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Effect of Doxorubicin Plus Olaratumab vs Doxorubicin Plus Placebo on Survival in Patients With Advanced Soft Tissue Sarcomas
The ANNOUNCE Randomized Clinical Trial

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IMPORTANCE Patients with advanced soft tissue sarcoma (STS) have a median overall survival of less than 2 years. In a phase 2 study, an overall survival benefit in this population was observed with the addition of olaratumab to doxorubicin over doxorubicin alone.

OBJECTIVE To determine the efficacy of doxorubicin plus olaratumab in patients with advanced/metastatic STS.

DESIGN, SETTING, AND PARTICIPANTS ANNOUNCE was a confirmatory, phase 3, double-blind, randomized trial conducted at 110 sites in 25 countries from September 2015 to December 2018; the final date of follow-up was December 5, 2018. Eligible patients were anthracycline-naive adults with unresectable locally advanced or metastatic STS, an Eastern Cooperative Oncology Group performance status of 0 to 1, and cardiac ejection fraction of 50% or greater.

INTERVENTIONS Patients were randomized 1:1 to receive doxorubicin, 75 mg/m^2 (day 1), combined with olaratumab (n = 258), 20 mg/kg in cycle 1 and 15 mg/kg in subsequent cycles, or placebo (n = 251) on days 1 and 8 for up to 8 21-day cycles, followed by olaratumab/placebo monotherapy.

MAIN OUTCOMES AND MEASURES Dual primary end points were overall survival with doxorubicin plus olaratumab vs doxorubicin plus placebo in total STS and leiomyosarcoma (LMS) populations.

RESULTS Among the 509 patients randomized (mean age, 56.9 years; 58.2% women; 46.0% with LMS), all were included in the primary analysis and had a median length of follow-up of 31 months. No statistically significant difference in overall survival was observed between the doxorubicin plus olaratumab group vs the doxorubicin plus placebo group in either population (total STS: hazard ratio, 1.05 [95% CI, 0.84-1.30], P = .69, median overall survival, 20.4 months vs 19.7 months; LMS: hazard ratio, 0.95 [95% CI, 0.69-1.31], P = .76, median overall survival, 21.6 months vs 21.9 months). Adverse events of grade 3 or greater reported in 15% or more of total patients with STS were neutropenia (46.3% vs 49.0%), leukopenia (23.3% vs 23.7%), and febrile neutropenia (17.5% vs 16.5%).

CONCLUSIONS AND RELEVANCE In this phase 3 clinical trial of patients with advanced STS, treatment with doxorubicin plus olaratumab vs doxorubicin plus placebo resulted in no significant difference in overall survival. The findings did not confirm the overall survival benefit observed in the phase 2 trial.

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Visual Abstract

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Supplemental content

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Soft tissue sarcomas (STSs) are rare, heterogeneous malignancies of connective tissues that arise from mesenchymal precursors most often in the extremities and comprise about 1% of cancers in adults.[1,2] The most common of the more than 50 biologically distinct histologies identified are leiomyosarcoma (LMS), liposarcoma (LPS), and undifferentiated pleomorphic sarcoma (UPS).[1,2] Standard first-line systemic therapy for advanced disease includes doxorubicin alone or in combination. Recent first-line phase 3 trials comparing doxorubicin monotherapy with gemcitabine plus docetaxel[3] or doxorubicin plus ifosfamide,[4] palifosfamide,[5] or evofosfamide[6] did not improve historic median overall survival of about 14 to 19 months and 2-year survival rates of 20% to 30%. Consequently, there is a need for new, effective treatments.

Platelet-derived growth factor receptors (PDGFRs) are homodimers and heterodimers of alpha and beta isoforms. The PDGF-PDGFR signaling pathway is active in mesenchymal stem cell differentiation.[7] Dysfunction of this pathway has been observed in STS.[7] Olaratumab, a recombinant, fully human IgG subclass 1 monoclonal antibody, binds to PDGFR-α and blocks downstream signaling induced by ligands PDGF-AA, -BB, and -CC.[8] In a randomized, open-label, phase 2 trial, up to 8 cycles of doxorubicin plus olaratumab (doxorubicin + olaratumab) followed by olaratumab monotherapy improved median progression-free survival (PFS) by 2.5 months and median overall survival by 11.8 months, vs single-agent doxorubicin, in patients with advanced STS.[9] In the LMS subgroup, median overall survival was 15.1 months longer for doxorubicin + olaratumab over doxorubicin alone.[9] Based on these results, olaratumab + doxorubicin received regulatory approvals in many regions worldwide, including the United States, Europe, Canada, Korea, and Brazil. Most approvals were granted under the condition that the sponsor conduct a confirmatory phase 3 study.

The phase 3 ANNOUNCE trial was a randomized, placebo-controlled study of doxorubicin with or without olaratumab in patients with locally advanced or metastatic STS that aimed to confirm the results of the phase 2 trial.

Key Points

Question In patients with advanced soft tissue sarcoma (STS), does the addition of olaratumab to doxorubicin improve overall survival?

Findings In this randomized clinical trial of 509 adults with advanced STS, there was no significant difference in overall survival between patients who received doxorubicin plus olaratumab and patients who received doxorubicin plus placebo in the total STS and leiomyosarcoma populations (total STS: hazard ratio, 1.05; median, 20.4 vs 19.7 months; leiomyosarcoma: hazard ratio, 0.95; median, 21.6 vs 21.9 months).

Meaning There was no significant difference in overall survival with the addition of olaratumab to doxorubicin in patients with advanced STS.

