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FDA Approval Summary: Eribulin for Patients with Unresectable or Metastatic Liposarcoma Who Have Received a Prior Anthracycline-Containing Regimen

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Abstract

On January 28, 2016, the FDA approved eribulin (Halaven; Eisai Inc.) for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen. The approval was based on results from a single, randomized, open-label, active-controlled trial (Trial E7389-G000–309) enrolling 452 patients with advanced, locally recurrent or metastatic liposarcoma or leiomyosarcoma. Patients were randomized to eribulin 1.4 mg/m2 intravenously (i.v.) on days 1 and 8 or dacarbazine 850, 1,000, or 1,200 mg/m2 i.v. on day 1 of a 21-day cycle. There was a significant improvement in overall survival [OS; HR, 0.75; 95% confidence interval (CI), 0.61–0.94; $P = 0.0119$, stratified log-rank] for the overall population. Estimated median OS was 13.5 months (95% CI, 11.1–16.5) in the eribulin arm and 11.3 months (95% CI, 9.5–12.6) in the dacarbazine arm (HR, 0.75; 95% CI, 0.61–0.94; $P = 0.011$).There were no differences in PFS for the overall population. The effects of eribulin were limited to patients with liposarcoma ($n = 143$) based on preplanned, exploratory subgroup analyses of OS (HR, 0.51; 95% CI, 0.35–0.75) and progression-free survival (PFS; 0.52; 95% CI, 0.35–0.78). Response rates in both treatment arms were less than 5% in the overall population and in the

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liposarcoma subgroup. The safety profile was similar to that previously reported for eribulin. The FDA determined that, based on the data reviewed, the benefit–risk assessment for eribulin is positive for patients with advanced, pretreated liposarcoma.

Introduction

Soft-tissue sarcomas (STS) are a heterogeneous group of tumors that arise from mesenchymal cells and include over 50 different histologic subtypes (1, 2). The most common STS histologic subtypes are undifferentiated pleomorphic sarcoma, gastrointestinal stromal tumor, liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor (3). It is estimated that there will be 12,310 new cases and 4,990 deaths from all STS in the United States in 2016, which will account for <1% of all newly diagnosed cancers (4). Surgery and/or radiation are the mainstays of treatment for localized disease. Still, 40% to 50% of patients with high-risk features (including large and intermediate or high-grade tumors) will eventually develop metastatic disease (5). The outcome for patients with metastatic disease is dismal, with a median survival of approximately 11 to 15 months (6). Doxorubicin, alone or in combination with ifosfamide, is the systemic treatment option for metastatic STS for most histologic subtypes. However, chemosensitivity varies across different STS histologic subtypes. As more is learned about the biologic differences of these tumors, the treatment of advanced STS is becoming increasingly driven by histology and molecular alterations.

At the time of approval of eribulin mesylate (Halaven; Eisai Inc.), three drugs were FDA approved for the treatment of STS: doxorubicin, pazopanib, and trabectedin (7). The activity of doxorubicin was first described in the 1970s, and response rates of 10% to 25% have been reported (8). Often, doxorubicin is administered in combination with ifosfamide, which has demonstrated an improvement in response rate and progression-free survival (PFS) but has not shown an improvement in overall survival (OS) over doxorubicin alone (9, 10).

The FDA approved pazopanib in 2012 for patients with advanced STS who have received prior chemotherapy. The trial supporting this approval excluded patients with gastrointestinal stromal tumors (GIST) and liposarcoma; thus, labeling contains a limitationof use stating that the efficacy of pazopanib has not been demonstrated in patients with GIST and liposarcoma. Approval was based on demonstration of an improvement in PFS [HR, 0.35; 95% confidence interval (CI), 0.26–0.48; P<0.001], with a median PFS of 4.6 months in the pazopanib arm and 1.6 months in the placebo arm in a randomized (2:1), placebo-controlled trial enrolling 369 patients. There was no difference in OS between the two arms (11).

