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ORIGINAL REPORT

Phase II Study of ET-743 in Advanced Soft Tissue Sarcomas: A European Organisation for the Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group Trial

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
This nonrandomized multicenter phase II study was performed to evaluate the activity and safety of Ecteinascidin (ET-743) administered at a dose of 1.5 mg/m^2 as a 24-hour continuous infusion every 3 weeks in patients with pretreated advanced soft tissue sarcoma.

Patients and Methods
Patients with documented progressive advanced soft tissue sarcoma received ET-743 as second- or third-line chemotherapy. Antitumor activity was evaluated every 6 weeks until progression, excessive toxicity, or patient refusal.

Results
One hundred four patients from eight European institutions were included in the study (March 1999 to November 2000). A total of 410 cycles were administered in 99 assessable patients. Toxicity mainly involved reversible grade 3 to 4 asymptomatic elevation of transaminases in 40% of patients, and grade 3 to 4 neutropenia was observed in 52% of patients. There were eight partial responses (PR; objective regression rate, 8%), 45 no change (NC; > 6 months in 26% of patients), and 39 progressive disease. A progression arrest rate (PR + NC) of 56% was observed in leiomyosarcoma and 61% in synovialosarcoma. The median duration of the time to progression was 105 days, and the 6-month progression-free survival was 29%. The median duration of survival was 9.2 months.

Conclusion
ET-743 seems to be a promising active agent in advanced soft tissue sarcoma, with no cumulative toxicities. The 6-months progression-free survival observed in advanced soft tissue sarcoma compares favorably with those obtained with other active drugs tested in second-line chemotherapy in previous European Organisation for the Research and Treatment of Cancer trials. The median overall survival was unusually long in these heavily pretreated patients mainly due to the high number of patients who benefit from the drug in terms of tumor control.

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INTRODUCTION

Results of first-line chemotherapy in adult advanced soft tissue sarcoma remain disappointing. Only two drugs, doxorubicin and ifosfamide, have demonstrated a relatively consistent single-agent activity yielding response rates of 10% to 25%.[1-4] Importantly, despite higher response rates achieved in some studies using combination chemotherapy, multidrug regimens have not demonstrated any advantage in terms of overall survival when compared with single-agent doxorubicin given at optimal doses.[1] In the

last 20 years, new drugs have not demonstrated any relevant activity in advanced soft tissue sarcoma.[5] So patients who relapse after anthracycline-based regimens are appropriate candidates for new investigational strategies. Moreover, despite this high unmet medical need, pharmaceutical research in this disease is limited.

Ecteinascidin (ET-743) is a novel tetrahydroisoquinoline compound isolated from the marine ascidian *Ecteinascidia turbinata*.[6] ET-743 is a unique DNA-interacting agent with covalent binding to the DNA minor groove.[7] ET-743 blocks cell cycle progression in G2/M phase through a *p-53*–independent apoptotic process[8] and inhibits the transcriptional activation of inducible genes.[9] In addition, ET-743 has shown important preclinical activity against a number of human solid tumor cell lines and xenografts, including sarcomas, with minimal or no cross-resistance to several conventional chemotherapeutic agents.[10,11]

Based on these preclinical findings, 163 patients were included in five phase I studies assessing six different schedules of administration with doses of ET-743 ranging from 0.05 mg/m^2 to 1.9 mg/m^2.[12-16] Dose-limiting toxicities were transient ALT and AST elevation and neutropenia. Activity (one complete remission [CR] and three partial responses [PRs]) was seen in patients with advanced soft tissue sarcoma using the 24- and 3-hour infusion schedules. Due to the large amount of information available with the 24-hour continuous infusion, this schedule was selected for the phase II programs in soft tissue sarcoma at the recommended dose of 1.5 mg/m^2.

PATIENTS AND METHODS

Patient Population

Patients eligible for entry in the study were required to have histologically proven measurable metastatic or unresectable locoregional recurrent soft tissue sarcoma. Patients were registered in three specific strata: group A: non–gastrointestinal stromal tumor (GIST) patients with prior chemotherapy, response evaluation with WHO criteria; group B: GIST patients without prior chemotherapy, response evaluation with WHO criteria; group C: non-GIST patients with prior chemotherapy, response evaluation with both Response Evaluation Criteria in Solid Tumors (RECIST) and WHO criteria (after the completion of group A).