Methods

Trial Oversight

This trial was conducted at 110 sites in 25 countries from September 2015 to December 2018. The protocol was approved by the institutional review board at each participating center, and the study was performed in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent prior to any trial procedures. Interim safety analyses were performed with regular frequency by an independent data monitoring committee. One blinded interim efficacy analysis, without formal stopping rules due to the confirmatory nature of the trial, was performed. The complete trial protocol is available in Supplement 1.

Patients

Patients aged 18 years or older were eligible if they had locally advanced or metastatic STS not amenable to curative treatment. Patients with grade I LPS were eligible only at the time of radiologic progression or with histological evidence of aggressive transformation. Patients were required to have evaluable disease by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1[10]; an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; no prior anthracycline treatment; available tumor tissue for central review; adequate hematologic, organ, and coagulation function; a cardiac ejection fraction of 50% or greater; a negative pregnancy test result; agreed to use appropriate contraceptive methods; and a life expectancy of at least 3 months. Histological review of submitted tissue samples was centrally performed but not required prior to randomization.

Patients were ineligible if they had Kaposi sarcoma or gastrointestinal stromal tumor, a prolonged QTcB (>450 milliseconds for males and >470 milliseconds for females calculated by the Bazett formula: QTc = QT [heart rate/60]$^{1/2}$ = QT [duration of ventricular cardiac cycle]$^{-1/2}$), untreated central nervous system metastases, prior radiotherapy to the mediastinum/pericardium or whole pelvis, other active cancer, planned elective or cancer surgery during study treatment, uncontrolled intercurrent illnesses, known allergy to any study treatments, or if breastfeeding.

Trial Design and Interventions

Eligible patients were randomized 1:1 by Interactive Web Response System to receive doxorubicin + olaratumab or doxorubicin plus placebo (doxorubicin + placebo). Randomization was stratified by number of prior systemic therapies for advanced or metastatic disease (none vs ≥1), histology (LMS vs LPS vs UPS vs other subtypes), ECOG PS (0 vs 1), and geographic region (North America vs Europe vs rest of world). Race/ethnicity data, as self-reported by participants through fixed categories on a study case report form, were collected for description of the study population. Patients, medical staff, investigators, and the sponsor were blinded to treatment. Treatment consisted of 21-day cycles of olaratumab or placebo (days 1 and 8) in combination with

doxorubicin 75 mg/m^2 (day 1) for up to 8 cycles, followed by olaratumab or placebo monotherapy. The olaratumab dose was 20 mg/kg in cycle 1 and 15 mg/kg in subsequent cycles. The olaratumab loading dose was selected to achieve steady-state olaratumab serum levels within the first cycle and to minimize the number of patients with trough concentration at the end of cycle 1 (C_{min1}) below the level associated with efficacy in the phase 2 trial.[11] Premedication with antihistamines and corticosteroids for olaratumab/placebo was recommended at study open and subsequently required by protocol amendment due to the risk of severe infusion-related reactions. The cardioprotectant dexrazoxane was allowed at investigator discretion prior to doxorubicin administration starting at cycle 1 and recommended starting with cycle 5.

Cardiac evaluation by echocardiogram or multigated acquisition scan was performed after 4, 6, and 8 cycles, then every 3 months for the first year, every 6 months for the second year, and annually thereafter. Tumor assessments were performed by computed tomography or magnetic resonance imaging scan every 6 weeks using RECIST 1.1 until tumor progression. Patients continued treatment until progressive disease, unacceptable toxicity, patient/physician decision, or significant nonadherence. If doxorubicin was discontinued for toxicity or reasons other than disease progression prior to cycle 8, blinded olaratumab/placebo monotherapy was permitted to continue at that time.

End Points and Assessments

Dual primary end points of overall survival (time from randomization to death from any cause) compared doxorubicin + olaratumab vs doxorubicin + placebo in (1) all randomized patients (total STS population) and in (2) the subset of randomized patients with LMS.

Secondary objectives tested in type I error-controlled fashion were PFS (determined by investigator assessment according to RECIST 1.1)[10] and objective response rate (ORR), defined as the proportion of patients achieving best overall response of complete response plus partial response. Supportive prespecified secondary objectives are described in eTable 1 in Supplement 2. Those reported here are disease control rate, defined as the proportion of patients achieving best overall response of complete response plus partial response plus stable disease; adverse events (AEs); pharmacokinetics; and patient-reported outcomes assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 version 3 (EORTC-QLQ-C30) and modified Brief Pain Inventory–Short Form (mBPI-sf) scales. A high score on the 100-point scales of the EORTC-QLQ-C30 represents a high/healthy level of functioning, a high quality of life, or a high level of symptomology/problems. A change of 10 points or more in these categories was considered clinically meaningful. On the 10-point mBPI-sf scale, 0 was the best possible pain score. Time to first worst pain score was defined as an increase from baseline of 2 points or more with no change in analgesic use or an increase from baseline of 1 point or more with an increase in analgesic use of 1 level or more.

For exploratory analyses, tumor tissue was assessed by immunohistochemistry for expression of PDGFR-α[12] and PDGFR-β to test for correlation to overall survival and PFS in prespecified (PDGFR-α) and post hoc (PDGFR-β) analyses. Other prespecified exploratory analyses included exposure to doxorubicin, olaratumab, and dexrazoxane and postdiscontinuation therapy received by patients.

Statistical Analysis

Primary and secondary efficacy analyses were performed on an intention-to-treat basis in all patients in the group to which they were randomized, regardless of actual treatment received. Statistical tests for both primary end points of overall survival and key secondary end points of PFS and ORR were conducted according to the graphical method of Maurer and Bretz[13] to control the overall type I error rate at 0.025 bx(1-sided). The overall α was split between the dual primary end points of overall survival in the total STS population (α = .02) and LMS subpopulation (α = .005). A total of 322 overall survival events in the total STS population provided an 80% statistical power at a 1-sided .02 significance level, assuming the true hazard ratio (HR) for overall survival was 0.723. Assumptions regarding effect size were made with input from investigators and global sarcoma experts. Assuming a 30% censoring rate, a sample size of 460 randomized patients was required. The study was designed to be positive if either or both primary end points were met.