The FDA approved trabectedin in October 2015 for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who have received a prior anthracycline-containing regimen. Approval was based on an improvement in PFS in a randomized (2:1) open-label, active-controlled trial enrolling 518 patients with leiomyosarcoma or liposarcoma comparing trabectedin to dacarbazine. The trial demonstrated an improvement in PFS (HR, 0.55; 95% CI, 0.44–0.70; P < 0.001), with a

median PFS of 4.2 months in the trabectedin arm and 1.5 months in the dacarbazine arm. There was no difference in OS between the treatment arms (12–14).

Eribulin mesylate is a synthetic analogue of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai* (15). Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into nonproductive aggregates (16, 17). Eribulin received FDA approval on November 15, 2010, for the treatment of patients with metastatic breast cancer who have received an anthracycline and a taxane in either the adjuvant or metastatic setting, and at least two prior chemotherapeutic regimens for metastatic disease. The approval was based on an improvement in OS compared with physician's choice chemotherapy (18).

Clinical Trial Design

Trial E7389-G000–309 (Trial 309) was a randomized, open-label, multicenter trial comparing eribulin to dacarbazine in patients with advanced (locally recurrent, locally advanced, and/or metastatic) liposarcoma or leiomyosarcoma who had at least two prior regimens for advanced disease (19).

Patients were randomized 1:1 to receive eribulin 1.4 mg/m^2 by intravenous (i.v.) infusion on days 1 and 8 of a 21-day cycle ordacarbazineateither850mg/m^2,1,000mg/m^2,or1,200mg/m^2 i.v. (dose chosen by the investigator prior to randomization) on day 1 of a 21-day cycle. Treatment continued until disease progression or unacceptable toxicity. Randomization was stratified by histology (liposarcoma vs. leiomyosarcoma), region (region 1: United States and Canada vs. region 2: Western Europe, Australia, and Israel vs. region 3: Eastern Europe, Latin America, and Asia), and number of prior regimens for advanced STS (2 vs. >2). Key eligibility criteria were age ≥18 years; histologically confirmed diagnosis of advanced (locally recurrent, locally advanced, or metastatic disease incurable by surgery or radiotherapy) liposarcoma (including dedifferentiated, myxoid/round cell, and pleomorphic subtypes; patients with well-differentiated liposarcoma were not eligible) or leiomyosarcoma; Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, 1, or 2; radiographic evidence of disease progression within 6 months prior to randomization; prior treatment with at least two standard systemic regimens for STS, one of which must have included an anthracycline (unless contraindicated); adequate renal, bone marrow, blood coagulation, and liver function; and measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Radiologic studies of tumor response were performed every 6 weeks for the first 12 weeks and every 9 weeks thereafter. Tumor response was evaluated by the investigator according to RECIST v1.1.

The primary endpoint was OS. Based on an HR of 0.71 assuming median 6 months for dacarbazine and 8.5 months for eribulin, a total of 353 deaths was required to have a power of 90% at an alpha level of 0.05 (two-sided). Assuming an enrolment rate of 20 patients per month, it was estimated that approximately 450 patients needed to be randomized. There was one planned interim OS analysis at 247 (70%) deaths using O'Brien Fleming approach for alpha allocation. Other efficacy endpoints included PFS, clinical benefit

rate, objective response rate (ORR), and quality-of-life scores. There was no prespecified statistical procedure to adjust for multiple testing of other efficacy endpoints.

Results

A total of 452 patients were randomized at 110 sites worldwide: 228 to the eribulin arm and 224 to the dacarbazine arm. Four hundred and fifty patients received at least one dose of study drug (227 with eribulin and 223 with dacarbazine). One patient randomized to the eribulin arm incorrectly received dacarbazine and is included in the dacarbazine group for the safety analysis and in the eribulin group for the efficacy analysis. The inspection of one foreign clinical site by the FDA Office of Scientific Investigations (OSI) revealed substantial deficiencies in trial conduct such that the data for the six patients enrolled at this site was considered unreliable. Therefore, the data described below and reflected in the prescribing information for eribulin is based upon 446 patients from 109 sites worldwide: 225 in the eribulin arm and 221 in the dacarbazine arm.

