 2). Corresponding disease control rates were 62% (50 patients) and 45% (17 patients), respectively.

Among patients evaluable for assessment of tumor shrinkage in the aldoxorubicin group, 50 of 76 (66%) patients by investigator assessment (**Figure 3**A) and 46 of 73 (63%) patients by independent assessment (Figure 3B) had any amount of tumor shrinkage. In the doxorubicin group, 15 of 34 (44%) patients by investigator assessment (Figure 3C) and 13 of 32 (41%) patients by independent assessment (Figure 3D) had any amount of tumor shrinkage.

Adverse Events and Cardiac Safety

The median (range) number of cycles completed was 6 (1-8; 4 patients were permitted to receive up to 8 cycles) in the aldoxorubicin group and 4 (1-6) in the doxorubicin group. The most frequent nonhematologic adverse events (all grades; ≥20% of patients) were nausea, stomatitis, fatigue, alopecia, decreased appetite, and vomiting in the aldoxorubicin group, and alopecia and nausea in the doxorubicin group. Adverse events occurring more frequently with

Figure 2. Kaplan-Meier Estimates of Survival



aldoxorubicin than with doxorubicin included nausea (38 [46%] vs 11 [28%]), stomatitis (26 [31%] vs 5 [12%]), fatigue (24 [29%] vs 6 [15%]), decreased appetite (20 [24%] vs 2 [5%]), and vomiting (19 [23%] vs 7 [17%]). Diarrhea occurred more frequently with doxorubicin than with aldoxorubicin (7 [17%] vs 7 [8%]). Adverse events occurring in at least 10% of patients in either treatment group are presented in eTable 2 in Supplement 2.