Results from GIST patients (group B) will be separately reported. The present report is based on pooled data of groups A and C, since inclusion criterias and study design were similar for the two groups. Response evaluations of the two groups of patients were performed according to WHO criteria of response in the present article. Comparison between WHO and RECIST criteria of response for group C will be presented separately.

All patients were to have a documented progressive disease at inclusion, with defined index lesions at physical examination, on x-rays, and on computed tomography scan. No concurrent antitumor therapy was allowed. Other eligibility criteria were age older than 18 years; performance status 0 or 1; no functionally important cardiovascular disease, no prior cancer (except adequately treated in situ carcinoma of cervix or basal cell carcinoma); presence of measurable lesions not previously irradiated, no CNS metastases; adequate bone marrow reserve (neutrophils $>$ 2,000/mm^3, platelet count $>$ 100,000/mm^3); and adequate renal and hepatic function: serum creatinine less than 120 μmol/L or calculated creatinine clearance (Cockroft method) greater than 60 mL/min, bilirubin $\leq$ 30 μmol/L, AST and ALT less than 1.5 U/L ($<$ 2.5 U/L in case of liver metastases), alkaline phosphatase less than 2.5 U/L and albumine $\geq$ 25 g/L. In groups A and C (non-GIST) patients were allowed only 1 line of previous combination chemotherapy or 2 single agent regimens, discontinued for at least 4 weeks. After the second amendment, prior therapy was limited to 1 single agent regimen.

Mesothelioma, chondrosarcoma, neuroblastoma, osteosarcoma, Ewing's sarcoma, embryonal rhabdomyosarcoma, and dermatofibrosarcoma were excluded. In addition, all patients were required to give written informed consent. Before inclusion, patient eligibility was evaluated by use of a protocol-specific eligibility checklist.

Treatment

ET-743 was supplied as a sterile lyophilized product. Each vial contained either 40 μg or 250 μg of ET-743 in 0.05M phosphate buffer pH 4, with mannitol (50 mg) as an excipient. Vials were reconstituted by adding 1 mL of sterile water for injection. The contents of the vial had to be further diluted in a minimum of 250 mL of 0.9% saline. Drug vials were stored between $-$10°C and $-$20°C and protected from light. ET-743 is stable for at least 18 months under these storage conditions.

ET-743 was administered at a dose of 1.5 mg/m^2 intravenously as a 24 hour continuous infusion every 3 weeks using a central venous line. The total dose has to be diluted in 500 mL of 0.9% saline. Antiemesis prophylaxis included ondansetron or granisetron, corticostreroids, and/or metoclopramide.

Follow-Up Investigations and Dose Modifications

The National Cancer Institute Common Toxicity Criteria (CTC version 2.0, 1998) were used for classification of adverse events. Blood counts and serum chemistry had to be performed less than 14 days before the start of treatment. A full blood count and transaminases (AST and ALT) was repeated every week of each course of chemotherapy. Blood chemistry evaluations were performed every 3 weeks.

Drug administration was postponed by 1 week if there was no full hematologic recovery (ANC granulocytes $>$ 1.5 $\times$ 10^9/L; platelets $>$ 100 $\times$ 10^9/L) from the previous course of treatment. Patients delayed by more than 2 weeks went off study. Drug doses were adjusted according to the nadir blood counts: 1.5 mg/m^2 in case of grade 4 neutropenia for less than 5 days and/or more than 50 $\times$ 10^9/L platelets; 1.35 mg/m^2 in case of febrile neutropenia and/or less than 50 $\times$ 10^9/L platelets. If during a subsequent cycle there was a further episode of febrile neutropenia, the patient was withdrawn from the study.

Drug administration was postponed by 1 week if there was no recovery of increased ASAT and ALAT to grade 1. The dose of ET-743 was reduced by 25% if there was no recovery to grade 1 after a 1-week delay, or in cases of reversible grade 3 to 4 hepatic toxicities between cycles (except nausea and vomiting). In October 1999, after entry of 19 patients, a third amendment required normal alkaline phosphatase (ALP) at inclusion and ET-743 dose reduction (to 1.2 mg/m^2) in case of any elevation of bilirubin/ALP between the 3-week cycles.

