Original Article

Overall Survival and Histology-Specific Subgroup Analyses From a Phase 3, Randomized Controlled Study of Trabectedin or Dacarbazine in Patients With Advanced Liposarcoma or Leiomyosarcoma

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BACKGROUND: We performed a randomized phase 3 study of trabectedin versus dacarbazine in previously-treated patients with liposarcoma/leiomyosarcoma (LPS/LMS). **METHODS:** Patients were randomized 2:1 to trabectedin (n = 384) or dacarbazine (n = 193) administered intravenously every 3 weeks. The primary objective was overall survival (OS). Secondary objectives were progression-free survival, objective response rate, safety, and patient-reported outcomes, all previously reported and demonstrating superior disease control with trabectedin. Results of the final OS analysis in preplanned subgroups of patients with LPS/LMS are presented. **RESULTS:** At the time of the final OS analysis, 577 patients had been assigned randomly, including 423 (73%) with LMS and 154 (27%) with LPS. The median duration of treatment exposure was higher in the trabectedin arm compared with the dacarbazine arm (4 vs 2 cycles), as was the proportion of patients receiving an extended number of therapy courses (≥6 cycles: 42% vs 22%). This pattern was consistent across histological subgroups: the median number of treatment cycles (4 vs 2 for both subgroups) and proportion of patients with ≥6 treatment cycles (LMS, 43% vs 24%; LPS, 40% vs 16%). Despite improved disease control by trabectedin, no improvement in OS was observed; the final median OS for trabectedin versus dacarbazine was 13.7 versus 13.1 months (*P* = .49). Sensitivity analyses of OS suggest confounding by post-study anticancer therapies, which were utilized in most patients in both treatment arms (71% vs 69%, respectively). **CONCLUSION:** The final OS results demonstrated comparable survival between LPS/LMS patients receiving trabectedin or dacarbazine, which is consistent with the interim analysis results. Both LPS and LMS demonstrated improved disease control with trabectedin. *Cancer* 2019;125:2610-2620. © 2019 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

KEYWORDS: dacarbazine, trabectedin, leiomyosarcoma, liposarcoma, soft tissue sarcoma.

INTRODUCTION

Effective treatment for patients with advanced soft-tissue sarcoma (STS) remains an area of unmet need. First-line chemotherapy for advanced STS is evolving, with anthracycline-based treatment[1,2] or gemcitabine plus docetaxel[3-5] as commonly used regimens.[6] The optimal approach for patients following failure of first-line chemotherapy is less well-defined.

Trabectedin is an antineoplastic alkaloid agent with a complex, multimodal mechanism of action,[7] binding the minor groove of the DNA double helix, bending it toward the major groove, and initiating a cascade of events that may interfere with transcription and inhibit activities of DNA binding factors and DNA repair processes downstream.[8-10] In vitro, trabectedin can inhibit tumor growth by modulating production of certain chemokines, cytokines, and other factors involved in inflammation[8,9] in the tumor microenvironment.

Trabectedin was approved in the European Union in 2007 for the treatment of advanced, unresectable STS in patients following failure of anthracyclines and ifosfamide or who were unfit to receive those agents.[9,11] In 2015, trabectedin was approved in the United States for patients with unresectable or metastatic liposarcoma (LPS) or leiomyosarcoma (LMS) who had received a prior anthracycline-containing regimen.[12] United States approval was based on progression-free survival (PFS) and objective response rate (ORR) results and safety data from a phase 3 trial (ET743-SAR-3007)[13] that was limited to patients with LPS/LMS and was based upon the previously demonstrated superior efficacy in LPS/LMS compared with other STS subtypes.[14] Trabectedin demonstrated a 45% reduction in risk of disease progression or death (hazard ratio [HR], 0.55; $P < .001$) with a median PFS of 4.2 versus 1.5 months[13] and a safety profile consistent with the well-characterized toxicities observed in previous trabectedin studies.[13-15] Herein, we report the final overall survival (OS) results and preplanned histology-specific subgroup analyses from this phase 3, randomized controlled trial.

MATERIALS AND METHODS

Patients
Inclusion and exclusion criteria have been previously reported.[13] Eligible patients were aged ≥15 years with unresectable, locally advanced, or metastatic LPS (pleomorphic, dedifferentiated, or myxoid/round cell) or LMS (uterine vs nonuterine) who were previously treated with at least a regimen containing an anthracycline and ifosfamide or an anthracycline and ≥1 additional cytotoxic chemotherapy regimens. Review boards at all participating institutions approved the study, which was conducted in accordance with the Declaration of Helsinki. Prior to any study-related procedures, all patients provided written informed consent.

Study Design
This was a phase 3, randomized, multicenter, active-controlled, open-label, parallel-group study conducted between May 2011 and January 2015. Per protocol, a final analysis of OS—defined as time between randomization and death due to any cause—was to be conducted after 376 death events had occurred, with a protocol-specified interim analysis after 50% of those deaths had occurred. At clinical cutoff for the interim analysis (September 16, 2013), 63 of 173 (36%) patients (dacarbazine) and 126 of 345 (37%) patients (trabectedin) had died. The final OS analysis was conducted following a clinical cutoff of January 5, 2015, after 123 of 193 (64%) patients (dacarbazine) and 258 of 384 (67%) patients (trabectedin) had died.