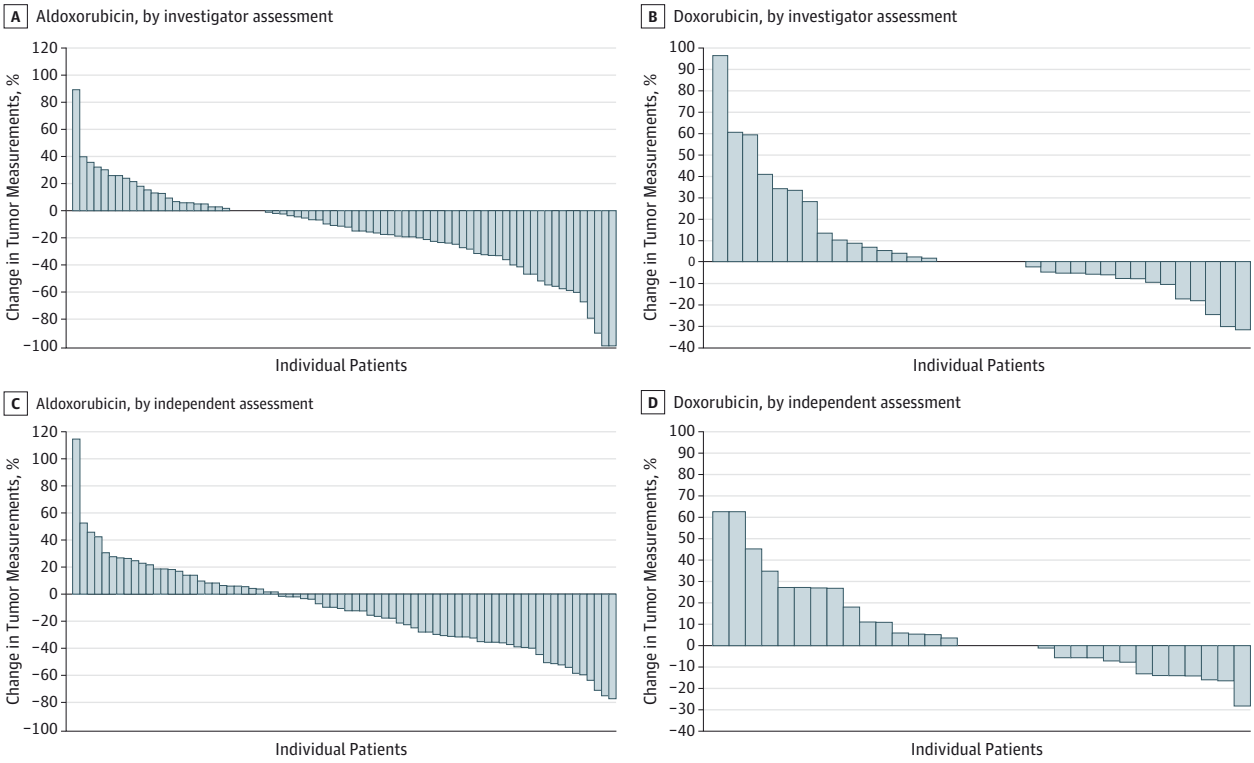
Table 2. Best Overall Tumor Responses

Patients With Response	Assessment, No. (%)			
	Investigator		Central Laboratory	
	Aldoxorubicin Group (n = 83)	Doxorubicin Group (n = 40)	Aldoxorubicin Group (n = 80)[a]	Doxorubicin Group (n = 38)[a]
CR	2 (2)	0	0	0
PR	17 (20)	2 (5)	20 (25)	0
Overall response (CR+PR)	19 (23)	2 (5)	20 (25)	0
SD	45 (54)	25 (62)	30 (38)	17 (45)
Disease control (CR+PR+SD)	64 (77)	27 (68)	50 (62)	17 (45)
Progressive disease	13 (16)	11 (28)	24 (30)	17 (45)
Not evaluable	6 (7)	2 (5)	6 (8)	4 (11)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

[a] For 3 patients in the aldoxorubicin group and 2 patients in the doxorubicin group, the independent central laboratory did not identify a measurable lesion at screening.

Figure 3. Waterfall Plots of Percent Change in the Sum of Diameters of Only Target Lesions



Patients without postbaseline tumor assessment data or for whom the independent assessor did not identify a measurable lesion were not included in these analyses.

Overall, 66 patients (80%) in the aldoxorubicin group and 23 patients (58%) in the doxorubicin group had at least 1 adverse event of grade 3 or 4 severity. Serious adverse events are summarized in eTable 3 in Supplement 2. Grade 3 or 4 neutropenia was more frequent with aldoxorubicin than with doxorubicin (24 [29%] vs 5 [12%]). Grade 3 or 4 adverse events occurred more frequently with aldoxorubicin than with doxorubicin, with the exception of anemia (14 [17%] vs 8 [20%]) and febrile neutropenia (12 [14%] vs 7 [18%]), both of which occurred more frequently with doxorubicin than with aldoxorubicin.

Five (6%) patients in the aldoxorubicin group and 3 (8%) patients in the doxorubicin group discontinued study treatment because of an adverse event. Ten patients terminated the study because of death: 6 (7%) in the aldoxorubicin group from disease progression and 4 (10%) in the doxorubicin group from disease progression (n = 2), septic shock (n = 1), and unknown cause (n = 1).

Cardiac events are summarized in eTable 4 in Supplement 2. No patient experienced clinically significant abnormal cardiac function, as measured by clinical symptoms, echocardiography, or multigated acquisition scan, during treatment (cycles 2, 4, 6), at the end of treatment, or afterward during the follow-up period (at 2, 5, 8, or 11 months after the end of treatment). Three patients in the doxorubicin group, but none in the aldoxorubicin group, had left ventricular ejection frac-

tion (LVEF) values that decreased below 50% of institutional reference ranges during the study. The total number of patients who experienced at least a 10% decrease in LVEF values at any cycle of treatment was 9 (12%) in the aldoxorubicin group and 11 (29%) in the doxorubicin group. During the follow-up period, the proportion of patients with at least a 10% decrease in LVEF values ranged from 0% to 11% for the aldoxorubicin group and from 0% to 33% for the doxorubicin group, depending on the time point assessed.

Median serum troponin levels for the aldoxorubicin group were unchanged from baseline during treatment, at the end of treatment, and during the follow-up period (eTable 4 in Supplement 2). For the doxorubicin group, median troponin levels were increased from baseline at cycles 4 and 6, at the end of treatment, and at 2 months after the end of treatment. By 5 months after the end of treatment, median serum troponin levels in the doxorubicin group had returned to baseline values.

Discussion

Aldoxorubicin for first-line treatment of advanced soft-tissue sarcoma showed superior efficacy over doxorubicin that was confirmed by independent, blinded, central radiology laboratory assessment, a level of data review that minimizes certain biases.[19,20] Median OS (by investigator assessment) was longer with aldoxorubicin than with doxorubicin for all patients (15.8 vs 14.3 months) and for patients without prior adjuvant or neoadjuvant chemotherapy (15.8 vs 13.8 months), although differences between groups were not statistically significant. This study was not powered to determine differences in OS between treatment groups, so the observed nonsignificantly improved OS with aldoxorubicin requires confirmation in larger, adequately powered studies.