Evaluation of Response

Response was evaluated every two cycles (every 6 weeks), with repeated clinical and appropriate radiologic assessments based on the extent of the disease defined at presentation. Antitumor activity was evaluated according to the WHO[17] criteria in group A and to both WHO and RECIST criteria[18] in group C. For all responding patients, two independent investigators reviewed hospital records and all available films. A response was accepted only if they reached consensus. In the absence of consensus, the worst response category was assigned.

Patients were considered assessable for response if they had received a minimum of two cycles of treatment. In case of rapidly progressive disease after one course, the patient was removed from study and classified as "treatment failure." If response had not been assessed, patients were included in the following categories: early death from toxicity in case of death occurring within 6 weeks due to signs of toxicity; early death from malignant disease if death occurred within 6 weeks after commencing chemotherapy due to soft tissue sarcoma and without signs of toxicity; early death from other cause if death occurred in the same period of a cause not related to malignant disease.

Patients who had stable disease or who exhibited CR or PR remained on treatment until disease progression, unacceptable toxicity, or patient refusal. Patients with evidence of drug-related clinical benefit were allowed to continue on therapy after six cycles.

The duration of response was measured from the date of inclusion to the date of documented progression. If a new treatment was started before progression, the duration of response (or stabilization) was censored on the day of start of the new treatment. The progression-free survival was measured from the date of inclusion to the date of documented progression; patients who had not progressed at the date of last follow-up and patients who died from a cause other than their sarcoma were censored at the date of last follow-up, or death. Survival was measured from the date of inclusion to the date of death. Patients alive at the time of the analysis were censored at the date of last follow-up.

Dose Intensity

The duration of treatment was calculated as the time from the start of the first cycle to 21 days after the last cycle. For each cycle, the body-surface area was recomputed as a function of the weight on the day of administration. The total dose was the sum of all delivered doses and was calculated per square meter. The dose intensity was calculated by dividing the total administered dose by the total duration. It was expressed as a percentage of the theoretical dose intensity.

Statistical Design

The main objective of this study was to assess the therapeutic activity and toxicity of ET-743 in patients with advanced soft tissue sarcoma. The Simon two stages design has been separately applied to the two cohorts of patients (groups A and C). Overall survival, time to progression, and duration of response were estimated by the Kaplan-Meier method. All eligible patients were included in the analysis of side effects unless they had not received any treatment.

RESULTS

Patient Characteristics

From March 1999 to November 2000, 104 adult patients with non-GIST advanced soft tissue sarcoma from eight European centers were enrolled in the study. Ten patients (10%) were considered not eligible for the following reasons: five patients were withdrawn before protocol treatment (increase of liver function tests in one patient, no previous chemotherapy in one patient, five previous chemotherapy regimen in one patient, CNS metastases before first cycle in one patient, and one patient withdrew inform consent). For five patients actually treated, reasons for ineligibility were: no target lesions in two patients, no previous chemotherapy regimen in one patient, increase of alkaline phosphatase in one patient, and one patient was included while the study was formally closed. The median delay between the date of registration and the date of first treatment was 1 day (range, 0 to 13 days).

All analyses (except demographic data) are reported for 99 patients who have received at least one cycle of ET-743. Seventy-six (73%) of 104 cases were centrally reviewed for pathology. In 55 cases (72%), the reviewed diagnosis corresponded with the local diagnosis. For the remaining 21 cases, diagnosis changed in histological subtype (from unclassified, miscellaneous, and malignant fibrous histiocytoma to specific histologic subtype in the majority of cases). The analysis is based on the review diagnosis when available, and on the local diagnosis for other cases, as is the case for all European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC STBSG) trials.

Patient characteristics are listed in Table 1. The median age of the 53 male and 51 female patients was 53 years (range, 18 to 92 years). Sixty-three percent of patients had a performance status of 1. Despite exclusion of GIST in these two groups of patients, 43 patients (41%) had leiomyosarcomas arising from a wide range of sites (16 uterus, eight retroperitoneum, six visceral, six extremities, three trunk, four others). Ninety percent of patients had grade 2 and 3 sarcomas. Previous systemic treatments are reported in Table 2. In line with inclusion criteria, all patients had received prior chemotherapy: 23% receiving two prior chemotherapy regimen (patients included before second amendment) and 51% at least two different drugs. More than 50% of patients had at least two metastatic sites at inclusion. The median diameter of target lesions was 62 mm (range, 17 to 232 mm).