The demographics and baseline disease characteristics of patients randomized in Trial 309 were similar (Table 1), except that a greater proportion of patients in the eribulin arm were female and more patients in the dacarbazine arm had an ECOG PS of 1 or 2. The majority of patients were White, and the largest group was treated in region 2 (46%). More patients with leiomyosarcoma (68%) than liposarcoma (32%) were treated on this trial. The majority of patients (67%) had high-grade tumors. At the time of enrollment, half the patients had received more than two prior systemic therapies for their disease.

At the time of data cutoff for the final OS analysis, only two patients (one in each arm) remained on study therapy. Progression of disease was the most common reason (86% in both arms) for treatment discontinuation. Eight percent of patients in the eribulin arm and 4% of patients in the dacarbazine arm discontinued therapy for study drug toxicity. Eight(3.6%) patients in the eribulin arm and 14 (6.3%) patients in the dacarbazine arm withdrew study consent.

Efficacy

The efficacy results from Trial 309 are summarized in Table 2 and Fig. 1. There was a significant improvement in OS (HR, 0.75; 95% CI, 0.61–0.94; $P = 0.0119$, stratified log-rank) in the intent-to-treat trial population. The median OS was 13.5 months (95% CI, 11.1–16.5) for patients randomized to the eribulin arm and 11.3 months (95% CI, 9.5–12.6) for patients randomized to the dacarbazine arm.

In a prespecified, exploratory subgroup analysis based on histologic subtype, OS was longer for those in the liposarcoma subgroup who were randomized to eribulin (stratified HR, 0.51; 95% CI, 0.35–0.75) compared with patients in the liposarcoma subgroup randomized to dacarbazine. The median OS for patients with liposarcoma on the eribulin arm was 15.6 months (95% CI, 10.2–18.6) and 8.4 months (95% CI, 5.2–10.1) for patients on the dacarbazine arm. Therewas noapparent difference in OS for patients with leiomyosarcoma (HR, 0.90; 95% CI, 0.69–1.18). The median OS was 12.8 months (95% CI, 10.3–14.8)

and 12.3 months (95% CI, 11.0–15.1) for patients on the eribulin and dacarbazine arms, respectively.

Additional exploratory analyses of OS by patients with liposarcoma based on subtype also suggest an effect favoring treatment with eribulin as follows:

- Dedifferentiated: (HR, 0.45; 95% CI, 0.25–0.82); median 16.7 months(95%CI,10.5–18.9)and8.1months(95%CI,4.2–10.6)
- Myxoid/round cell: (HR, 0.79; 95% CI, 0.42–1.47); median 12.5 months (95% CI, 6.5–18.6) and 9.6 months (95% CI, 4.1–15.5)
- Pleomorphic: (HR, 0.21; 95% CI, 0.06–0.76); median 22.2 months [95% CI, 5.9–not reached (NR)] and 6.7 months (95% CI, 3.2–10.1)

There was no difference in PFS or confirmed ORR for the overall population (stratified HR, 0.86; 95% CI, 0.69–1.06). The median PFS was 2.6 months (95% CI, 2.0–2.8) versus 2.6 months (95% CI, 1.7–2.7) for eribulin and dacarbazine, respectively. The ORR was 4% (95% CI, 1.8–7.5) in the eribulin arm versus 5% (95% CI, 2.5–8.7) in the dacarbazine arm. Figure 1 shows the Kaplan–Meier curve of PFS for the overall population in Trial 309.

The exploratory analysis of PFS in patients with liposarcoma appeared to favor the eribulin arm (HR, 0.52; 95% CI, 0.35–0.78). The median PFS was 2.9 months versus 1.7 months for the eribulin and dacarbazine arms, respectively. In contrast, the exploratory analysis of PFS in patients with leiomyosarcoma did not suggest any difference (HR, 1.05; CI, 0.81–1.35). The median PFS was 2.2 months versus 2.6 months for the eribulin and dacarbazine arms, respectively. Figure 1 shows the Kaplan–Meier curve for PFS by histologic subtype.