Efficacy Evaluations
The primary endpoint was OS. Investigator assessment of response data was used to evaluate secondary endpoints related to disease control, including PFS, ORR, time to progression, and duration of response. Clinical benefit rate (CBR, defined as complete + partial responses + stable disease with duration of ≥18 weeks) and duration of stable disease were analyzed as parameters for prolonged disease control. Investigator assessments of PFS were validated through an audit of approximately 60% of radiological scans by blinded, independent radiologists' review.[13] Following clinical cutoff for final OS, prespecified subgroup analyses were conducted for patients with LMS compared with patients with LPS.

The time to initiation of post-study anticancer therapy was performed as an exploratory analysis. This was defined as time between the date of randomization and the initiation date of any post-study surgery, radiation, or drug therapy. Four post hoc analyses were conducted to investigate the potential confounding effect of post-study anticancer therapies on the OS endpoint. Two of these analyses were also conducted for the interim analysis. Because greater proportions of patients in both arms received post-study anticancer therapy in the final OS analysis compared with the interim analysis, two additional sensitivity analyses were performed to adjust for the potential confounding effect of treatment change (Supporting Information).

Safety Evaluations
Detailed safety assessments have been reported previously.[13]

Statistical Analyses
The primary statistical methodology for comparing treatment impact on OS was the unstratified log-rank test. To detect a difference between a median OS of 10.0 and 13.5 months, respectively, in the dacarbazine and trabectedin arms (HR, 0.74) at an overall 2-sided significance level
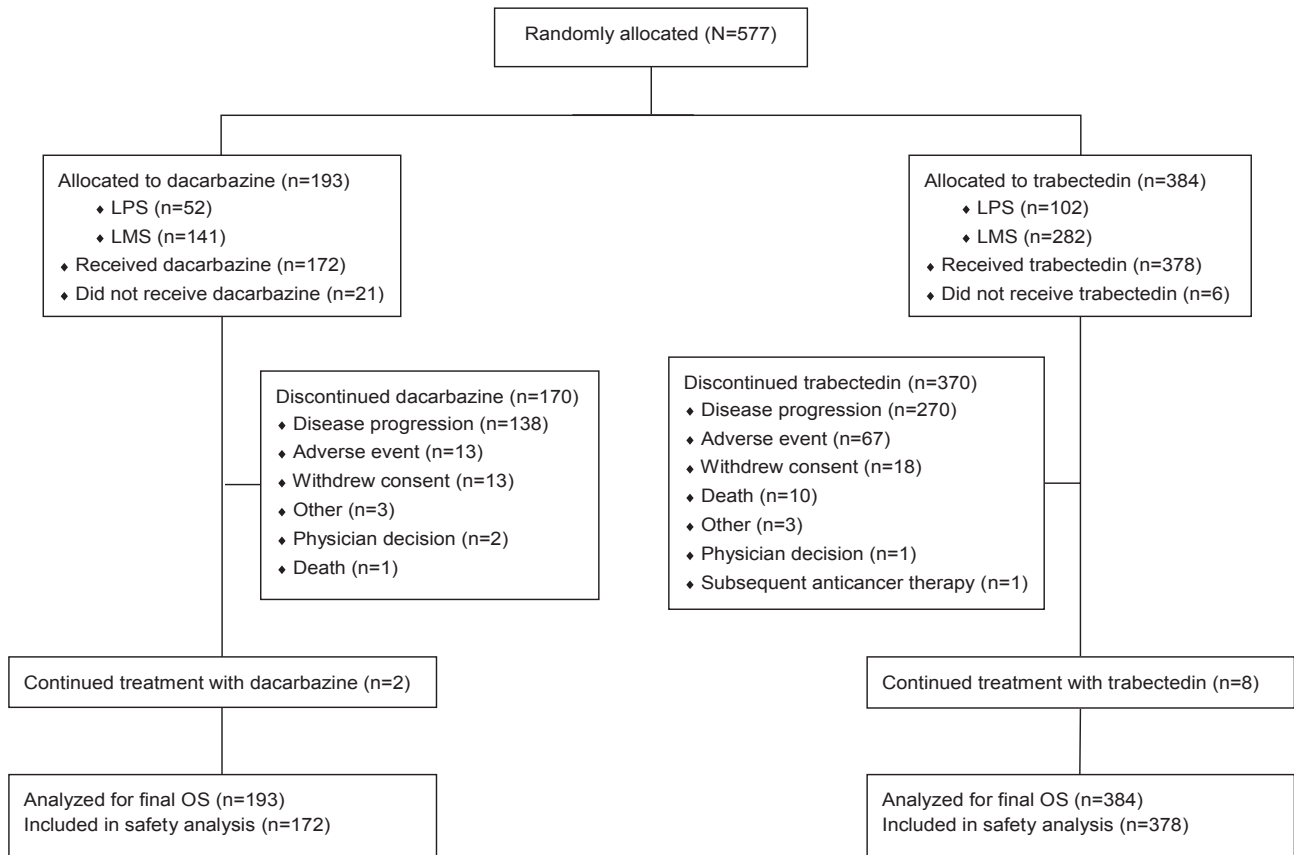
Figure 1. CONSORT diagram. LMS, leiomyosarcoma; LPS, liposarcoma; OS, overall survival.