Treatment, Dose Intensity, and Tolerance

The median number of cycles given per patient was three (range, 1 to 18 cycles). The number of cycles of ET-743 administered during the entire treatment is listed in Table 3. Thirty patients (30%) received at least six chemotherapy cycles, and six patients received more than 11 cycles of ET-743. Sixty-three patients (60%) discontinued therapy due to progression of disease: 12 for toxicity reasons, and five patients refused to continue the treatment.

Table 1. Patient Characteristics

	Patients	
	No.	%
Included	104	
Eligible	94	90.0
Treated	99	95.0
Male/Female	53/51	
Age, years		
Median	53	
Range	18-92	
PS 0	38	36.5
PS 1	66	63.5
Initial site of disease		
Lower arm	29	27.8
Uterus	18	17.3
Retroperitoneum	18	17.3
Trunk	12	11.5
Visceral intra-abdominal	10	9.6
Girdle	8	7.6
Head and neck	4	3.8
Upper arm	4	3.8
Unknown	1	
Leiomyosarcoma	43	41.0
Synovialosarcoma	18	17.3
Liposarcoma	10	9.6
Miscellaneous	9	8.6
Undifferentiated	7	6.7
Malignant fibrous histiocytoma	6	5.7
Unclassified	5	4.8
Neurosarcoma	3	2.8
Angiosarcoma	1	
Rhabdomyosarcoma	1	
Fibrosarcoma	1	

Abbreviation: PS, performance status.

Table 2. Tumor Sites at Inclusion, and Prior Treatments

	Patients	
	No.	%
Disease at inclusion		
Lung metastases	73	70
Liver	16	15.5
Bone metastases	14	13.6
Other soft tissue	35	34
Local disease	32	31
No. of sites involved		
1	48	46.6
2	29	28.2
≥ 3	27	25.2
Prior chemotherapy		
Adjuvant	6	5.8
Advanced disease	90	86.5
Both	8	7.7
Prior No. of chemotherapy regimens		
1	78	75
2	24	23
≥ 3	2	2
Prior No. of drugs		
1	51	49
2	35	33
≥ 3	18	18

There was a total of 410 cycles of ET-743 administered. Treatment was considered "delayed" when the actual delay exceeded 3 days. Doses were considered "reduced" when less than 90% of the dose of the preceding cycle, on a mg/m^2 basis, was administered. The actual body-surface area (computed on the basis of weight on the day of treatment) was used in these calculations.

Dose was reduced at least once in 31% of the patients and in 9% of the cycles. Most of the dose reductions (53%) were owing to nonhematologic toxicities. The start of the cycle was delayed at least once in 49% of the patients and in 44% of the cycles. Delays were due mainly to hematologic toxicities (62% of delays). The median duration of treatment was 84 days (range, 21 to 446 days), the median dose of ET-743 was 4,496 mg/m^2, and the median relative dose intensity was 91% (Table 4).

Toxicity, summarized in Table 5, was mainly hepatic and hematologic. Grade 3 to 4 neutropenia and thrombocytopenia were documented in 52.5% and 18.2% of patients, respectively. The median nadirs of neutrophils and platelets were 0.9 and 165 10^9/L, respectively. Sixteen percent of patients experienced grade 3 to 4 anemia. The incidence of febrile neutropenia was 9%: 15% of patients in group A versus 3% of patients in group C (all patients in group C were included after the third amendment of October 1999). Hematologic toxicity was not cumulative. A reversible grade 3 to 4 transient elevation of transaminases was seen in 35.3% and 44.5% of patients for AST and ALT, respectively. In addition, 42% and 63% of patients had an elevation (≥ grade 1) of bilirubin and alkaline phosphatase, respectively, between cycles. Liver toxicity was also not cumulative.

Four treatment-related deaths occurred in group A, whereas no toxic death was reported in group C. These four patients died after the first or second cycle of ET-743 in a context of multiorgan failure, including febrile neutropenia, creatinine elevation (> grade 1), liver dysfunctions, and septic shock. The incidence of severe toxicities (grade 3 to 4 toxicity) was consequently analyzed, and a statistical correlation was found between liver dysfunctions and these severe toxicities. After a protocol amendment (October 1999) requiring normal ALP at inclusion and ET-743 dose reduction (to 1,200 mg/m^2) in case of a rise in bilirubin/ALP between cycles, the incidence of serious toxicity significantly decreased. The grade 3 to 4 toxicities encountered in patients included before and after this amendment are listed in Table 6.