Safety

Of the 452 patients randomized in Trial 309, 444 received at least one dose of study drug and were included in the safety analysis. The median duration of treatment was similar: 10 weeks (range, 3–112 weeks) in the eribulin group versus 9 weeks (range, 3–110 weeks) in the dacarbazine group. More patients in the eribulin group (7.5%) discontinued therapy due to an adverse reaction when compared with the dacarbazine group (4.9%). The most common adverse reactions leading to eribulin discontinuation were fatigue (0.9%), peripheral neuropathy (0.9%), and thrombocytopenia (0.9%). Twenty-six percent of patients required at least one dose reduction of eribulin. The most frequent adverse reactions that led to dose reduction were neutropenia (18%) and peripheral neuropathy (4%).

Table 3 displays common adverse reactions in Trial 309. The most common adverse drug reactions (≥20%) in patients in the eribulin group, which occurred more commonly than in the dacarbazine group were neutropenia (63% vs. 30%), alopecia (35% vs. 2.7%), constipation (32% vs. 26%), peripheral neuropathy (29% vs. 8%), and pyrexia (28% vs. 14%). Other clinically important common adverse reactions of eribulin were fatigue/asthenia (63%) and nausea (41%). Grade 3 and 4 adverse reactions occurred in 67% of patients in the eribulin group and 56% of patients in the dacarbazine group. The most frequent (≥5%) grade 3 to 4 adverse reactions in the eribulin group were neutropenia (32%), hypokalemia (5%), and hypocalcemia (5%). Nonfatal serious adverse reactions occurred in 33% of patients

in the eribulin group and 31% of patients in the dacarbazine group. In the eribulin group, serious adverse reactions that occurred in 2% of patients were neutropenia (5%), pyrexia (4%), and anemia (2%). Two deaths occurred in the eribulin group due to neutropenic sepsis.

Discussion

In Trial 309, randomization was stratified by STS subtype, as liposarcoma and leiomyosarcoma are biologically and histologically different diseases. Although treatment with eribulin resulted in a statistically significant improvement in OS for the overall population in Trial 309, based on exploratory subgroup analyses, the treatment effect of eribulin appeared to be driven entirely by the stratified subgroup of patients with liposarcoma (HR, 0.51; 95% CI, 0.35–0.75), which made up only 34% of the trial population. There was no improvement in median OS for patients with leiomyosarcoma treated with eribulin (HR, 0.90; 95% CI, 0.69–1.18). This differential treatment effect by STS histologic subtype was also observed in the supportive efficacy endpoint, PFS. The improvement in OS in the patients with liposarcoma was accompanied by a corresponding improvement in PFS in this subgroup and the absence of improvement in PFS in patients with leiomyosarcoma. The OS benefit appeared to be consistent for all of the liposarcoma subtypes included in the trial. In addition, the differential treatment effect is plausibly explained by the biological differences between liposarcoma and leiomyosarcoma (3, 20). Taken together, the data submitted in the application led to the conclusion that substantial evidence of effectiveness had been demonstrated for, and was limited to, patients with liposarcoma.

A safety analysis was performed for patients with liposarcoma and compared with the overall safety population in Trial 309 as well as the postmarketing experience with eribulin in the metastatic breast cancer population. No new or differential safety signals were identified. The primary safety risks of eribulin are neutropenia and peripheral neuropathy and were deemed acceptable in light of a severe and life-threatening disease with an unmet medical need.