For the primary and secondary efficacy analyses conducted using the time-to-event methodology, if an event of interest was not observed, censoring rules were applied (refer to the statistical analysis plan in Supplement 1 for censoring rules). For response analyses (ORR and disease control rate), patients with missing data were considered nonresponders. For health outcomes/quality-of-life analyses, patients with a missing baseline (cycle 1) assessment or without at least 1 subsequent assessment during the study period were excluded. Patients with a baseline worst pain score of 8 or more or missing baseline score were excluded from mBPI-sf analysis.

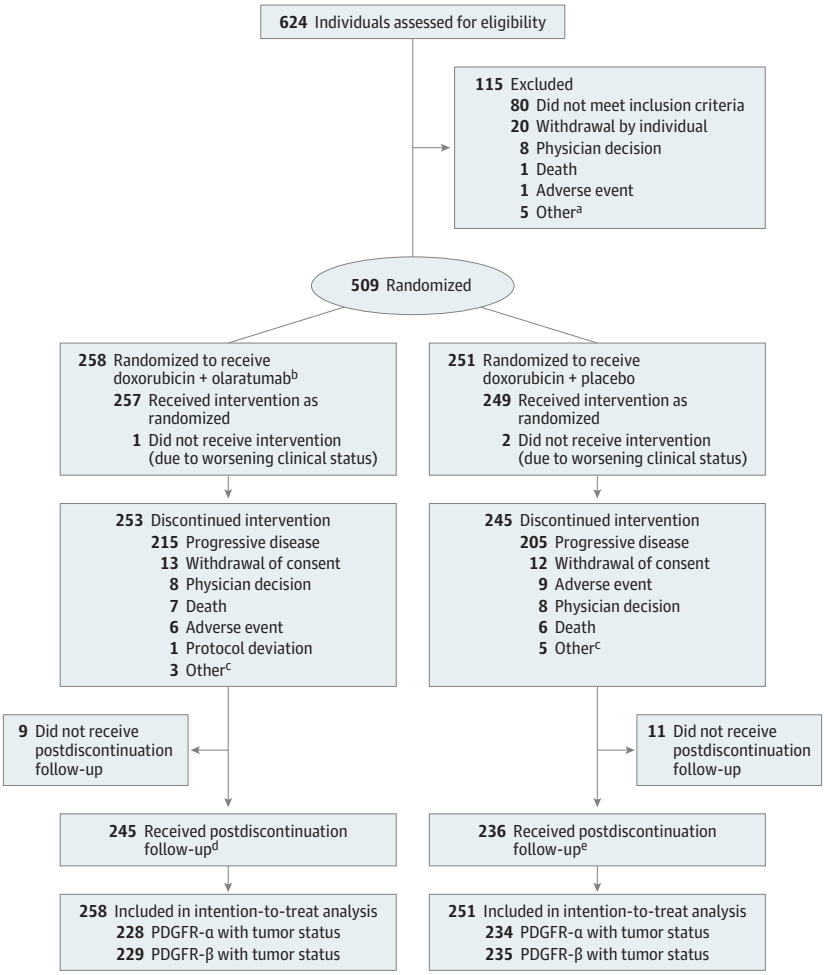
The overall survival and PFS analyses were based on the stratified log-rank test. The overall survival and PFS curves, medians with 95% CIs and survival rates at various time points for each treatment group, were estimated using the Kaplan-Meier method. The HRs were estimated using a stratified Cox proportional hazards model.[14] Unstratified models were used for subgroup analyses related to patient demographics or baseline disease characteristics. The proportional hazards assumption was checked using graphical diagnostics based on the Schoenfeld residuals[15] and plots of the log-negative-log of the estimated survival density function vs the log of time. Preplanned subgroup analyses for overall survival are listed in eTable 2 in Supplement 2. Statistical analyses were performed using SAS version 9.1.2 software (SAS Institute).

Results

Patients

Between September 2015 and July 2016, 624 patients provided informed consent to enroll in the trial (**Figure 1** [total STS]; eFigure 1 in Supplement 2 [LMS]). Of the patients who

Figure 1. Flow of Patient Disposition in the Total Soft Tissue Sarcoma Population



PDGFR indicates platelet-derived growth factor receptor.

[a] Individuals assessed for study eligibility were excluded prior to randomization for any reason other than those prespecified.

[b] A total of 106 patients received 1 dose or more of olaratumab monotherapy.

[c] Study treatment in either group was discontinued for any reason other than those prespecified.

[d] The 245 patients who received postdiscontinuation follow-up includes the 1 patient who did not receive intervention due to worsening clinical status preceding death.

[e] The 236 patients who received postdiscontinuation follow-up includes the 2 patients who did not receive intervention due to worsening clinical status preceding death.

were screened for study participation, 115 were ineligible and 509 were randomized to doxorubicin + olaratumab (n = 258) or doxorubicin + placebo (n = 251). One patient randomized to the doxorubicin + olaratumab group and 2 patients randomized to the doxorubicin + placebo group did not receive any study treatment. Baseline characteristics of the total STS population are presented in **Table 1**. Demographics were well balanced between treatments except for a higher percentage of men randomized to the doxorubicin + olaratumab group than to the doxorubicin + placebo group (44.2% vs 39.4%). Extent of disease was well balanced, with 83.7% of patients in the doxorubicin + olaratumab group and 82.1% of patients in the doxorubicin + placebo group having metastatic disease at randomization. Only 73 patients (28.3%) in the doxorubicin + olaratumab group and 69 patients (27.5%) in the doxorubicin + placebo group received prior systemic therapy. Of these 142 patients, 78 (54.9%) had 1 prior treatment regimen with gemcitabine and docetaxel. Tumor histology and grade were both well balanced between treatments (eTable 3 in Supplement 2). Most patients had LMS or LPS. Twenty-two unique histologies comprised the "other" category. For LMS, the uterus was the primary tumor site in both treatment groups (46 patients [38.7%] in the doxorubicin + olaratumab group, 48 patients [41.7%] in the doxorubicin + placebo group).