Other toxicities included creatinine elevations (grade 1 in 21% of patients), fatigue (grade 1 and 2 in 62% of

Table 3. Total Number of Administered Cycles (N = 104)

	No. of Cycles												
	0	1	2	3	4	5	6	7	8	11	14	15	18
No.	5	21	24	5	13	6	14	3	7	2	2	1	1
%	4.8	20.2	23.1	4.8	12.5	5.8	13.5	2.9	6.7	1.9	1.9	1	1

patients), diarrhea (grade 1 and 2 in 15% of patients), and vomiting (severe in 9% of patients). Of note, there was no alopecia and no cardiac toxicity.

Response to Therapy

At the time of the analysis (October 2003), the estimated median follow-up (Kaplan-Meier estimate) was 34 months. The response analysis was done in included patients (N = 104), eligible patients (n = 94), and treated patients (n = 99). Progression-free and overall survival analyses have been performed in all patients (intent-to-treat basis; N = 104).

Data on tumor response (included, eligible, and treated patients) to therapy are listed in Table 7. Among the 99 treated patients, there were eight PR (objective regression rate, 8.1%), 45 no change (NC; 40.5%), and 39 progressive disease (39.4%). Responses were observed in leiomyosarcoma of all origins (n = 5), in synovial sarcoma, liposarcoma, and malignant fibrous histiocytoma. The median duration of response was 352 days (50 weeks). Fourteen patients exhibited a tumor reduction of more than 15% (range, 15% to 47%). Twenty-six percent of patients experienced disease stabilization lasting for more than 6 months. Six patients underwent a radical surgical resection after ET-743 treatment and are considered free of disease after surgery. The median time to progression was 105 days (95% CI, 75 to 124; Fig 1). The 3-, 6-, and 12-month progression-free survival figures were 52%, 29%, and 17%, respectively (Table 8). Median overall survival was 278 days (9.2 months; 95% CI, 238 to 368). Forty-two percent of patients were alive at 12 months. Eleven patients were still alive after a median follow-up of approximately 3 years (Fig 2).

A progression arrest of tumor growth (PR + NC) was seen 24 (56%) of 43 leiomyosarcomas, 11 (61%) of 18 synovial sarcomas, five (83%) of six malignant fibrous histiocytoma, and in four (40%) of 10 liposarcomas. The outcome is similar in patients receiving one or two previous chemotherapy lines and in patients having a chemoresistant (doxorubicin and/or ifosfamide) or chemosensitive sarcoma.

Table 4. Dose Intensity (N = 104)

No. of cycles	
Median	3
Range	1-18
Total dose, mg/m^2	
Median	4,496
Range	1,471-22,601
Total duration, days	
Median	84
Range	21-446
Relative dose intensity, % protocol dose intensity	
Median	91
Range	43-102

DISCUSSION

The current standard chemotherapy regimen for advanced soft tissue sarcoma includes doxorubicin and/or ifosfamide, though efficacy results of the use of these two drugs in adult advanced soft tissue sarcoma remain disappointing. A retrospective study by the EORTC STBSG demonstrated that only 8% of patients with advanced/metastatic disease treated using a doxorubin-containing regimen are

Table 5. Grade 3 to 4 Hematological and Nonhematological Toxicity per Patient During the Whole Treatment

	Patients (n = 99)	
	No.	%
WBC (grade 3-4)	41	41.4
ANC (grade 3-4)	52	52.5
Febrile neutropenia	9	9.1
ANC nadir (× 10^9/L)		
Median	0.9	
Range	0.08-12.4	
Platelets (grade 3-4)	18	18.2
Platelet nadir (× 10^9/L)		
Median	165	
Range	3-411	
Anemia (grade 3-4)	16	16.1
AST (grade 3-4)	35	35.3
ALT (grade 3-4)	44	44.5
Bilirubin (≥ grade 2)	18	18.2
AlkP (≥ grade 2)	18	18.2
Creatinine elevation (≥ grade 2)	13	13.1
Nausea (grade 3-4)	7	7.1
Vomiting (grade 3-4)	9	9.1

Abbreviations: ANC, absolute neutrophil count; AlkP, alkaline phosphatase.