of 0.05 with an 80% power required 376 death events. Employing a group sequential method with the O'Brien-Fleming boundaries, as implemented by the Lan-DeMets alpha spending function, 1 interim analysis and 1 final analysis were planned for OS. The cumulative alpha spent was 0.003 and 0.047 for the interim and final OS analyses, respectively. The PFS and ORR for the histological subgroups were tested using the Hochberg test procedure to control an overall type I error rate at the 2-tailed 0.05 level. Employing a Cox proportional hazards model, efficacy analyses were also conducted to include covariates of baseline Eastern Cooperative Oncology Group (ECOG) performance status score (0, 1), number of lines of prior chemotherapy (1, ≥2), L-sarcoma subtype (LPS, LMS), and age. Descriptive statistics were used in safety data analysis.

RESULTS
Patient Disposition and Baseline Demographics
After the interim analysis of OS, an additional 59 patients had enrolled, reflecting a total randomized population of 577 patients (384 trabectedin, 193 dacarbazine). Of these, 550 patients (378 trabectedin, 172 dacarbazine) received the study drug. The most frequent reason for nontreatment was withdrawal of consent for both the trabectedin and dacarbazine arms (0.8% vs 9.8%, respectively). At the time of final OS analysis, 370 patients (trabectedin) and 170 patients (dacarbazine) had discontinued study treatment, with disease progression most commonly cited as the reason for discontinuation in each arm (71% and 80%, respectively) (Fig. 1).

Of the 577 randomized patients, 423 (73%; 282 trabectedin, 141 dacarbazine) and 154 (27%; 102 trabectedin, 52 dacarbazine) had LMS and LPS, respectively. Patient demographics were generally well-balanced across both treatment arms (Table 1). Demographics with mild imbalances (≥5% frequency difference in trabectedin vs dacarbazine) were age ≥65 years (24% vs 19%), body mass index ≥30 (41% vs 36%), and female sex (68% vs 73%), which reflected the increased proportion of patients with uterine LMS histology (51% vs 62%) randomized to dacarbazine. Approximately 88% had ≥2

TABLE 1. Patient Demographics and Baseline Disease Characteristics by Histologic Subgroup

	Liposarcoma (n = 154)		Leiomyosarcoma (n = 423)		Total (n = 577)	
	Dacarbazine (n = 52)	Trabectedin (n = 102)	Dacarbazine (n = 141)	Trabectedin (n = 282)	Dacarbazine (n = 193)	Trabectedin (n = 384)
Age, y						
<65	42 (81)	79 (78)	114 (81)	211 (75)	156 (81)	290 (76)
≥65	10 (19)	23 (23)	27 (19)	71 (25)	37 (19)	94 (24)
Median (range)	53 (17-74)	57 (18-81)	56 (19-79)	57 (26-81)	56 (17-79)	57 (18-81)
Sex						
Men	31 (60)	71 (70)	22 (16)	51 (18)	53 (28)	122 (32)
Women	21 (40)	31 (30)	119 (84)	231 (82)	140 (73)	262 (68)
Race						
American Indian or Alaska Native	2 (4)	0	2 (1)	1 (0.4)	4 (2)	1 (0.3)
Asian	5 (10)	6 (6)	6 (4)	5 (2)	11 (6)	11 (3)
Black or African American	0	10 (10)	22 (16)	38 (14)	22 (11)	48 (13)
White	42 (81)	79 (78)	102 (72)	221 (78)	144 (75)	300 (78)
Other	0	1 (1)	0	4 (1)	0	5 (1)
Unknown	1 (2)	1 (1)	4 (3)	7 (3)	5 (3)	8 (2)
Not reported	2 (4)	5 (5)	5 (4)	6 (2)	7 (4)	11 (3)
Ethnicity						
Hispanic or Latino	9 (17)	9 (9)	14 (10)	25 (9)	23 (12)	34 (9)
Not Hispanic or Latino	40 (77)	91 (89)	113 (80)	245 (87)	153 (79)	336 (88)
Unknown	1 (2)	2 (2)	8 (6)	2 (1)	9 (5)	4 (1)
Not reported	2 (4)	0	6 (4)	10 (4)	8 (4)	10 (3)
Baseline BMI, kg/m^2						
<30	38 (73)	60 (59)	86 (61)	167 (59)	124 (64)	227 (59)
≥30	14 (27)	42 (41)	55 (39)	115 (41)	69 (36)	157 (41)
Median (range)	26.17 (13.3-40.5)	28.44 (18.8-58.7)	28.13 (15.4-66.7)	28.03 (14.5-78.1)	27.51 (13.3-66.7)	28.11 (14.5-78.1)
Baseline BSA, m^2	45 (87)	102 (100)	127 (90)	276 (98)	172 (89)	378 (98)
Median (range)	1.85 (1.3-2.3)	1.91 (1.3-2.6)	1.73 (1.4-2.4)	1.74 (1.3-2.4)	1.77 (1.3-2.4)	1.78 (1.3-2.6)
Histology						
Leiomyosarcoma	0	0	141 (100)	282 (100)	141 (73)	282 (73)
Uterine	0	0	88 (62)	144 (51)	88 (46)	144 (38)
Nonuterine	0	0	53 (38)	138 (49)	53 (27)	138 (36)
Liposarcoma	52 (100)	102 (100)	0	0	52 (27)	102 (27)
Myxoid +/− round cell	19 (37)	42 (41)	0	0	19 (10)	42 (11)
Pleomorphic	5 (10)	11 (11)	0	0	5 (3)	11 (3)
Dedifferentiated	28 (54)	49 (48)	0	0	28 (15)	49 (13)
Baseline ECOG PS score						
0	26 (50)	51 (50)	67 (48)	133 (47)	93 (48)	184 (48)
1	26 (50)	51 (50)	74 (53)	149 (53)	100 (52)	200 (52)
No. of lines of prior chemotherapy						
1	15 (29)	24 (24)	11 (8)	22 (8)	26 (14)	46 (12)
2	26 (50)	47 (46)	57 (40)	129 (46)	83 (43)	176 (46)
3	2 (4)	21 (21)	46 (33)	78 (28)	48 (25)	99 (26)
4	5 (10)	7 (7)	17 (12)	32 (11)	22 (11)	39 (10)
>4	4 (8)	3 (3)	10 (7)	21 (7)	14 (7)	24 (6)
Time from last disease progression to randomization, months						
Median (range)	0.67 (0.1-4.1)	0.92 (0.1-8.5)	0.92 (0.1-9.8)	0.85 (0.0-13.7)	0.85 (0.1-9.8)	0.85 (0.0-13.7)