Efficacy

No statistically significant difference in overall survival was observed between treatments in the total STS population, with a median overall survival of 20.4 months vs 19.7 months for the doxorubicin + olaratumab (n = 258) and doxorubicin + placebo (n = 251) groups, respectively (HR, 1.05 [95% CI, 0.84-1.30]; P = .69) (**Figure 2**A). The median length of follow-up was 31 months. Similarly, no survival benefit in the doxorubicin + olaratumab group was observed in the LMS population, with a median overall survival of 21.6 months vs 21.9 months for the doxorubicin + olaratumab (n = 119) and doxorubicin + placebo (n = 115) groups (HR, 0.95 [95% CI, 0.69-1.31]; P = .76) (Figure 2B). Prespecified subgroup analyses did not reveal improvement in overall survival in the doxorubicin + olaratumab group in any notable clinical subgroup (**Figure 3**).

For the doxorubicin + olaratumab and doxorubicin + placebo groups, respectively, median PFS was 5.4 months vs 6.8 months in the total STS population (Figure 2C) and 4.3 months vs 6.9 months in the LMS population (Figure 2D).

Table 1. Baseline Patient Characteristics of the Total Soft Tissue Sarcoma Population

Characteristic	No. (%)	
	Doxorubicin + olaratumab (n = 258)	Doxorubicin + placebo (n = 251)
Age, median (range), y	57.0 (23-84)	57.0 (20-82)
<65	180 (69.8)	180 (71.7)
≥65	78 (30.2)	71 (28.3)
Sex		
Male	114 (44.2)	99 (39.4)
Female	144 (55.8)	152 (60.6)
Race[a]		
White	186 (72.1)	193 (76.9)
Asian	50 (19.4)	48 (19.1)
Black or African American	12 (4.7)	2 (0.8)
Other[b]	10 (3.9)	8 (3.2)
Hispanic or Latino ethnicity[a]	26 (10.1)	29 (11.6)
Geographic region		
Europe	108 (41.9)	106 (42.2)
North America	88 (34.1)	85 (33.9)
Rest of the world	62 (24.0)	60 (23.9)
EGOG PS[c]		
0 (Capable of normal activity)	153 (59.3)	150 (59.8)
1 (Restricted in strenuous activity)	105 (40.7)	101 (40.2)
Histology		
Leiomyosarcoma	119 (46.1)	115 (45.8)
Liposarcoma	48 (18.6)	43 (17.1)
Pleomorphic sarcoma	34 (13.2)	30 (12.0)
Other[d]	57 (22.1)	63 (25.1)
Duration of disease, median (range), mo	11.3 (0-260)	11.8 (0-192)
Metastatic disease at randomization	216 (83.7)	206 (82.1)
Prior systemic therapies[e]	73 (28.3)	69 (27.5)
Neoadjuvant	1 (0.4)	1 (0.4)
Adjuvant	8 (3.1)	10 (4.0)
Locally advanced	14 (5.4)	9 (3.6)
Metastatic	59 (22.9)	54 (21.5)
Prior radiation therapy	87 (33.7)	85 (33.9)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

[a] Race/ethnicity were self-reported by participants through fixed categories on study case report form.

[b] Other race categories were American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, and not reported.

[c] The ECOG PS 5-point scale defines 0 as fully active, able to carry on all predisease performance without restriction, and defines 1 as restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.

[d] One patient had lymphoma, which is not a subtype of soft tissue sarcoma, and therefore enrollment of this patient was a protocol violation.

[e] Prior systemic therapies were not mutually exclusive.

Between the doxorubicin + olaratumab and doxorubicin + placebo groups, respectively, the ORR in the total STS population was 14% (36/258) vs 18.3% (46/251) and in the LMS population was 13.4% (16/119) vs 22.6% (26/115). Disease control rate in the total STS population was 67.4% (174/258) vs 75.7% (190/251) and in the LMS population was 63.0% (75/119) vs 82.6% (95/115). Response rate data are included in eTables 4 and 5 in Supplement 2.

Postdiscontinuation therapies in the total STS population were similar in both treatment groups, apart from more doxorubicin + placebo patients who received radiation after discontinuation from study treatment. The most common postdiscontinuation therapies are included in eTable 6 in Supplement 2.

Consistent with a shorter PFS in the doxorubicin + olaratumab group, doxorubicin exposure was lower in the doxorubicin + olaratumab group than in the doxorubicin + placebo group (median cycles, 6 vs 7 [range, 1-8 in both groups]; median weeks, 18 vs 23; median cumulative dose, 409 mg/m^2 vs 483 mg/m^2), as was olaratumab or placebo exposure (median cycles, 6 vs 8 [range, 1-53 vs 1-51]; median weeks, 19 vs 26; median cumulative dose, 186 mg/kg vs 250 mg/kg). Olaratumab serum concentrations were comparable with those seen in prior trials. Due to loading dose design, the median C_{min1} was 142.34, and was higher than the C_{min1} from previous olaratumab trials,[8] placing patients in a C_{min1} range previously associated with efficacy.

