CCR Drug Updates

Clinical Cancer Research

FDA Approval Summary: Trabectedin for Unresectable or Metastatic Liposarcoma or Leiomyosarcoma Following an Anthracycline-Containing Regimen

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Abstract

On October 23, 2015, the FDA approved trabectedin, a new molecular entity for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen. Approval was based on results of a single, randomized, active-controlled, 518-patient, multicenter study comparing the safety and efficacy of trabectedin 1.5 mg/m^2 as a 24-hour continuous intravenous (i.v.) infusion once every 3 weeks with dacarbazine 1,000 mg/m^2 i.v. once every 3 weeks. Treatment with trabectedin resulted in a statistically significant improvement in progression-free survival (PFS), with a PFS of 4.2 months and 1.5 months for trabectedin and dacarbazine, respectively (HR, 0.55; 95% confidence interval, 0.44–0.70; unstratified log-rank test, $P < 0.001$). The most common adverse reactions ($\geq$20%) were nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, and headache. Serious adverse reactions included anaphylaxis, neutropenic sepsis, rhabdomyolysis, hepatotoxicity, cardiomyopathy, and extravasation resulting in tissue necrosis. A postmarketing trial was required to evaluate the serious risk of cardiomyopathy. This approval provides another treatment option in a setting where no drug has been shown to improve overall survival. A key regulatory consideration during review of this application was the use of PFS as an endpoint to support regular approval of trabectedin. *Clin Cancer Res; 23(24); 7448–53. ©2017 AACR.*

Introduction

Liposarcoma and leiomyosarcoma represent 40% to 50% of all cases of unresectable or metastatic soft-tissue sarcoma (STS). Approximately 12,310 new cases of adult STS and 4,990 deaths due to STS were projected in 2016 (1). The median overall survival (OS) from time of diagnosis is typically 8 to 18 months. Approximately half of the patients diagnosed with liposarcoma and leiomyosarcoma (L-type STS) present with metastatic disease. At the time of the review of the New Drug Application (NDA) for trabectedin, only two approved drugs existed for the treatment of STS. In 1974, the FDA approved doxorubicin for the treatment of STS; however, the increasing risk of cardiomyopathy with cumulative doses typically limits doxorubicin treatment to 450 to 600 mg/m^2. In 2012, the FDA approved pazopanib for patients with advanced STS who have received prior chemotherapy, but efficacy has not been demonstrated for patients with adipocytic STS (2).

The FDA granted orphan drug designation for trabectedin for the treatment of STS in 2004. On November 24, 2014, Janssen submitted an NDA for trabectedin for treatment of patients with unresectable or metastatic liposarcoma and leiomyosarcoma who received a prior anthracycline-containing regimen based on the results of study ET743-SAR-3007, an active-controlled (dacarbazine), randomized trial. Herein, we summarize the FDA review and approval of this marketing application.

Chemistry

Trabectedin (YONDELIS; Janssen Research & Development, LLC) is an alkylating drug that binds guanine residues forming DNA adducts, resulting in a bending of the DNA helix to the major groove and triggering a cascade of events affecting the activity of DNA binding proteins, including some transcription factors, and DNA repair pathways, resulting in perturbation of the cell cycle and eventual cell death (3–5). Trabectedin, which is administered as a 24-hour intravenous (i.v.) infusion, contains no preservative and unlike other antineoplastic drugs, does not directly inhibit the growth of microbial agents under direct challenge studies. The risk of iatrogenic infection arising from possible bacterial contamination was assessed by review of infectious complications observed in clinical trials and postmarketing experience outside the United States. Although no safety signal was identified, trabectedin should be administered through a 0.2 μm in-line filter to mitigate potential infectious risks.

Nonclinical Pharmacology and Toxicology

Toxicology studies of trabectedin conducted in mice, rats, dogs, and monkeys predicted the observed adverse reaction profile

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observed in clinical studies. The toxicology studies also identified testicular degeneration in rats, suggesting impairment of male fertility. Dedicated nonclinical fertility studies with trabectedin were not performed. Studies with radiolabeled trabectedin demonstrated placental transfer and fetal uptake of trabectedin. Dedicated nonclinical embryofetal development studies were not interpretable, as exposures achievable with the recommended human dose could not be achieved in animals due to maternal toxicity; therefore, the basis for labeling statements regarding the risk of embryofetal toxicity is the mechanism of action of trabectedin rather than animal data. Trabectedin is genotoxic in both *in vitro* and *in vivo* studies. Carcinogenicity studies were not required based on the limited survival of patients receiving second- or greater-line therapy with trabectedin (median survival of 13.7 months for the trabectedin arm in study ET743-SAR-3007).