Abbreviations: BMI, body mass index; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; PS, performance status.
Data are presented as n (%) unless specified otherwise.

prior lines of chemotherapy, and the median time from last disease progression to randomization was <1 month in both treatment arms (0.85 months each).

Exposure to Study Treatment
Patients in both treatment arms received inpatient or outpatient study treatment according to local preference.

Approximately 73% of trabectedin patients and 98% of dacarbazine patients received study treatment as outpatients. Consistent with the interim analysis, the median number of treatment cycles in the trabectedin arm was twice that of the dacarbazine arm (4 vs 2 cycles, respectively). The proportion of patients receiving extended courses of therapy increased in both treatment groups, relative to the

TABLE 2. Cumulative Treatment Exposure

	Liposarcoma (n = 147)		Leiomyosarcoma (n = 403)		Total (n = 550)	
	Dacarbazine (n = 45)	Trabectedin (n = 102)	Dacarbazine (n = 127)	Trabectedin (n = 276)	Dacarbazine (n = 172)	Trabectedin (n = 378)
Total treatment cycles	2 (1-21)	4 (1-41)	2 (1-30)	4 (1-44)	2 (1->30)[a]	4 (1->44)[a]
Cumulative treatment cycles, n (%)						
≥6	7 (16)	41 (40)	30 (24)	118 (43)	37 (22)	159 (42)
≥9	3 (7)	28 (28)	14 (11)	70 (25)	17 (10)	98 (26)
≥12	1 (2)	22 (22)	7 (6)	45 (16)	8 (5)	67 (18)
Cumulative dose[b]	2.0 (1.0-19.4)	4.2 (1.5-61.5)	2.1 (0.8-30.0)	6.0 (1.5-54.5)	2.0 (0.8-30.0)	5.9 (1.5-61.5)
Dose intensity, per cycle[b]	0.99 (0.5-1.0)	1.3 (0.7-1.6)	0.98 (0.4-1.0)	1.3 (0.7-1.6)	0.98 (0.4-1.0)	1.3 (0.7-1.6)
Relative dose intensity, %	0.99 (0.5-1.0)	0.89 (0.4-1.1)	0.98 (0.4-1.0)	0.87 (0.5-1.0)	0.98 (0.40-1.0)	0.88 (0.4-1.1)

Data are presented as median (range) unless specified otherwise.

[a]Patients with 44 and 30 cycles in the trabectedin and dacarbazine arms, respectively, were ongoing at the time of clinical cutoff for final overall survival analysis.