Tumor tissue for PDGFR status was available for analysis in 91% of patients (n = 462 for PDGFR-α, n = 464 for PDGFR-β). Exploratory Cox regression analyses of overall survival dichotomized by PDGFR-α and PDGFR-β tumor status found no association between PDGFR-α or PDGFR-β expression and olaratumab response in the total STS population (eTable 7 and eFigure 2 in Supplement 2 [overall survival by PDGFR-α tumor status, PDGFR-β tumor status not shown]). In the doxorubicin + olaratumab and doxorubicin + placebo groups, respectively, median overall survival by PDGFR tumor status was 17.2 months vs 19.1 months for PDGFR-α positive, 23.6 months vs 21.9 months for PDGFR-α negative, 18.8 months vs 19.9 months for PDGFR-β positive, and 28.3 months vs 20.6 months for PDGFR-β negative. For patients with tumors that were both PDGFR-α and PDGFR-β negative, median overall survival was 28.5 months vs 20.6 months in the doxorubicin + olaratumab and doxorubicin + placebo groups, respectively.

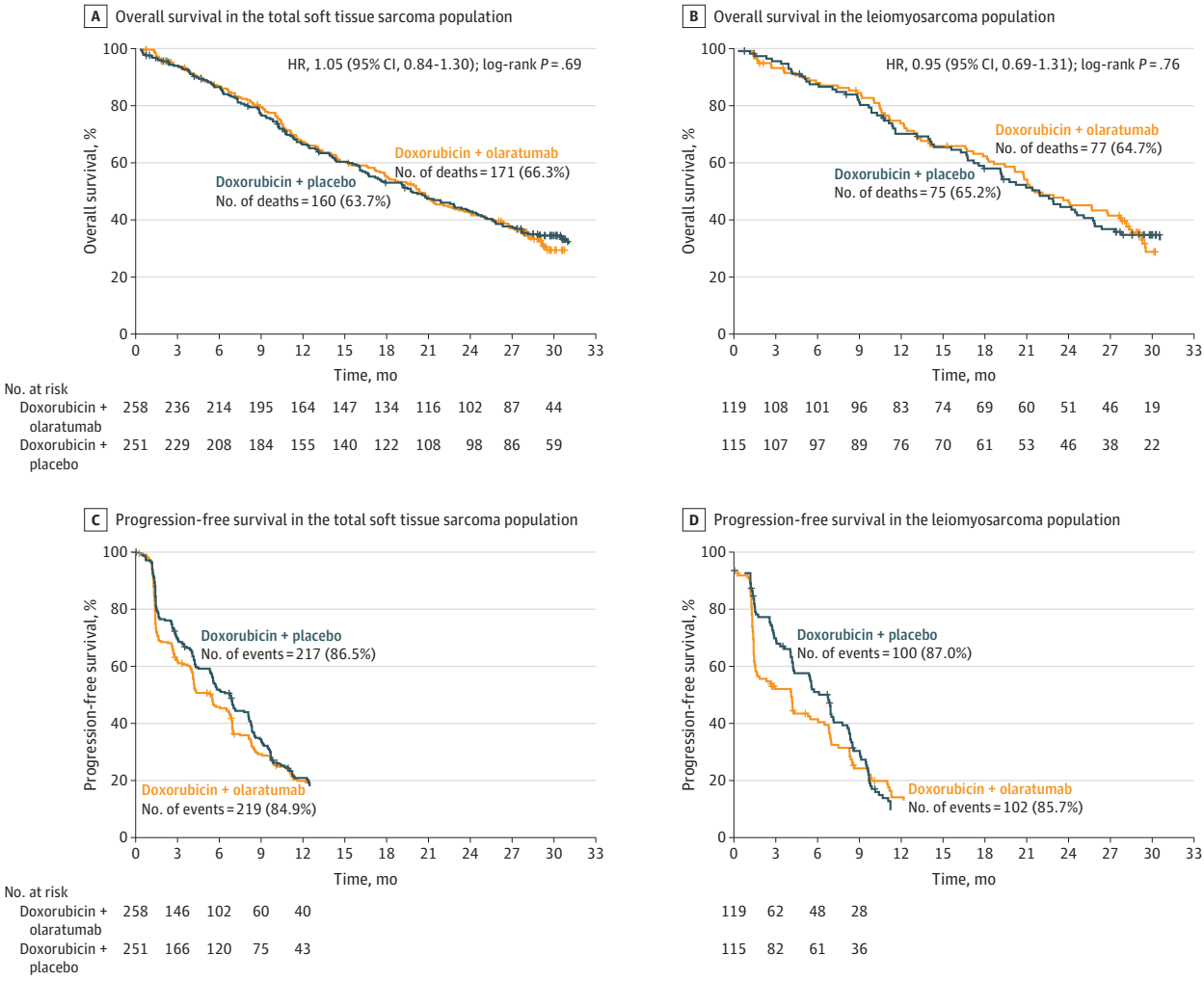
Quality of Life

Of the 398 patients (78.2%) evaluated with EORTC-QLQ-C30 in the total STS population, the median time to first worsening of the Global Health Status was 1.5 months in the doxorubicin + olaratumab group vs 1.8 months in the doxorubicin + placebo group. Of the 417 patients (81.9%) evaluated with mBPI-sf in the total STS population, the median time to first worsening of worst pain score was 7.7 months in the doxorubicin + olaratumab group vs 8.1 months in the doxorubicin + placebo group.