Clinical Pharmacology

Although an MTD of 1.8 mg/m^2 was identified in early clinical trials, the recommended trabectedin dosage regimen of 1.5 mg/m^2 as a 24-hour i.v. infusion once every 3 weeks (Q3W) is based on the regimen employed in study ET743-SAR-3007 and other late-stage trials conducted in STS (6). The pharmacokinetics of trabectedin is characterized by a rapid initial decline and a slower exponential phase following infusion, with a terminal half-life of approximately 175 hours (7.3 days). No accumulation is observed following multiple dosing at 3-week intervals, as the trough concentrations are orders lower than the peak concentrations. Population pharmacokinetic analyses suggest that the pharmacokinetics of trabectedin is dose proportional (over the dose range of 0.024 to 1.8 mg/m^2), and exposure is time independent. The estimated mean (percent coefficient of variation) clearance of trabectedin is 31.5 L/hr (50%). Trabectedin is mainly excreted in feces, with minimal urine excretion.

CYP3A is the predominant CYP enzyme responsible for the hepatic metabolism of trabectedin. Drug interactions between trabectedin and strong inhibitors and inducers of CYP3A enzymes were identified in clinical pharmacology studies and may be clinically important. Specifically, a 66% increase in trabectedin exposure was observed with coadministration with a strong CYP3A inhibitor (ketoconazole), and a 31% decrease in trabectedin exposure was observed with coadministration with a strong CYP3A inducer (rifampin). Product labeling recommends avoidance of strong CYP3A inhibitors and inducers in patients taking trabectedin or when such a drug is required for short-term use, to administer drugs affecting CYP3A between 1 week after the trabectedin infusion and the day prior to the next trabectedin infusion.

Clinical Trial Design

The primary source of clinical data supporting approval was study ET743-SAR-3007 (ClinicalTrials.gov identifier NCT01343277), a randomized (2:1), open-label, active-controlled trial comparing the safety and efficacy of trabectedin to dacarbazine in patients with unresectable or metastatic L-type sarcoma who had received prior anthracycline-containing systemic therapy. Patients were randomized to trabectedin 1.5 mg/m^2 as a 24-hour i.v. infusion once Q3W or dacarbazine 1,000 mg/m^2 as an i.v. infusion (20 to 120 minutes) Q3W. All patients in the trabectedin arm received dexamethasone 20 mg i.v. bolus prior to each dose to mitigate the risks of grade 3 and 4 toxicities, including hepatotoxicity. Patients in the dacarbazine arm were not offered trabectedin at the time of disease progression. Randomization was stratified by L-sarcoma subtype (liposarcoma vs. leiomyosarcoma), Eastern Cooperative Oncology Group (ECOG) Performance Status (PS; 0 vs. 1), and number of prior chemotherapy regimens (1 vs. $\geq$2). The major efficacy outcomes were investigator-assessed progression-free survival (PFS) according to RECIST 1.1, OS, objective response rate (ORR), and duration of response. The study was designed to have more than 90% power to detect an HR of 0.667 with a two-sided alpha of 0.05, assuming a median PFS of 2.5 months for the dacarbazine arm and 3.75 months for the trabectedin arm.

The original primary endpoint for study E743-SAR-3007 was OS. However, following FDA approval of pazopanib based on an improvement in PFS and prior to the data cutoff data for the PFS analysis in study E743-SAR-3007, Janssen proposed and the FDA agreed to consider the results of mature PFS and ORR results as a basis for possible accelerated approval for trabectedin. Janssen also agreed to conduct a blinded-independent review [blinded independent review committee (BIRC)] of PFS and ORR in retrospective audit in an agreed-upon subset (high accruing sites) as a supportive analysis and to evaluate for potential ascertainment bias as the first stage of the Dodd two-stage plan. The BIRC reviewed all available radiologic scans from approximately 19 investigative sites ($\geq$9 patients per site) in 307 patients (59% of the intent-to-treat population). For the BIRC analysis, symptomatic progression in the absence of radiographic evidence was not considered a PFS event. No clinical data other than prior radiotherapy were provided to the BIRC.