[b]Units of measure are g/m^2 for dacarbazine and mg/m^2 for trabectedin.

interim analysis, with more trabectedin-treated patients receiving ≥6 cycles (42% vs 22%), ≥9 cycles (26% vs 10%), and ≥12 cycles (18% vs 5%). At clinical cutoff, 8 (2%) and 2 (1%) patients had ongoing treatment with trabectedin and dacarbazine, respectively, and the maximum number of cycles received was 44 (ongoing) for trabectedin and 30 (ongoing) for dacarbazine. Treatment exposure for each agent was similar within the LPS and LMS patient subgroups (Table 2). Dose reductions and cycle delays, in accordance with protocol guidelines, were reported in 42% and 63% of trabectedin patients, respectively, compared with 12% and 42% of dacarbazine patients, respectively (Supporting Table 1). Dose reductions occurred most often in response to transaminase elevations, whereas dose delays were most often a result of hematologic toxicity (data not shown). Dose modifications did not appear to impact treatment efficacy, as 62% of trabectedin-treated patients achieving long-term exposure (≥6 cycles) underwent ≥1 dose reduction.

Efficacy

At the time of the final OS analysis, the median duration of survival follow-up was 21.2 months. Data were censored for 126 (33%) patients in the trabectedin arm and 70 (36%) in the dacarbazine arm. A total of 381 deaths had occurred: 258 (67%) and 123 (64%) in the trabectedin and dacarbazine arms, respectively. The median OS was 13.7 months (95% confidence interval [CI], 12.2-16.0) for the trabectedin arm and 13.1 months (95% CI, 9.1-16.2) for the dacarbazine arm. The unstratified final OS analysis showed no statistically significant improvement, with an overall reduction in risk of death by 7.3% in the trabectedin arm compared with the dacarbazine arm (HR, 0.93; 95% CI, 0.75-1.15; P = .49) (Fig. 2A).

A multivariate analysis of OS assessing age, subtype (LPS vs LMS), number of lines of prior chemotherapy (≥2 vs 1), and ECOG performance status score (1 vs 0) was performed. The number of lines of prior chemotherapy and ECOG performance status score were identified as parameters that independently predicted improved OS. Survival outcomes were better for patients with 1 prior lines of chemotherapy and an ECOG performance status score of 0 (Supporting Table 2). Subgroup analysis of 19 different demographic and baseline characteristics showed estimated HRs for OS consistent with the HR for the overall study population (0.93) (Supporting Fig. 1).

The use of post-study anticancer therapy was more balanced between treatment arms at the time of final OS analysis (71% vs 69% for trabectedin and dacarbazine, respectively) than at the time of interim analysis (47% vs 56%); however, qualitative differences were observed in patterns of therapies received (Supporting Table 3). Although post-study anticancer therapies were used at similar rates in both treatment arms, improved disease control observed in patients treated with trabectedin resulted in a correspondingly prolonged time to starting any post-study anticancer therapy in the trabectedin arm compared with the dacarbazine arm (median 6.8 vs 3.5 months; HR, 0.53; 95% CI, 0.43, 0.65; P < .001) (Fig. 3) (Supporting Table 3).