Differences in response rate between independent and investigator reviews, as observed in our study, are not unprecedented. In a phase 3 study of pazopanib hydrochloride vs placebo for second-line or later treatment of metastatic soft-tissue sarcoma, tumor response rates for pazopanib therapy were 6% by independent review and 9% by investigator review.[21] Regarding the low response rate for doxorubicin that we observed, published response rates (investigator assessment using World Health Organization criteria[22] or RECIST 1.0[23]) for first-line, single-agent doxorubicin (70, 75, or 80 mg/m^2) for advanced soft-tissue sarcoma range from 9% to 27%.[8,16-18,24-27] The investigator-assessed response rate of 5% for doxorubicin in our study is consistent with the low end of the published range. Moreover, similar rates of tumor shrinkage with doxorubicin were documented by investigator and independent assessment (44% and 41%), suggesting that the application of response criteria was not excessively discrepant.

Grade 3 or 4 neutropenia occurred more frequently with aldoxorubicin than with doxorubicin therapy, but febrile neutropenia did not. Grade 3 or 4 mucositis and nausea and/or vomiting occurred more frequently with aldoxorubicin than with doxorubicin therapy, but those events were not treatment limiting and occurred at only 2 of the 31 study sites. Aldoxorubicin-related adverse events were overall consistent with those known to occur with doxorubicin treatment, generally resolved between cycles of treatment, and did not result in treatment discontinuation or delays in most patients.

The median cumulative dose of aldoxorubicin received in our study was 2100 mg/m^2 (dose equivalent of 1560 mg/m^2 doxorubicin), more than 5-fold the median cumulative dose of doxorubicin (300 mg/m^2) received, yet there was no evidence of clinically significant decrease in LVEF or reports of congestive heart failure in either study group. Historically, rates of congestive heart failure have ranged from 0.7% to 83% with cumulative doxorubicin doses of 300 to 950 mg/m^2.[6] Although an earlier phase 1 study of aldoxorubicin showed that additional treatment cycles were feasible,[12] the number of cycles in the present study was capped at 6 (except for 4 participants), which may partially account for the lack of cardiotoxic effects observed. In an ongoing phase 3 study of aldoxorubicin vs investigator's choice for treatment of patients with advanced soft-tissue sarcoma who have experienced relapse or lack of response to prior chemotherapies, a protocol amendment was made to allow treatment with aldoxorubicin until disease progression or unacceptable toxic effects (NCT02049905). The primary end point of this large, multinational clinical trial is PFS, and OS is a secondary end point.

Our efficacy results were consistent with those of a phase 3 study of doxorubicin plus ifosfamide vs doxorubicin as first-line treatment of advanced soft-tissue sarcoma.[8] By investigator assessment, median PFS was 7.4 months with doxorubicin plus ifosfamide and 4.6 months with doxorubicin, median OS was 14.3 and 12.8 months, and overall response rates were 26.4% and 13.6%, respectively. (In our study, by investigator assessment, median PFS was 8.3 months with aldoxorubicin and 4.6 months with doxorubicin, median OS was 15.8 and 14.3 months, and overall response rates were 23% and 5%, respectively.) The most common grade 3 or 4 adverse events with doxorubicin plus ifosfamide therapy were hematologic events that occurred at higher frequencies, including febrile neutropenia (46%). Notably, patients in the phase 3 study were overall younger (median age, 47 years in the combination group) than patients in our study (median age, 55 years in the aldoxorubicin group).

The results of this study should be interpreted in the context of the limitations of the study design. Specifically, the study is limited by its relatively small size and open-label design, which, by virtue of how the study drugs needed to be administered, could not be blinded. This could have potentially led to bias in how responses and tumor progressions were evaluated, but this situation was controlled by having a blinded central radiology review for response and progression assessment. This approach to avoid bias is uncommon in phase 2 trials, as well as almost all sarcoma phase 3 studies. Imprecision in progression assessment is inherent to studies in which computed tomography scans are taken only every 6 to 12 weeks, and censoring will also contribute to imprecise assessment of end points. Investigator evaluation of nonlaboratory adverse events can also be imprecise and potentially biased on the basis of prior knowledge of a drug's profile.