Adverse Events

A total of 506 treated patients (257 in the doxorubicin + olaratumab group, 249 in the doxorubicin + placebo group) were included in the analysis of AEs. Overall, AEs in both treatment groups were consistent with known toxicities of doxorubicin; the only AEs of grade 3 or greater occurring in 10% or more of patients in either group were hematologic toxicities. **Table 2** shows all AEs by treatment group that occurred

Figure 2. Overall Survival and Progression-Free Survival in the Total Soft Tissue Sarcoma (STS) and Leiomyosarcoma (LMS) Populations



The curves stop when the number of patients was less than 15%. Tick marks on the curves denote censored observations. In the doxorubicin + placebo and doxorubicin + olaratumab treatment groups, respectively, the median overall survival (interquartile range [IQR]) was 19.7 months (IQR, 9.9-35.5) vs 20.4 months (IQR,10.4-not estimated) in the total STS population and 21.9 months (IQR, 10.8-32.3) vs 21.6 months (IQR, 11.2-not estimated) in the LMS population; the median progression-free survival was 6.8 months (IQR, 2.6-10.7) vs 5.4 months (IQR, 1.4-10.2) in the total STS population and 6.9 months (IQR, 3.1-9.8) vs 4.3 months (IQR, 1.4-11.1) in the LMS population. The median length of follow-up was 31 months in both treatment groups.

in 5% or more of doxorubicin + olaratumab-treated patients. Febrile neutropenia was the only AE reported as "serious" (as determined by investigator, regardless of grade) that occurred in 5% or more of patients (n = 33 in both groups [12.8% olaratumab, 13.3% placebo]). Infusion-related reactions of immediate hypersensitivity (defined by Standardized Medical Dictionary for Regulatory Activities Queries of anaphylaxis, angioedema, or hypersensitivity) occurred more frequently in doxorubicin + olaratumab-treated patients (any grade, 11.7%; grade ≥3, 2.3%) than in doxorubicin + placebo-treated patients (any grade, 7.2%; grade ≥3, 0.8%).

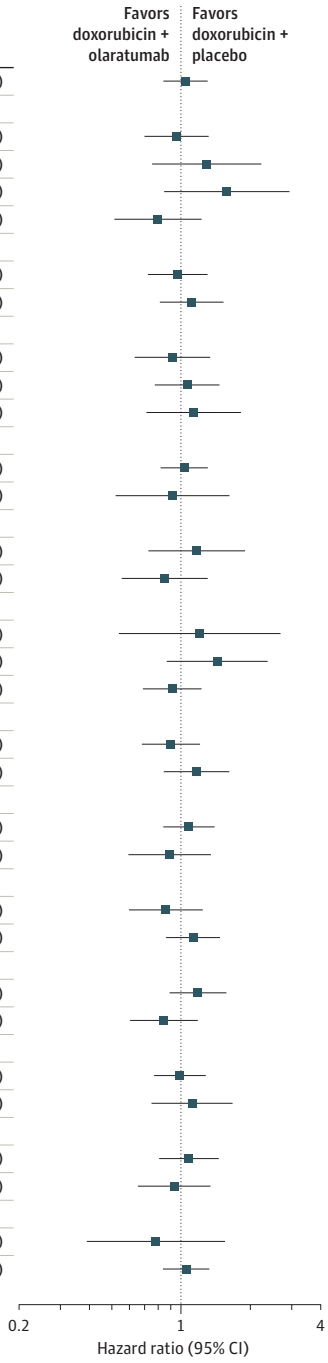
An assessment of cardiotoxicity associated with doxorubicin treatment in this trial has been presented.[16] Cardiac dysfunction of grade 3 or greater was similar in both groups (5 patients [1.9%] in the doxorubicin + olaratumab group, 6 patients [2.4%] in the doxorubicin + placebo group). Median follow-up for cardiac events was 28 weeks. Dexrazoxane was received by 63.0% of doxorubicin + olaratumab-treated patients (initiated at cycle 1 in 39.5%) vs 65.1% of doxorubicin + placebo-treated patients (initiated at cycle 1 in 25.9%). The AEs of cardiac dysfunction and decreased left ventricular ejection fraction are shown in eTable 8 in Supplement 2.

Discussion

This trial failed to demonstrate an overall survival benefit of doxorubicin + olaratumab compared with doxorubicin + placebo in patients with advanced STS. Both treatment groups showed similar toxicity rates, with only infusion-related reactions occurring more frequently in olaratumab-treated patients. These findings considerably differed from the

Figure 3. Overall Survival in Prespecified Subgroups in the Total Soft Tissue Sarcoma (STS) Population

Source	No. of events/No. of patients: Doxorubicin + olaratumab	Doxorubicin + placebo	Hazard ratio (95% CI)
Overall	171/258	160/251	1.05 (0.84-1.30)
Histological tumor type			
Leiomyosarcoma	77/119	75/115	0.96 (0.70-1.32)
Liposarcoma	29/48	24/43	1.29 (0.75-2.22)
Pleomorphic sarcoma	27/34	16/30	1.58 (0.85-2.93)
Other	38/57	45/63	0.80 (0.52-1.23)
ECOG performance status			
0	89/153	87/150	0.97 (0.72-1.30)
1	82/105	73/101	1.11 (0.81-1.53)
Geographic region			
North America	56/88	55/85	0.92 (0.63-1.34)
Europe	79/108	71/106	1.06 (0.77-1.47)
Rest of world	36/62	34/60	1.14 (0.71-1.81)
Disease stage at randomization			
Metastases	149/216	133/206	1.03 (0.82-1.31)
No metastases	22/42	27/45	0.92 (0.52-1.62)
Leiomyosarcoma primary site			
Uterine	34/46	33/48	1.17 (0.72-1.89)
Nonuterine	43/73	42/67	0.85 (0.56-1.30)
Grade of STS at diagnosis			
1 (Low)	10/16	15/28	1.20 (0.54-2.68)
2 (Intermediate)	38/60	26/47	1.43 (0.87-2.36)
3 (High)	92/130	90/128	0.92 (0.69-1.23)
Duration of disease, mo			
<12	93/130	88/124	0.92 (0.68-1.23)
≥12	78/127	72/127	1.15 (0.83-1.58)
No. of prior systemic therapies			
0	128/190	119/191	1.07 (0.83-1.37)
≥1	43/68	41/60	0.92 (0.60-1.41)
Prior radiation			
Yes	58/87	57/85	0.86 (0.60-1.24)
No	113/171	103/166	1.13 (0.86-1.47)
Sex			
Female	100/144	94/152	1.18 (0.89-1.57)
Male	71/114	66/99	0.85 (0.60-1.18)
Age subgroup, y			
<65	119/180	116/180	0.99 (0.77-1.28)
≥65	52/78	44/71	1.12 (0.75-1.67)
PDGFR-α			
Positive	91/133	85/134	1.09 (0.81-1.47)
Negative	57/95	62/100	0.93 (0.65-1.34)
Albumin level, g/L			
<35	16/20	17/19	0.78 (0.39-1.55)
≥35	152/233	140/226	1.05 (0.84-1.32)