Given the prevalence of post-study anticancer therapy use, post hoc sensitivity analyses were conducted to investigate a potential confounding effect of those therapies on OS. A stronger trend toward improved survival was observed when OS analyses excluded patients with post-study anticancer therapy or censored them at initiation of that therapy (Supporting Fig. 2). An analysis
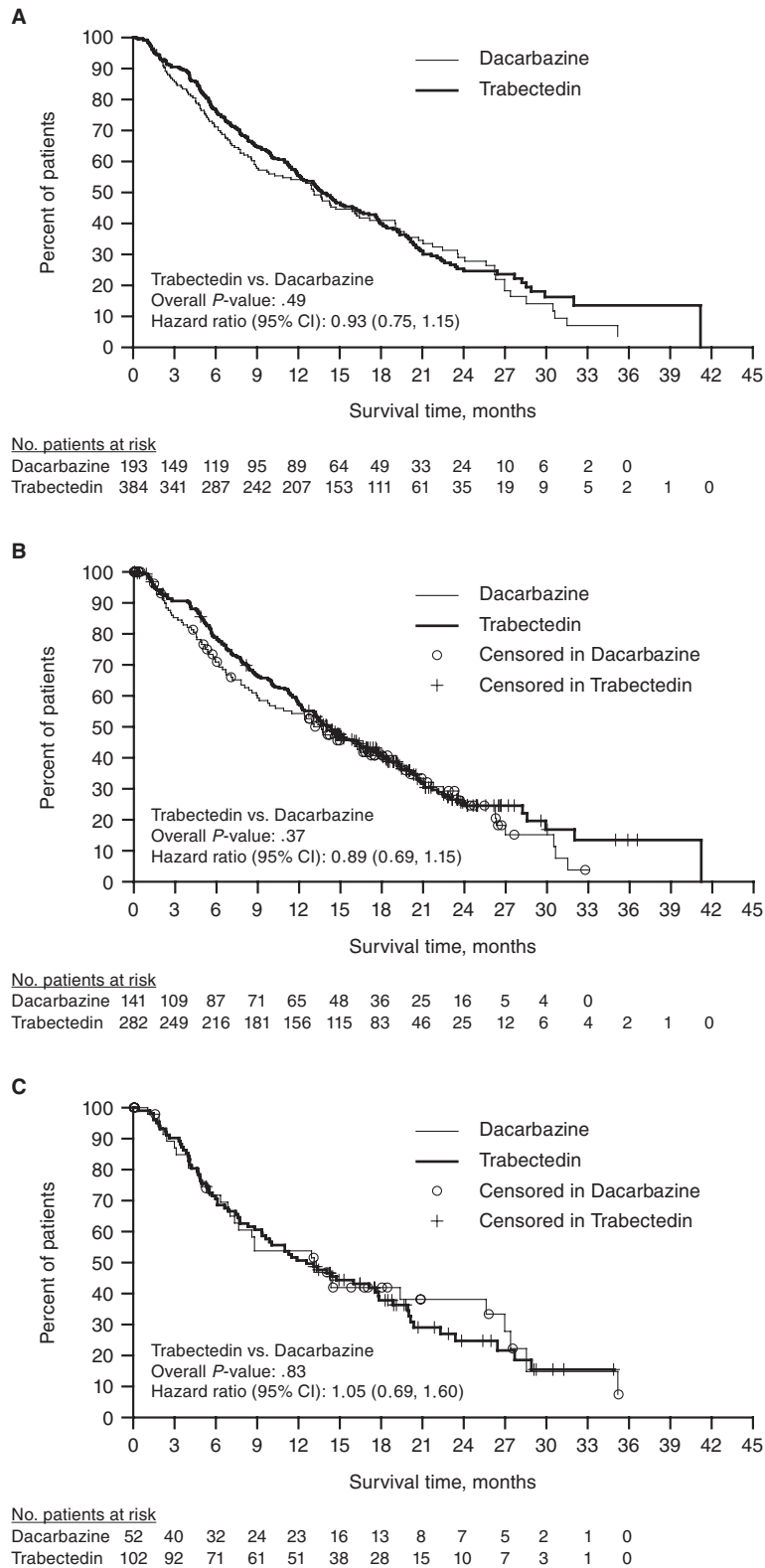
Figure 2. Kaplan-Meier estimate of overall survival (OS) at the final analysis. (A) OS for total patient population. (B) OS for patients with leiomyosarcoma. (C) OS for patients with liposarcoma. The median OS (95% confidence interval [CI]) for patients with leiomyosarcoma was 14.1 (12.2-16.5) versus 13.6 (9.1-17.2) months ($P = .37$) for patients in the trabectedin versus dacarbazine arms; for those with liposarcoma, the median OS was 13.1 (7.0-25.6) versus 12.6 (9.3-17.8) months ($P = .83$).
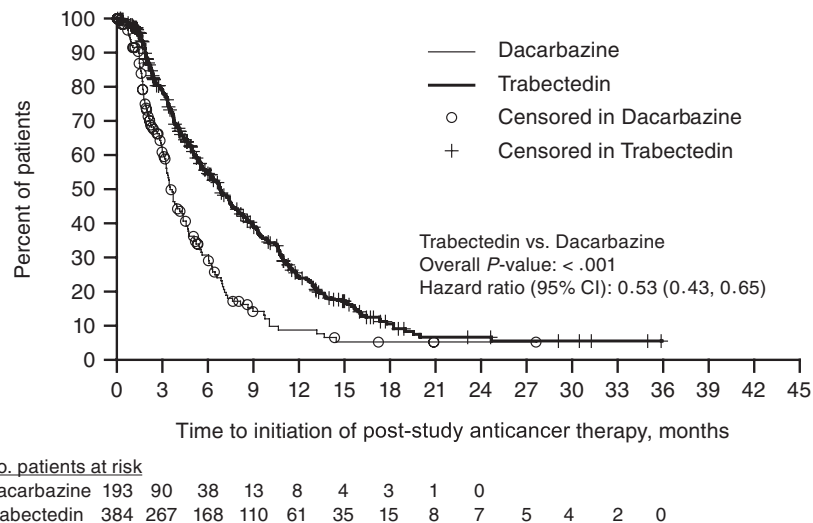
Figure 3. Time to post-study anticancer therapy utilization in trabectedin versus dacarbazine. CI, confidence interval.

with post-study anticancer therapy as a time-dependent covariate and an inverse probability of censoring weighted analysis were conducted. At the final OS analysis, the HR prior to receiving post-study anticancer therapy was 0.67 (95% CI, 0.45-1.01; $P = .06$) versus after receiving post-study anticancer therapy (HR, 1.23), which reflected earlier initiation of post-study anticancer therapy within the dacarbazine arm (95% CI, 0.95-1.59; $P = .11$) (Table 3).