Efficacy

At the time of the PFS analysis, a total of 518 patients (intent-to-treat population) were randomized: 345 to the trabectedin arm and 173 patients to the dacarbazine arm. The baseline demographic and disease characteristics were similar between the two arms. The median patient age was 56 years (range, 17–81); 30% were male; 76% were Caucasian, 12% African American, and 4% Asian; 73% had leiomyosarcoma and 27% liposarcoma; 49% had an ECOG PS of 0; and 89% received at least two prior chemotherapy regimens. The most common ($\geq$20%) prestudy chemotherapeutic agents administered were doxorubicin (90%), gemcitabine (81%), docetaxel (74%), and ifosfamide (59%). Approximately 10% of patients had received pazopanib.

The study demonstrated a statistically significant improvement in investigator-assessed PFS for the trabectedin arm compared with dacarbazine [HR, 0.55; 95% confidence interval (CI), 0.44–0.70; unstratified log-rank test, $P < 0.001$; see Fig. 1]. The estimated median PFS was 4.2 months for the patients randomized to trabectedin and 1.5 months for patients randomized to dacarbazine. The BIRC-assessed subgroup analysis of radiographic PFS (rPFS) per RECIST 1.1 was conducted in approximately 60% of the intent-to-treat population. The estimated overall HR for rPFS in this subgroup was 0.55 (95% CI, 0.40–0.75), which appears similar to that observed with the investigator-based analyses. Exploratory analyses for PFS in subgroups defined by demographic (e.g., age, race, sex, or country) and baseline disease characteristics (e.g., ECOG, L-type sarcoma subtype, line of chemotherapy, disease status after last treatment, prior surgery, or radiotherapy) favored the trabectedin arm for all subgroups evaluated.

The final analysis of OS failed to demonstrate a difference between treatment arms (HR, 0.93; 95% CI, 0.75–1.15; unstratified log-rank test, $P = 0.49$; see Table 1). The estimated median

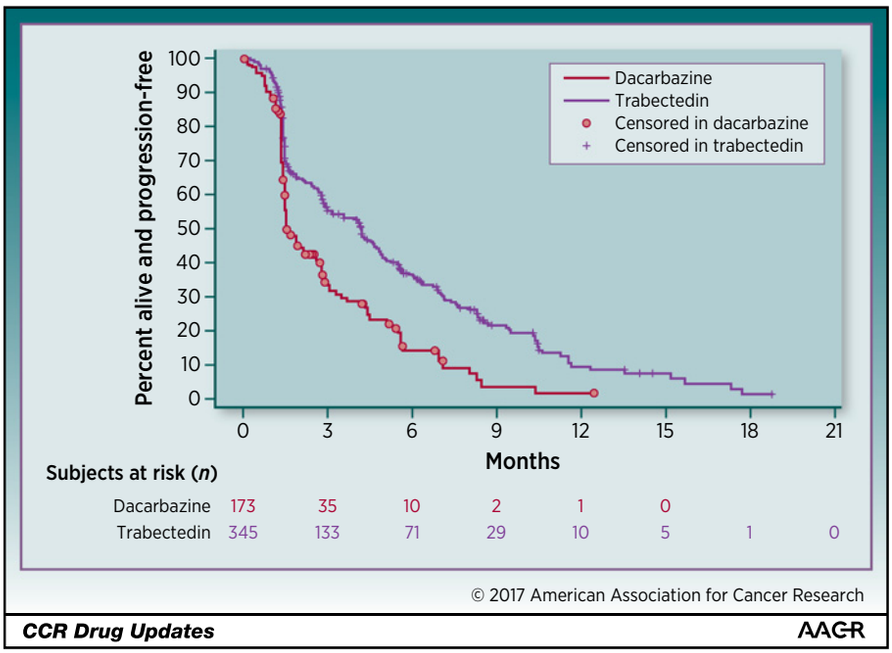

Figure 1.
Kaplan–Meier curves of PFS for trial ET743-SAR-3007 (11).

OS was 13.7 months (95% CI, 12.2–16.0) for the trabectedin arm and 13.1 months (95% CI, 9.1–16.2) for the dacarbazine arm. In addition, there was no improvement in ORR (trabectedin 7% vs. dacarbazine 6%).