ECOG indicates Eastern Cooperative Oncology Group; PDGFR, platelet-derived growth factor receptor.

Hazard ratios and 95% CIs (Wald) were estimated using stratified Cox model for overall and unstratified Coxmodels for subgroups.

results of the randomized phase 2 trial[9] that demonstrated substantial improvement in overall survival with higher but acceptable toxicity rates in the doxorubicin + olaratumab group compared with doxorubicin alone.

No single reason has been identified for the differential outcomes between the phase 2 and 3 trials. No discrepancies in trial conduct or data integrity were noted. If olaratumab has some activity in STS, it is therefore likely that the disparate results were due to the cumulative effect of multiple contributing factors within and between these studies. Possible explanations include inherent differences in design elements between the phase 2 and 3 trials, respectively: open label vs blinded with placebo control, primary end point of PFS vs overall survival, and enrollment limited to the United States vs globally. If olaratumab has no activity in STS, the outcome of the phase 2 trial might be attributed to patients randomized to single-agent doxorubicin who crossed over to olaratumab monotherapy after documented disease progression, possibly

Table 2. Adverse Events by Treatment Occurring in ≥5% of Patients in the Doxorubicin Plus Olaratumab Group

Treatment-emergent adverse event, MedDRA preferred term	No. (%)			
	Doxorubicin + olaratumab (n = 257)[a]		Doxorubicin + placebo (n = 249)[a]	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Nausea	153 (59.5)	7 (2.7)	166 (66.7)	6 (2.4)
Neutropenia[b]	142 (55.3)	119 (46.3)	144 (57.8)	122 (49.0)
Fatigue[b]	139 (54.1)	14 (5.4)	147 (59.0)	12 (4.8)
Alopecia	112 (43.6)	1 (0.4)	124 (49.8)	1 (0.4)
Anemia[b]	110 (42.8)	35 (13.6)	113 (45.4)	31 (12.4)
Musculoskeletal pain[b]	92 (35.8)	5 (1.9)	85 (34.1)	3 (1.2)
Mucositis[b]	89 (34.6)	10 (3.9)	101 (40.6)	7 (2.8)
Leukopenia[b]	81 (31.5)	60 (23.3)	78 (31.3)	59 (23.7)
Constipation	79 (30.7)	1 (0.4)	87 (34.9)	2 (0.8)
Diarrhea	74 (28.8)	2 (0.8)	75 (30.1)	3 (1.2)
Decreased appetite	71 (27.6)	2 (0.8)	92 (36.9)	1 (0.4)
Vomiting	63 (24.5)	6 (2.3)	69 (27.7)	2 (0.8)
Thrombocytopenia[b]	58 (22.6)	24 (9.3)	62 (24.9)	21 (8.4)
Pyrexia	48 (18.7)	1 (0.4)	46 (18.5)	0
Dyspnea	46 (17.9)	4 (1.6)	36 (14.5)	2 (0.8)
Abdominal pain[b]	45 (17.5)	2 (0.8)	53 (21.3)	3 (1.2)
Dysgeusia	45 (17.5)	0	51 (20.5)	0
Febrile neutropenia	45 (17.5)	45 (17.5)	41 (16.5)	41 (16.5)
Cough	43 (16.7)	0	61 (24.5)	1 (0.4)
Headache	43 (16.7)	2 (0.8)	42 (16.9)	0
Edema	34 (13.2)	1 (0.4)	23 (9.2)	0
Infusion-related reaction	30 (11.7)	6 (2.3)	18 (7.2)	2 (0.8)
Dyspepsia	28 (10.9)	0	29 (11.6)	0
Dizziness	27 (10.5)	1 (0.4)	34 (13.7)	0
Upper respiratory tract infection	25 (9.7)	0	25 (10.0)	1 (0.4)
Insomnia	23 (8.9)	0	30 (12.0)	0
Dry mouth	22 (8.6)	0	19 (7.6)	0
Alanine aminotransferase increased	19 (7.4)	3 (1.2)	19 (7.6)	4 (1.6)
Dehydration	19 (7.4)	2 (0.8)	10 (4.0)	2 (0.8)
Lymphopenia[b]	19 (7.4)	13 (5.1)	17 (6.8)	7 (2.8)
Urinary tract infection	19 (7.4)	5 (1.9)	22 (8.8)	1 (0.4)
γ-Glutamyltransferase increased	18 (7.0)	3 (1.2)	17 (6.8)	5 (2.0)
Neuropathy[b]	17 (6.6)	0	24 (9.6)	1 (0.4)
Hypertension[b]	16 (6.2)	5 (1.9)	20 (8.0)	6 (2.4)
Rash[b]	16 (6.2)	0	23 (9.2)	0
Oropharyngeal pain	15 (5.8)	0	18 (7.2)	0
Hypokalemia[b]	14 (5.4)	7 (2.7)	12 (4.8)	3 (1.2)
Pruritus	14 (5.4)	0	23 (9.2)	0

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

[a] Common Terminology Criteria for Adverse Events version 4.0 was used to categorize TEAEs. Grades 1-5 were defined as: mild (grade 1), moderate (grade 2), severe or medically significant but not immediately life-threatening (grade 3), life-threatening (grade 4), and death related to TEAE (grade 5).