The FDA conducts a risk-based approach to timely identification of clinical investigator sites for on-site inspection by the FDA during the review of marketing applications. The purpose of these inspections is to audit and verify clinical trial data submitted to the FDA in a marketing application and to ensure that investigators, sponsors, and contract research organizations who conduct such clinical studies comply with United States laws and regulations covering good clinical practice. Although the overall results of the trial were deemed reliable, FDA inspections were conducted of the applicant and of three clinical study sites. One of these three clinical sites revealed significant issues related to trial conduct and patient monitoring, indicating that at this clinical site, the trial was not conducted in accordance with good clinical practice (GCP) guidelines. The data were deemed unreliable, and the six patients enrolled at this site were removed from both the safety and efficacy analyses. The FDA conducted an additional sensitivity analysis of the primary endpoint of Trial 309, including the six patients at this site, and the overall trial results did not change. The FDA’s inspection of other clinical sites and the sponsor did not reveal any significant issues. Although inspectional findings serious enough to warrant exclusion of data from the

assessment of a drug's safety and effectiveness is uncommon, this finding reinforces the need for continued risk-based selection of clinical sites for inspection by the FDA.

In summary, based upon review of the clinical data from this single randomized trial, the benefits of improvement in survival and PFS outweighed the risks of transient neutropenia and peripheral neuropathy for the treatment of adult patients with unresectable or metastatic liposarcoma.

References

1. Clark MA, Fisher C, Judson I, Thomas JM. Soft-tissue sarcomas in adults. N Engl J Med 2005;353:701–11. [PubMed: 16107623]
2. Casali PG, Blay JY. Soft tissue sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2010:v198–203. [PubMed: 20555081]
3. Fletcher CM, Bridge JA, Hogendoorn PW, Mertens F, editors. World Health Organization Classification of tumours of soft tissue and bone. 4th ed. Lyon (France): IARC Press; 2013.
4. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2016. CA Cancer J Clin2016;66:7–30.
5. Maki RG. Role of chemotherapy in patients with soft tissue sarcomas. Expert Rev Anticancer Ther 2004;4:2,229–36. [PubMed: 15056053]
6. Van Glabbeke M, van Oosterom AT, Oosterhuis JW, Mouridsen H, Crowther D, Somers R, et al. Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2185 patients treated with anthracycline-containing first-line regimens—A European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol 1999;17:150–7. [PubMed: 10458228]
7. Drugs Approved for Soft Tissue Sarcoma, National Cancer Institute, updated Dec. 10, 2015. Available from: http://www.cancer.gov/about-cancer/treatment/drugs/soft-tissue-sarcoma.
8. Benjamin RS, Wiernik PH, Bachur NR. Adriamycin: a new effective agent in the therapy of disseminated sarcomas. Med Pediatr Oncol 1975;1:63. [PubMed: 1232527]
9. Lorigan P, Verweig J, Papai Z, Rodenhuis S, Le Cesne A, Leahy MG, et al. Phase III trial of two investigational schedules of ifosfamide compared with standard-dose doxorubicin in advanced or metastatic soft tissue sarcoma: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol 2007;25:3144–50. [PubMed: 17634494]
10. Judson I, Verweij J, Gelderblom H, Hartmann JT, Schoffski P, Blay JY, et al. 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;15:415–23. [PubMed: 24618336]
11. Pazopanib (Votrient), GlaxoSmithKline, USPI 09/22/2015, Drugs@FDA. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022465s021lbl.pdf.
12. Yovine A, Riofrio M, Blay JY, Brain E, Alexandre J, Kahatt C, et al. Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. J Clin Oncol 2004;22:890–9. [PubMed: 14990645]
13. Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Staddon A, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. J Clin Oncol 2016;34:786–93. [PubMed: 26371143]
14. Trabectedin (Yondelis), Janssen Products, USPI 10/23/2015, Drugs@FDA. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207953s000lbl.pdf.
15. Hirata Y, Uemura D. Halichondrins: antitumor polyether macrolides from a marine sponge. Pure Appl Chem 1986;58:701–10.
16. Okouneva T, Azarenko O, Wilson L, Littlefield BA, Jordan MA. Inhibition of centromere dynamics by eribulin (E7389) during mitotic metaphase. Mol Cancer Ther 2008;7:2003–11. [PubMed: 18645010]

17. Towle MJ, Salvato KA, Budrow J, Wels BF, Kuznetsov G, Aalfs KK, et al. In vitro and in vivo anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B. Cancer Res 2001;61: 1013–21. [PubMed: 11221827]

18. Cortes J, Vahdat L, Blum JL, Twelves C, Campone M, Roche H, et al. Phase II study of the halichondrin b analog eribulin mesylate in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline, a taxane, and capecitabine. J Clin Oncol 2001;28: 3922–8.