Safety

The FDA reviewed safety data from 378 patients with liposarcoma or leiomyosarcoma exposed to at least one cycle of trabectedin 1.5 mg/m^2 as a 24-hour infusion once Q3W in study ET743-SAR-3007 and pooled safety data from 755 trabectedin-treated patients with STS enrolled in six additional open-label, single-arm studies (377 patients). In the pooled safety population, 197 (26%) patients were exposed to trabectedin for ≥6 months and 57 (8%) patients exposed to trabectedin for ≥1 year. The median age was 54 years (range, 18–81 years), 63% were female, and all patients had metastatic STS.

Serious adverse reactions in clinical trials included anaphylaxis, neutropenic sepsis, rhabdomyolysis, hepatotoxicity, and cardiomyopathy. The finding of cardiomyopathy was identified in review of study ET743-SAR-3007; this unanticipated finding was not well characterized. Therefore, a postmarketing trial was required by the FDA to further evaluate the serious risk of cardiomyopathy in patients receiving trabectedin. In addition, a second postmarketing trial was required to evaluate the pharmacokinetics and determine the safe dose, if any, of trabectedin in patients with impaired hepatic function. Patients with elevated serum bilirubin levels above the upper limit of normal (ULN) or with an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level above 2.5 times the ULN were not eligible for study ET743-SAR-3007. Despite this restriction as well as the requirement for dexamethasone premedication in all patients, the incidence of grade 3 or 4 elevated liver function tests was 35%, and the incidence of drug-induced liver injury (Hy's law) was 1.3% in patients treated with trabectedin.

The most common adverse reactions to trabectedin (≥20%) were nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, and headache (see Table 2). The most common laboratory abnormalities (≥20%) were increases in AST or ALT, increased alkaline phosphatase, hypoalbuminemia, increased creatinine, increased creatinine phosphokinase, anemia, neutropenia, and thrombocytopenia.

In study ET743-SAR-3007, adverse reactions resulting in permanent discontinuation of trabectedin occurred in 26% (98/378) of patients; the most common adverse reactions requiring termination of trabectedin were increased liver function tests (defined as ALT, AST, alkaline phosphatase, bilirubin; 5.6%), thrombocytopenia (3.4%), fatigue (1.6%), increased

Table 1. Efficacy results for trial ET743-SAR-3007

Efficacy endpoint	Trabectedin, *N* = 345	Dacarbazine, *N* = 173
PFS		
PFS events, *n* (%)	217 (63%)	112 (65%)
Disease progression	204 (59%)	109 (63%)
Death	13 (4%)	3 (2%)
Median (95% CI, months)	4.2 (3.0–4.8)	1.5 (1.5–2.6)
HR (95% CI)[a]	0.55 (0.44–0.70)	
P value[b]	<0.001	
OS[c]		
Events, *n* (%)	258 (67%)	123 (64%)
Median (95% CI, months)	13.7 (12.2–16.0)	13.1 (9.1–16.2)
HR (95% CI)[a]	0.93 (0.75–1.15)	
P value[b]	0.49	
ORR (CR + PR)		
Patients, *n* (%)	23 (7%)	10 (6%)
95% CI[d]	(4.3–9.8)	(2.8–10.4)
Duration of response (CR + PR)		
Median (95% CI, months)	6.9 (4.5–7.6)	4.2 (2.9–NE)

Abbreviations: CR, complete response; NE, not estimable; PR, partial response.
[a]Cox proportional hazards model with treatment group as the only covariate.
[b]Unstratified log-rank test.
[c]Based on 384 patients randomized to trabectedin arm and 193 patients randomized to dacarbazine.
[d]Fisher exact CI.
Source: Drugs@FDA (11).