To our knowledge, aldoxorubicin is the first single agent to show significant superior activity over doxorubicin without substantially worsening toxicity.[28] Aldoxorubicin treatment showed no evidence of acute cardiotoxicity even at cumulative doses of doxorubicin-equivalents that were 2- to 4-fold higher than the recommended limit for native doxorubicin (400 to 600 mg/m^2). This result raises intriguing possibilities of further augmenting the efficacy of aldoxorubicin by combining it with doxorubicin hydrochloride (NCT01673438), ifosfamide (NCT02235701), or gemcitabine hydrochloride (NCT02235688), or enhancing the efficacy of combination regimens by allowing higher cumulative anthracycline doses. Aldoxorubicin suggests proof of principle that derivatizing an active chemotherapy compound to bind serum albumin can significantly enhance efficacy—without significantly intensifying toxicity.

Conclusions

Aldoxorubicin may be an important therapeutic option for patients with advanced soft-tissue sarcoma, as well as other solid tumor types. In addition to the phase 3 study for soft-tissue sarcoma, aldoxorubicin is currently under investigation in a phase 2b study in small-cell lung cancer, a phase 2 study of glioblastoma, and a pilot study of Kaposi sarcoma.

ARTICLE INFORMATION

Accepted for Publication: July 6, 2015.

Open Access: This article is published under the *JAMA Oncology* open access model and is free to read on the day of publication.

Published Online: September 17, 2015. doi:10.1001/jamaoncol.2015.3101.

Author Affiliations: Sarcoma Oncology Center, Santa Monica, California (Chawla); State Health Center, Oncology Department, Budapest, Hungary (Papai); State Healthcare Institute Republican Clinical Oncological Center of the Ministry of Health of the Republic of Tatarstan, Kazan, Republic of Tatarstan, Russia (Mukhametshina); Cancer Therapy and Research Center, San Antonio, Texas (Sankhala); now with Sarcoma Oncology Center, Santa Monica, California (Sankhala); Institute of Medical Radiology, Kharkiv, Ukraine (Vasylyev); Blokhin Cancer Research Center, Moscow, Russian Federation (Fedenko); Epworth Healthcare and Clinical Trials Research Centre, Richmond, Victoria, Australia (Khamly); Division of Oncology, Department of Medicine, Stanford School of Medicine, Stanford, California (Ganjoo); Curie Manavata Cancer Centre, Nashik, Maharashtra, India (Nagarkar); CytRx Corporation, Los Angeles, California (Wieland, Levitt).

Author Contributions: Drs Chawla and Sankhala had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Chawla, Wieland, Levitt.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Chawla, Ganjoo, Wieland, Levitt.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Levitt.
Administrative, technical, or material support: Papai, Vasylyev, Khamly, Nagarkar, Wieland.
Study supervision: Sankhala, Vasylyev, Khamly, Levitt.

Conflict of Interest Disclosures: Dr Chawla has received research support from CytRx and consulted for Amgen, Berg Pharma, CytRx, GlaxoSmithKline, Roche, and Threshold. Dr Sankhala has received research support from CytRx. Dr Fedenko has consulted for GlaxoSmith Kline, Johnson & Johnson, and Roche. Drs Wieland and Levitt are employees of CytRx and own stock in CytRx. No other disclosures are reported.

Funding/Support: This study was funded by CytRx Corporation.

Role of the Funder/Sponsor: CytRx Corporation collaborated in the design of the study with 5 academic advisors (S.P.C., K.S., K.G., and Shreyaskumar Patel, MD; MD Anderson Cancer Center, Houston, Texas; and Bartosz Chmielowski, MD; University of California Los Angeles). CytRx had no role in the conduct of the study, or collection, management, or analysis of the data. The study was conducted by INC Research (Raleigh, North Carolina), and data collection, management, and statistical analyses were performed by PRA International (Raleigh, North Carolina); both clinical research organizations were contracted by CytRx. CytRx collaborated with clinical study investigators on interpretation of the data. Drs Wieland and Levitt are employees of CytRx and had extensive involvement in all phases of this manuscript.

Additional Contributions: Anna Lau, PhD, and Patricia Segarini, PhD, of Percolation Communications LLC provided medical writing and editorial support, funded by CytRx.

REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER Stat Fact Sheets: soft tissue including heart cancer. http://seer.cancer.gov/statfacts/html/soft.html. Accessed June 4, 2014.

2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: soft tissue sarcoma. Version 2.2014. http://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed June 10, 2014.

3. Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of adriamycin cardiotoxicity. *Cancer*. 1973;32(2):302-314.

4. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl J Med*. 1991;324(12):808-815.

5. Lipshultz SE, Lipsitz SR, Mone SM, et al. Female sex and drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl J Med*. 1995;332(26):1738-1743.

6. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med*. 1979;91(5):710-717.

7. Adriamycin (doxorubicin hydrochloride). [package insert]. Bedford, OH: Bedford Laboratories; 2012.

8. Judson I, Verweij J, Gelderblom H, et al; European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol*. 2014;15(4):415-423.

9. Verma S, Younus J, Stys-Norman D, Haynes AE, Blackstein M; Members of the Sarcoma Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. Meta-analysis of ifosfamide-based combination chemotherapy in advanced soft tissue sarcoma. *Cancer Treat Rev*. 2008;34(4):339-347.

10. Kratz F, Warnecke A, Scheuermann K, et al. Probing the cysteine-34 position of endogenous serum albumin with thiol-binding doxorubicin derivatives: improved efficacy of an acid-sensitive doxorubicin derivative with specific albumin-binding properties compared to that of the parent compound. *J Med Chem*. 2002;45(25):5523-5533.

11. Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. *J Control Release*. 2000;65(1-2):271-284.

12. Chawla SP, Chua VS, Hendifar AF, et al. A phase 1B/2 study of aldoxorubicin in patients with soft tissue sarcoma. *Cancer*. 2015;121(4):570-579.

13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.

14. Collett D. *Modelling Survival Data in Medical Research*. Boca Raton, FL: Chapman and Hall/CRC; 1994.

15. Judson I, Verweij J, Gelderblom H, et al. Results of a randomised phase III trial (EORTC 62012) of single agent doxorubicin vs doxorubicin plus ifosfamide as first line chemotherapy for patients with advanced or metastatic soft tissue sarcoma: a survival study by the EORTC Soft Tissue and Bone Sarcoma Group. *Ann Oncol*. 2012;23:abstract LBA7.

16. Maurel J, López-Pousa A, de Las Peñas R, et al. Efficacy of sequential high-dose doxorubicin and ifosfamide compared with standard-dose doxorubicin in patients with advanced soft tissue sarcoma: an open-label randomized phase II study of the Spanish Group for Research on Sarcomas. *J Clin Oncol*. 2009;27(11):1893-1898.

17. Judson I, Radford JA, Harris M, et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue

sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer*. 2001;37(7):870-877.

18. Borden EC, Amato DA, Edmonson JH, Ritch PS, Shiraki M. Randomized comparison of doxorubicin and vindesine to doxorubicin for patients with metastatic soft-tissue sarcomas. *Cancer*. 1990;66(5):862-867.

19. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2007.

20. Ford R, Schwartz L, Dancey J, et al. Lessons learned from independent central review. *Eur J Cancer*. 2009;45(2):268-274.

21. van der Graaf WT, Blay JY, Chawla SP, et al; EORTC Soft Tissue and Bone Sarcoma Group; PALETTE study group. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2012;379(9829):1879-1886.

22. World Health Organization. *WHO Handbook for Reporting Results of Cancer Treatment*. WHO Offset Publication No. 48. Geneva, Switzerland: World Health Organization; 1979.

23. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst*. 2000;92(3):205-216.

24. Borden EC, Amato DA, Rosenbaum C, et al. Randomized comparison of three adriamycin regimens for metastatic soft tissue sarcomas. *J Clin Oncol*. 1987;5(6):840-850.

25. Nielsen OS, Dombernowsky P, Mouridsen H, et al. High-dose epirubicin is not an alternative to standard-dose doxorubicin in the treatment of advanced soft tissue sarcomas: a study of the EORTC Soft Tissue and Bone Sarcoma Group. *Br J Cancer*. 1998;78(12):1634-1639.

26. Santoro A, Tursz T, Mouridsen H, et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *J Clin Oncol*. 1995;13(7):1537-1545.

27. Schoenfeld DA, Rosenbaum C, Horton J, Wolter JM, Falkson G, DeConti RC. A comparison of adriamycin versus vincristine and adriamycin, and cyclophosphamide versus vincristine, actinomycin-D, and cyclophosphamide for advanced sarcoma. *Cancer*. 1982;50(12):2757-2762.

28. Sleijfer S, Seynaeve C, Verweij J. Using single-agent therapy in adult patients with advanced soft tissue sarcoma can still be considered standard care. *Oncologist*. 2005;10(10):833-841.