19. Schöffski P, Chawla S, Maki R, Italiano A, Gelderblom H, Choy E, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomized, open-label, multicenter, phase 3 trial. Lancet 2016;387:1629–37. [PubMed: 26874885]

20. Coindre JM, Terrier P, Guillou L, Le Doussal V, Collin F, Ranchere D, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer 2001;91:1914–26. [PubMed: 11346874]

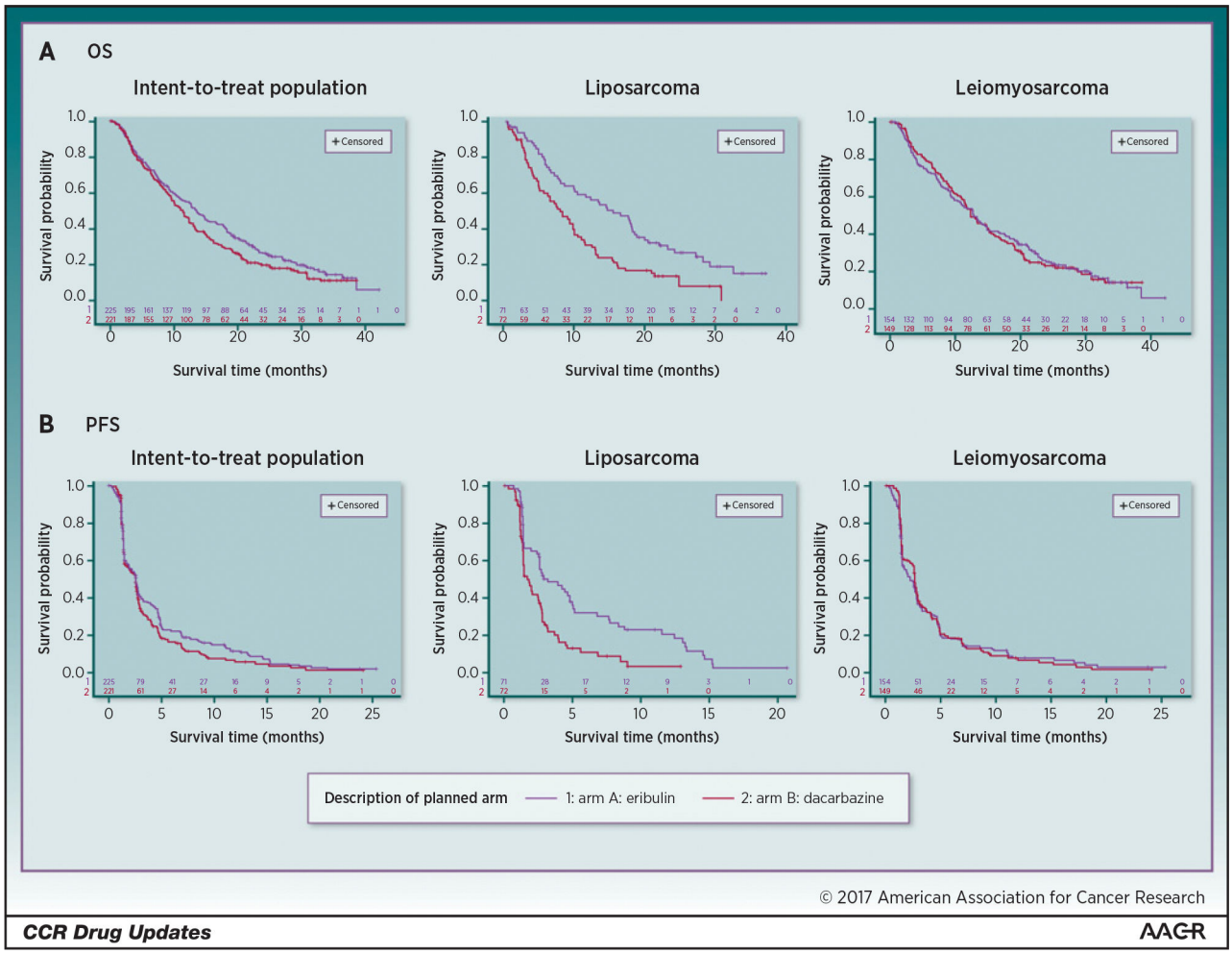

Figure 1.
Kaplan–Meier curves of OS and PFS in Trial 309.

Table 1.

Key baseline characteristics of patients in Trial 309[a]

	Eribulin (*N* = 225) *n* (%)	Dacarbazine (*N* = 221) *n* (%)
Sex		
Female	158 (70)	140 (63)
Male	67 (30)	81 (37)
Age		
Median, years	56	57
Range, years	28–83	24–83
<65	176 (78)	175 (79)
≥65	49 (22)	46 (21)
Region		
Region 1: United States and Canada	87 (39)	86 (39)
Region 2: Western Europe, Australia, Israel	103 (46)	102 (46)
Region 3: Eastern Europe, Latin America, Asia	35 (16)	33 (15)
Race		
White	159 (71)	165 (75)
Not applicable[b]	35 (16)	30 (14)
Asian[c]	18 (8)	16 (7)
Black or African American	6(3)	6(3)
Other	6 (3)	4 (2)
Native Hawaiian or other Pacific Islander	1 (<1)	0