Table 2. Selected adverse reaction occurring in >10% of patients receiving trabectedin and at a higher incidence than in the control arm for trial ET743-SAR-3007

System organ class	Trabectedin ($N = 378$)		Dacarbazine ($N = 172$)	
adverse reaction[a]	All grades[b] (%)	Grades 3–4 (%)	All grades (%)	Grades 3–4 (%)
Gastrointestinal disorders				
Nausea	75	7	50	1.7
Vomiting	46	6	22	1.2
Constipation	37	0.8	31	0.6
Diarrhea	35	1.6	23	0
General disorders and administration site conditions				
Fatigue[c]	69	8	52	1.7
Peripheral edema	28	0.8	13	0.6
Metabolism and nutrition disorders				
Decreased appetite	37	1.9	21	0.6
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	25	4.2	20	1.2
Nervous system disorders				
Headache	25	0.3	19	0
Musculoskeletal and connective tissue disorders				
Arthralgia	15	0	8	1.2
Myalgia	12	0	6	0
Psychiatric disorders				
Insomnia	15	0.3	9	0

[a]Limited to adverse reactions at a rate of ≥10% in the trabectedin arm and at a rate higher in the trabectedin arm compared with dacarbazine arm by ≥5% in overall incidence or by ≥2% for grade 3 to 4 adverse reactions.
[b]Toxicity grade is based on the NCI Common Terminology Criteria for Adverse Events Version 4.0.
[c]Fatigue is a composite of the following adverse event terms: fatigue, asthenia, and malaise.
Source: Drugs@FDA (11).

creatine phosphokinase (1.1%), and decreased ejection fraction (1.1%). Adverse reactions that led to dose reductions occurred in 42% (158/378) of patients treated with trabectedin; the most common such adverse reactions were increased liver tests (24%), neutropenia (including febrile neutropenia; 8%), thrombocytopenia (4.2%), fatigue (3.7%), increased creatine phosphokinase (2.4%), nausea (1.1%), and vomiting (1.1%). Adverse reactions led to dose interruptions in 52% (198/378) of patients treated with trabectedin; the most common such adverse reactions were neutropenia (31%), thrombocytopenia (15%), increased liver tests (6%), fatigue (2.9%), anemia (2.6%), increased creatinine (1.1%), and nausea (1.1%).

Regulatory Insights

PFS has been used in applications for oncology drugs to support either a "regular" approval or an "accelerated" approval (7). Approval of a drug under the provisions of 21 C.F.R., 314, subpart D (regular approval; ref. 8), is based on endpoints demonstrating clinical benefit, that is, how a patient feels, functions, or survives. The FDA may grant an accelerated approval under the provisions of 21 C.F.R. 314, subpart H (9), for a drug intended to treat patients with a serious or life-threatening disease based on demonstration of treatment effects on a surrogate or intermediate endpoint that is reasonably likely to predict clinical benefit and that provides a meaningful advantage over available therapy. As a condition of an accelerated approval, additional trials to verify and describe the clinical benefit of the drug have been required. For some diseases, especially rare diseases, powering a study for OS may take many years, limiting access of a potentially valuable drug to patients. For these patients, defining clinical benefit can also be challenging. A robust improvement in PFS that is statistically persuasive and is of large, clinically relevant magnitude—in the context of a favorable risk–benefit profile—can serve as evidence of direct clinical benefit or evidence that is reasonably likely to predict clinical benefit. One of the major considerations during review of the trabectedin application was assessing the clinical benefit of PFS for patients with unresectable or metastatic liposarcoma or leiomyosarcoma who have received a prior anthracycline-containing regimen.

The assessment of the relative risks and benefits of the use of trabectedin for the treatment of liposarcoma and leiomyosarcoma is based on the totality of evidence included in the NDA and consideration of expert opinion (see Table 3). Because of the absence of an improvement in survival, the FDA considered whether the improvement in PFS observed in study ET743-SAR-3007 was of sufficient magnitude to be considered direct evidence of benefit. Demonstration of effects on PFS that are large in magnitude was previously used as the basis for approval of pazopanib for STS and for other cancers (e.g., non–small cell lung cancer) where the absolute increase in PFS corresponds to increases in median PFS of several months.

Because of the limited number of therapeutic options for the treatment of liposarcoma, leiomyosarcoma, and other STS, the clinical meaningfulness of PFS has evolved over the past decade in discussion with key opinion leaders. PFS as an endpoint to support approval in patients with advanced STS after prior chemotherapy was discussed at a March 20, 2012, Oncologic Drug Advisory Committee (ODAC) for pazopanib (NDA 022465), and overall, the committee members supported PFS improvement of sufficient magnitude as a clinically meaningful endpoint (10). The trial supporting approval of pazopanib was a double-blind, placebo-controlled, multicenter study that compared pazopanib with placebo in patients with metastatic STS who had received prior systemic therapy that included anthracyclines. The primary analysis of PFS demonstrated a 3-month improvement in median PFS with pazopanib based on efficacy assessments by a blinded independent radiology review (HR, 0.35; 95% CI, 0.26–0.48; P value < 0.001). The Kaplan–Meier-estimated median PFS was