[b] The following consolidated terms included terms presented in parentheses: abdominal pain (abdominal pain upper, abdominal pain lower); anemia (hemoglobin decreased); fatigue (asthenia); hypertension (hypertension); hypokalemia (blood potassium decreased); leukopenia (white blood cell count decreased); lymphopenia (lymphocyte count decreased); mucositis (stomatitis, oropharyngeal pain, mucosal inflammation); musculoskeletal pain (arthralgia, back pain, pain in extremity, muscle spasms, myalgia, bone pain, musculoskeletal chest pain, groin pain, neck pain, flank pain); neuropathy (paresthesia, neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia); neutropenia (neutrophil count decreased); rash (rash, rash pruritic, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, rash generalized, rash macular); and thrombocytopenia (platelet count decreased).

creating a negative bias for survival. These patients could have experienced a more prolonged period of progression, through 2 clinical trial events, before moving on to other possibly effective agents. In contrast, patients with disease progression in the doxorubicin + olaratumab group of the blinded phase 3 trial could have moved off study to an agent with known efficacy because crossover of placebo-treated patients was not allowed.

Another potential explanation for the disparate findings between the phase 2 and 3 trials may be the inclusion of differing patient populations. The heterogeneity of STS histologies may have led to differences in outcomes, not only due to unique biology with differential sensitivity to systemic therapy, but also differences in the quality, number, and efficacy of available poststudy treatments, which could affect overall survival. Even a defined histology such as LMS has significant heterogeneity in underlying biology and clinical behavior, encompassing a spectrum of relatively indolent to extremely aggressive diseases, leading to unapparent, or not easily accounted for, but potentially meaningful differences in populations between the trials. Additionally, all patients in the phase 2 study had metastatic disease at enrollment, whereas

17.1% of patients in this trial had locally advanced, nonmetastatic disease. Factors related to enrolled histologies, choice of end point, extent of disease, and clinical behavior are some of the common explanations for why promising phase 2 data are not replicated in phase 3 STS trials; these and others are likely to be causes for the varied outcomes seen in the case of olaratumab in combination with doxorubicin.

This trial had the longest median overall survival in any recent first-line randomized phase 3 STS trial.[3-6] Along with these trials,[3-6] this study provides additional prospective evidence of the current improvement in median overall survival in advanced STS potentially due to improved multidisciplinary and supportive care and the availability of additional lines of effective systemic therapies for certain sarcoma subtypes. Earlier detection and initiation of treatment of metastatic disease could lead to improvement in measured survival, either through access to more effective therapies or potentially from lead time bias.[17,18]

Given that doxorubicin is a common denominator in the aforenoted studies[3-6] showing longer overall survival for patients with STS, specific consideration should be given to its effect on survival. Supportive care advances, such as dexrazoxane and granulocyte colony-stimulating factor, both of which were received by most patients in this trial, may contribute to clinicians' willingness to continue doxorubicin beyond the traditional cumulative limit of 450 mg/m^2. In this trial, treatment with up to 8 cycles (600 mg/m^2) of doxorubicin was allowed and was administered to 90 patients (17.9%), yet grade 3 or more cardiac AEs were uncommon. The relationship between higher doses of doxorubicin and improved overall survival of the entire cohort should be carefully examined in the context of cardiac data as it continues to emerge.

Despite the complexities of conducting studies in rare diseases such as STS, this trial clearly demonstrated that trials can rapidly accrue, enrolling more than 500 patients in 10 months. However, its negative results in conjunction with the previously noted recent negative STS trials[3-6] raises the question of whether performing trials recruiting all STS histologies is appropriate or rather if histology-specific or biomarker-driven trials will be required. This trial shows the importance of confirmatory phase 3 trials to validate results from smaller trials and exemplifies the role of accelerated/conditional approvals to provide access to promising medicines for patients with unmet medical needs until the potential of the medicine can be validated, provided there is an acceptable risk profile and plan for rapid validation. Although this study did not show any benefit from the addition of olaratumab to doxorubicin, it similarly did not demonstrate significant increases in drug-related toxicity and confirmed the incremental increase in survival for patients with STS treated with doxorubicin-based therapy. STSs remain an area of unmet medical need and a fertile ground for scientific discovery and drug development, and this trial provides several findings that can be applied to future clinical trials.

Limitations

This study has limitations. First, the mechanism of action of olaratumab is not completely understood. The lack of association between PDGFR-α or PDGFR-β expression and overall survival shown in exploratory analyses presented here and in the phase 2 trial[9] are worth noting as possible features of the mechanism of action of olaratumab that could have affected outcomes. These findings, although exploratory, emphasize the need for a better understanding of STS biologies to develop effective treatments.

Second, higher olaratumab doses were not tested prior to this trial; therefore, the dosing regimen studied may not have been maximized.

Conclusions

In this phase 3 clinical trial of patients with advanced STS, treatment with doxorubicin + olaratumab vs doxorubicin + placebo resulted in no significant difference in overall survival. The findings did not confirm the overall survival benefit observed in the phase 2 trial.

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