Country		
United States	79 (35)	78 (35)
France	35 (16)	30 (14)
Italy	15 (7)	23 (10)
Britain	10 (4)	10 (5)
Spain	10 (4)	13 (6)
ECOG PS		
0	108 (48)	87 (39)
1	114 (51)	121 (55)
2	3 (1)	13 (6)
Histology of primary tumor		
Adipocytic (total)[d]	71 (31)	72 (32)
Dedifferentiated	32 (14)	37 (17)
Myxoid/round cell	30 (13)	26 (12)
Pleomorphic	13 (6)	15 (7)
Leiomyosarcoma	154 (68)	149 (67)
Tumor grade		
High	148 (66)	150 (68)
Intermediate	76 (34)	68 (31)

	Eribulin (*N* = 225) *n* (%)	**Dacarbazine (*N* = 221) *n* (%)**
Not done	1 (<1)	3 (1)
Number of prior regimens		
1	2 (1)	3 (1)
2	111 (49)	100 (45)
>2	112 (50)	118 (53)
Planned starting dose of dacarbazine		
850 mg/m^2	50 (22)	44 (20)
1,000 mg/m^2	136 (60)	141 (64)
1,200 mg/m^2	39 (17)	36 (16)

[a] Data from one study site enrolling six patients were excluded.

[b] Information on race and ethnicity not collected in some countries (e.g., France).

[c] Includes Asian, Japanese, Chinese, other Asian.

[d] Total histology based on interactive voice response system (IVRS) randomization categorization; subtypes of liposarcoma based on case report forms.

Table 2.