Preplanned Histology-Specific Subgroup Analyses

In both LMS/LPS histologic subgroups, improvements in PFS, assessed at the time of the interim OS analysis, were of equal magnitude for patients treated with trabectedin vs dacarbazine (Fig. 4). For patients with LMS, the median PFS was 4.3 months (95% CI, 3.6-5.0 months) in the trabectedin arm versus 1.6 months (95% CI, 1.5-2.8 months) in the dacarbazine arm ($P < .001$). For patients with LPS, the median PFS (95% CI) was 3.0 months (95% CI, 1.5-4.8 months) in the trabectedin arm vs 1.5 months (95% CI, 1.4-2.7 months) in the dacarbazine arm ($P = .009$). Partial responses were observed in similar proportions for the trabectedin versus dacarbazine arms in both histologic subgroups (LMS, 10% vs 7%; LPS, 9% vs 6%). Among patients with LMS, the larger of the 2 subgroups, CBR was significantly higher in the trabectedin arm versus the dacarbazine arm (37% vs 20%; $P < .001$). The CBR among LPS patients, although similar in magnitude, did not reach statistical significance (28% vs 15% for trabectedin vs dacarbazine; $P = .096$) (Supporting Table 4). Results

TABLE 3. Sensitivity Analyses for Effect of Post-study Anticancer Therapy on Overall Survival

	HR (95% CI)	P
No post-study anticancer therapy	0.74 (0.49-1.11)	.14
Censored at post-study anticancer therapy	0.70 (0.47-1.06)	.09
Subsequent therapy as time-dependent covariate		
Prior to receiving post-study anticancer therapy	0.67 (0.45-1.01)	.06
After receiving post-study anticancer therapy	1.23 (0.95-1.59)	.11
Inverse probability of censoring weighted analysis	0.68 (0.45-1.02)	.06

Abbreviations: CI, confidence interval; HR, hazard ratio.

for OS were similar between trabectedin and dacarbazine, across both histologic subgroups, and consistent with the total study population OS, demonstrating no significant improvement (Fig. 2B,C).

Safety

The safety results from ET743-SAR-3007 have been reported previously and are consistent with the previously described safety profiles for each agent.[12,13] At the time of final OS analysis, no new or additional safety findings were noted.[13] The incidence of grade 3-4 toxicities were generally consistent for both treatment arms when assessed across the 2 histologic subgroups, with the most frequently observed severe toxicities reflecting laboratory-related parameters of hematologic toxicity and transient elevations in hepatic
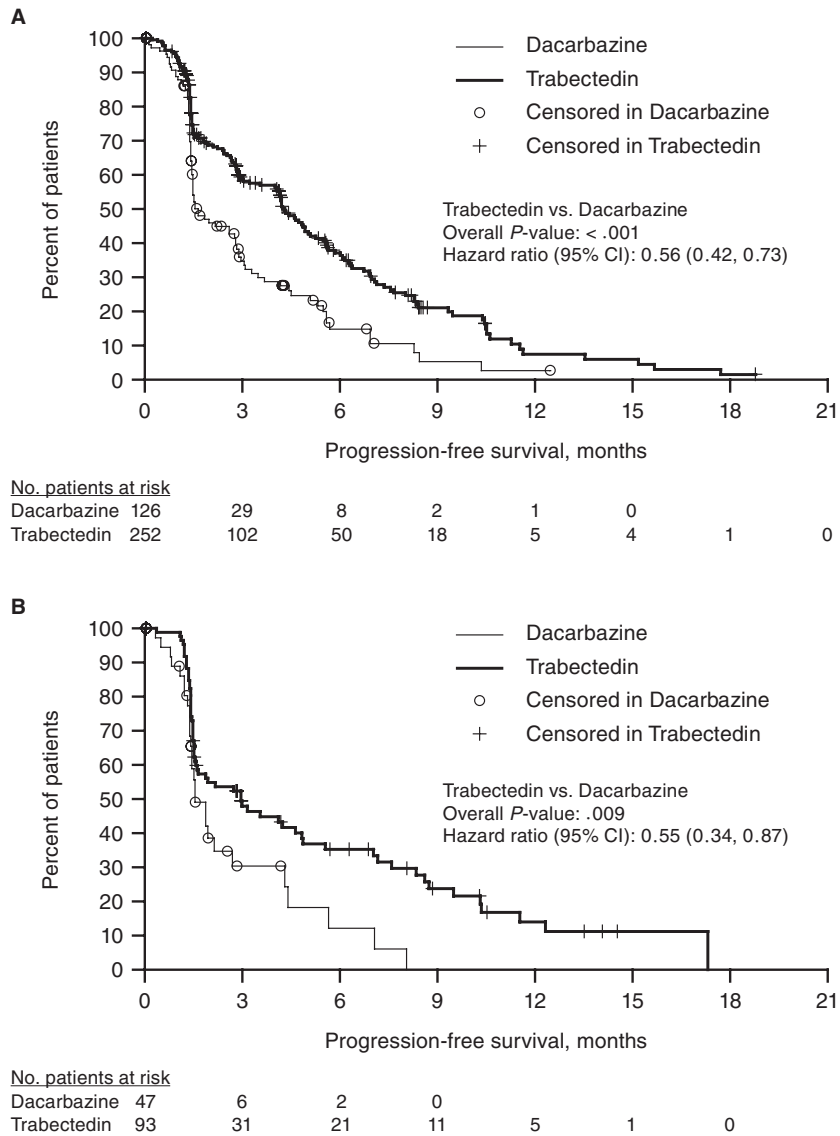
Figure 4. Kaplan-Meier estimate of progression-free survival (PFS) at final analysis. (A) PFS for patients with leiomyosarcoma. (B) PFS for patients with liposarcoma. CI, confidence interval.

alanine aminotransferase and aspartate aminotransferase. Febrile neutropenia was increased in the trabectedin arm for both histologic subgroups (4% for LMS and 7% for LPS) when compared with dacarbazine-treated patients (2% each for LMS or LPS) (Supporting Table 5). Although the incidence of patients who died within 60 days of first dose of study drug was similar in both treatment arms (7% each), deaths due to treatment-related adverse events were reported for 9 (2%) patients in the trabectedin arm and none in the dacarbazine arm. These deaths were primarily related to infections, rhabdomyolysis, and renal failure.