Table 3. FDA benefit–risk assessment

Dimension	Evidence and uncertainties	Conclusions and reasons
Analysis of condition	• Median OS of unresectable or metastatic STS is typically 8 to 13 months. • Liposarcoma and leiomyosarcoma represent 40% to 50% of STS; approximately half of these patients present with metastatic disease.	Unresectable or metastatic STS is a serious and life-threatening disease.
Current treatment options	• Doxorubicin is the only chemotherapy approved for first-line treatment. Pazopanib is approved, but use is limited based on histologic subtype; efficacy has not been demonstrated for patients with adipocytic STS.	Current treatment options are limited for patients with unresectable or metastatic STS.
Benefit	• Trabectedin resulted in a statistically significant 45% reduction in the risk of progressive disease or death compared with dacarbazine (HR, 0.55; 95% CI, 0.44–0.70; $P < 0.001$).	Trabectedin resulted in clinically meaningful improvements in PFS compared with dacarbazine.
Risk	• In the ET743-SAR-3007 trial, the most common adverse reactions ($\geq$20%) were nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, and headache. • The most common laboratory abnormalities ($\geq$20%) were increases in AST or ALT, increased alkaline phosphatase, hypoalbuminemia, increased creatinine, increased creatinine phosphokinase, anemia, neutropenia, and thrombocytopenia.	Observed survival benefits outweigh risks in this patient population, which represents an unmet medical need.
Risk management	• A postmarketing requirement to characterize the risk of cardiomyopathy and its sequelae in the patients exposed to trabectedin was recommended. • A second postmarketing requirement is required to evaluate the pharmacokinetics and determine the safe dose, if any, of trabectedin in patients with impaired hepatic function.	No significant safety concerns identified during review requiring risk management beyond labeling.

4.6 months in patients randomized to pazopanib as compared with 1.6 months in patients randomized to placebo with no effect on OS (HR, 0.87; 95% CI, 0.67–1.12; $P = 0.26$). The ODAC members agreed that a treatment effect resulting in longer PFS is valuable, because patients can harbor very large, bulky disease that can impinge on vital structures. ODAC members advised that patients can live with bulky disease and relatively minor morbidity, but rapid progression can lead to increased morbidity. The ODAC members also advised that, given the low incidence and heterogeneity of STS, completion of a trial adequately powered to detect small but clinically important effects on OS could take many years, limiting access of a potentially valuable drug to patients. Based on the advice of the ODAC, the FDA agreed that the increase in PFS demonstrated by pazopanib over placebo was clinically meaningful in patients with advanced STS who have received prior chemotherapy and granted pazopanib regular approval on April 26, 2012, for this indication.

Thus, when approached by Janssen regarding modification of the ongoing ET743-SAR-3007 trial, the FDA agreed that the proposal to detect an improvement of PFS at an HR of 0.55, corresponding to a 2.7-month improvement in median PFS over an active, commonly used off-label cytotoxic drug (dacarbazine), may represent clinical benefit. However, given the open-label nature of the trial, the FDA required supportive evidence of the effect on PFS as assessed by the BIRC in a defined subgroup.

This patient population represents an area of unmet medical need, as at the time the trabectedin NDA was submitted, there was only one approved drug (pazopanib) for treatment of patients with advanced STS who have received prior chemotherapy, and pazopanib has a limitation of use that the efficacy of pazopanib has not been demonstrated in patients with liposarcoma. The magnitude of improvement in PFS observed in study ET743-SAR-3007 was clinically meaningful in this rare disease population with limited therapeutic options that improve OS. The reliability of the improvement in PFS is supported by the consistency of the treatment effect across multiple subgroups, including those defined by STS subtype (leiomyosarcoma and liposarcoma), and supported by the BIRC assessment of PFS. The efficacy and safety results demonstrated in this trial support a conclusion that trabectedin has a favorable benefit–risk profile in patients with unresectable or metastatic liposarcoma or leiomyosarcoma who have received prior anthracycline therapy. The FDA granted regular approval to trabectedin for this indication on October 23, 2015.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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