Key efficacy results in Trial 309

	ITT population		Liposarcoma		Liposarcoma	
	Eribulin (*N* = 225)	**Dacarbazine (*N* = 221)**	**Eribulin (*N* = 71)**	**Dacarbazine (*N* = 72)**	**Eribulin (*N* = 154)**	**Dacarbazine (*N* = 149)**
OS						
Deaths, n (%)	173 (77)	179 (81)	52 (73)	63 (88)	121 (79)	116 (78)
Median OS (m) (95% CI)	13.5 (11.1–16.5)	11.3 (9.5–12.6)	15.6 (10.2–18.6)	8.4 (5.2–10.1)	12.8 (10.3–14.8)	12.3 (11.0–15.1)
Stratified HR (95% CI)		0.75 (0.61–0.94)		0.51 (0.35–0.75)	0.90 (0.69–1.18)	
PFS						
Events, n (%)	194 (86)	185 (84)	57 (80)	59 (82)	137 (89)	126 (85)
Median PFS (m) (95% CI)	2.6 (2.0–2.8)	2.6 (1.7–2.7)	2.9 (2.6–4.8)	1.7 (1.4–2.6)	2.2 (1.5–2.7)	2.6 (2.2–2.9)
Stratified HR (95% CI)		0.86 (0.69–1.06)		0.52 (0.35–0.78)	1.05 (0.81–1.35)	
ORR						
Events, n (%)	9 (4.0)	11 (5.0)	1 (1.4)	0	8 (5.2)	11 (7.4)
95% CI	1.8–7.5	2.5–8.7	0–7.6	0–4.2	2.3–10	3.7–12.8

Abbreviations: ITT, intent-to-treat; m, months.

Table 3.

Common adverse reactions[a] occurring in ≥10% of patients (all grades) in the eribulin arm at a higher incidence (≥5%) than in the dacarabzine arm or ≥2% (grade 3 or 4) in Trial 309

	Eribulin (*N* = 223)		Dacarbazine (*N* = 221)	
System organ class preferred term	**All grades *n* (%)**	**Grade 3–4 *n* (%)**	**All grades n (%)**	**Grade 3–4 *n* (%)**
All patients with adverse event	224 (99.1)	152 (67.3)	218 (97.3)	126 (56.3)
Blood and lymphatic system disorders				
Anemia[b]	158 (69.9)	9 (4.1)	116 (51.7)	13 (5.8)
Neutropenia[b]	142 (62.8)	72 (31.8)	67 (30.0)	20 (8.9)
Hepatobiliary disorders				
Increased ALT[b]	97 (42.9)	5 (2.3)	62 (27.8)	5 (2.3)
Increased AST[b]	81 (35.8)	2 (0.9)	36 (16.1)	1 (0.5)
Gastrointestinal disorders				
Constipation	71 (32.2)	2 (0.9)	58 (25.9)	1 (0.5)
Abdominal pain[c]	65 (29.1)	4 (1.8)	50 (22.6)	9 (4.1)
Stomatitis	31 (13.9)	2 (0.9)	11 (5.0)	1 (0.5)
Skin and subcutaneous tissue disorders				
Alopecia	79 (35.0)	NA[e]	6 (2.7)	NA[e]
Metabolism and nutrition disorders				
Hypokalemia[b]	68 (30.0)	12 (5.4)	31 (13.9)	6 (2.8)
Hypocalcemia[b]	63 (27.9)	11 (4.8)	41 (18.3)	3 (1.4)
Hypophosphatemia[b]	45 (19.9)	8 (3.2)	24 (11.2)	3 (1.4)
Nervous system disorders				
Peripheral neuropathy[d]	65 (29.1)	7 (3.1)	17 (7.6)	1 (0.5)
Headache	40 (17.9)	0	22 (9.9)	0
General disorders and administration site conditions				
Pyrexia	63 (27.9)	2 (0.9)	31 (13.8)	1 (0.5)

	Eribulin (*N* = 223)		Dacarbazine (*N* = 221)	
System organ class preferred term	**All grades *n* (%)**	**Grade 3–4 *n* (%)**	**All grades n (%)**	**Grade 3–4 *n* (%)**
Infections and infestations				
Urinary tract infection	25 (11.1)	5 (2.2)	12 (5.4)	1 (0.5)

[a] Adverse reactions were graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

[b] Based on laboratory testing. Each test incidence is based on the number of patients who had both baseline and at least one on-study measurement and at least one grade increase from baseline. Eribulin group (range, 221–222) and dacarbazine group (range, 214–215).

[c] Includes PT terms abdominal pain, upper abdominal pain, lower abdominal pain.

[d] Includes PT terms neuropathy peripheral, peripheral sensorimotor neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and parasthesia.

[e] Not applicable (NA; grading system does not specify >grade 2 for alopecia).