DISCUSSION

With the earliest phase 1 studies of trabectedin having been conducted in the late 1990s,[16-18] trabectedin is one of the most extensively studied therapeutics for treatment of STS. The reported PFS results of the randomized phase 3 ET743-SAR-3007 trial directly demonstrated the superior disease control of trabectedin over dacarbazine, confirming the results of the phase 2 STS-201 study[15] and historical comparisons that led to its initial approval in most countries outside the United States.[19] The corresponding safety profiles of trabectedin and dacarbazine, observed in ET743-SAR-3007, were

consistent with the safety profiles of both agents, with serious adverse events of grade 3-4 severity in the trabectedin arm characterized by transient elevations in hepatic transaminases and hematological toxicities. Toxicities were managed proactively in ET743-SAR-3007 through protocol-mandated monitoring and appropriate dose delays or dose reductions, minimizing toxicity and allowing patients to achieve prolonged disease control while maintaining their quality of life.[20]

The final OS analysis presented here from the ET743-SAR-3007 study reflected a median follow-up of 21.2 months and included 381 deaths (trabectedin, n = 258; dacarbazine, n = 123). Consistent with interim analysis findings, the final OS analysis did not demonstrate a statistically significant improvement in survival after treatment with trabectedin compared with dacarbazine (HR, 0.93; 95% CI, 0.75-1.15; P = .49) and was similar across both histologic subgroups.

Most patients in both treatment arms had received post-study anticancer therapies (71% and 69% for trabectedin and dacarbazine arms, respectively), which were initiated 3.3 months earlier in the dacarbazine arm, consistent with the earlier failure of this agent compared with trabectedin. Four different exploratory analyses evaluating influence of post-study anticancer therapy support a potential confounding effect of post-study anticancer therapy on OS results. Of note, the study was powered to detect a median survival difference of 10.0 and 13.5 months for dacarbazine and trabectedin, respectively. The improved performance of dacarbazine may reflect contribution of post-study anticancer therapies. The performance of the dacarbazine control arm in ET743-SAR-3007 stands in contrast to that observed in the recently reported eribulin phase 3 study, which enrolled a similar patient population contemporaneously with ET743-SAR-3007 and showed a median OS of 11.5 months in the dacarbazine control arm within the entire cohort and a median OS of 8.4 months within the LPS subgroup.[21-23] Differences in dacarbazine treatment dose, geographic distribution of patients, and baseline characteristics and stratification strategies may have contributed to the difference in survival outcomes in these 2 control arms.[22]

Although OS was not improved in this phase 3 trial, the previously described benefit in disease control with trabectedin—in terms of PFS, ORR, and CBR—was improved relative to dacarbazine in both histological subtypes studied. Similarly, greater proportions of trabectedin patients in both subgroups received extended treatment courses, with 40% of LPS and 43% of LMS

patients receiving ≥6 cycles (range, 1-41 and 1-44 cycles, respectively), versus 16% and 24% (range, 1-21 and 1-30 cycles, respectively) in the dacarbazine arm, reflecting both the efficacy and tolerability of trabectedin in these patients.

The results of this study distinguish trabectedin from 2 recently approved therapies, in which regulatory approvals were supported by data limited to either the LMS or LPS subtype: the pazopanib phase 3 PALETTE study included no patients with LPS based on results of a prior phase 2 study,[24] and the eribulin phase 3 study failed to demonstrate activity superior to dacarbazine in patients with LMS.[21,23] The findings highlight an unmet need in these histologic subtypes of STS and further support a role for trabectedin as a clinically meaningful treatment option for patients with unresectable, locally advanced, or metastatic LPS/LMS.

In conclusion, the final OS analysis of this phase 3 randomized trial demonstrated no statistically significant improvement in OS of trabectedin over dacarbazine, despite a significant and clinically relevant improvement in PFS with trabectedin that was observed equally in both histological subsets. Prevalent use of active post-study anticancer therapies may have confounded findings of the OS analysis. The improved OS in both arms may reflect an increasing number and variety of active therapies that are gradually improving the outcome for patients with metastatic sarcoma. The safety and efficacy results from this large prospective trial confirm and expand the favorable risk/benefit profile of trabectedin as a treatment option for LPS/LMS patients who have received prior anthracycline-based chemotherapy.

AUTHOR CONTRIBUTIONS

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