Table 6. Dose Limiting Toxicities Before and After Amendment of October 1999

	Before Amendment (n = 19)		After Amendment (n = 80)	
	No.	%	No.	%
Grade 3-4				
Leucopenia	10	52.7	31	38.8
Granulocytopenia	12	63.1	40	50.1
Febrile neutropenia	3	15.8	6	7
Thrombocytopenia	7	36.8	11	13.8
Anemia	5	25.4	11	13.8
Bilirubin	3	15.8	4	5
AST	5	26.3	30	37.5
ALT	7	36.9	37	46.3
Nausea	3	15.8	4	5
Vomiting	3	15.8	6	7.5
Grade 2-3 alkaline phosphatase	6	31.6	12	6.3
Grade 1-2 creatinine	9	47.4	20	25
Drug-related death	4		0	

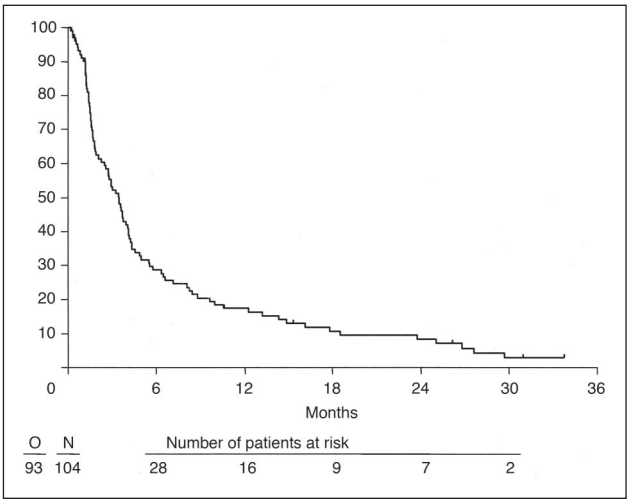

Fig 1. Time to progression of the 104 patients included in the trial.

alive at 5 years.[19] Moreover, the toxicity encountered with the use of high-dose ifosfamide regimens (> 9 g/m^2) precludes any use in nonselected patients for palliative therapeutic approaches,[20,21] representing approximately 80% of patients with metastatic disease.

There is a high unmet medical need for a third active drug in patients with advanced soft tissue sarcoma, who fail after a doxorubicin/ifosfamide combination (second metastatic line of chemotherapy) after the two single agents were administered consecutively (third line), or who rapidly relapse after the same combination is given in an adjuvant setting (first line). In these situations, none of all new drugs tested in the last 20 years in screening studies demonstrated any relevant activity in any of the histologic subtypes of soft tissue sarcoma,[5] with the exception of imatinib in GIST.

ET-743 is a novel marine-derived chemotherapy agent that has shown activity in soft tissue sarcoma in both preclinical development and in phase I trials.[22] These results prompted the EORTC STBSG to design a phase II study to assess the activity and toxicity of ET-743 administered at a dose of 1.5 mg/m^2 as a 24-hour continuous infusion every 3 weeks in patients with advanced soft tissue sarcoma.

The toxicity profile of this new DNA-interacting agent in this phase II trial in pretreated non-GIST patients corroborates the results observed in previous phase I studies testing the 24-hour infusion of ET-743 at the recommended dose.[13] A reversible asymptomatic grade 3 to 4 transient elevation of transaminases (between the third and seventh day after dosing) was seen in approximately 40% of patients, representing 20% of all cycles. This noncumulative toxicity was reduced by the prophylactic use of dexamethasone as an antiemetic agent (data non shown) and did not preclude administration of further cycles of ET-743. The low incidence of febrile neutropenic episodes (9%) compares favorably with those observed with doxorubicin (29%) and ifosfamide (40%) given at optimal doses (75 mg/m^2 and ≥ 9 g/m^2, respectively).[3,20,21,23] Moreover, the lack of cumulative toxicities observed with ET-743 allows a prolonged administration in nonprogressing patients, in contrast to the cardiac and renal toxicities of doxorubicin and ifosfamide, respectively, which preclude

Table 7. Response

	Included Patients		Eligible Patients		Treated Patients	
	No.	%	No.	%	No.	%
Partial response	8	7.7	8	8.5	8	8.1
No change	45	43.3	44	46.8	45	45.5
Progression	35	33.7	32	34	35	35.4
Early death (progressive disease)	4	3.8	3	3.2	4	4
Early death (toxicity)	4	3.8	4	4.3	4	4
Early death (other)	2	1.9	1	1.1	2	2
Not assessable	6	5.8	2	2.1	1	1
Total	104		94		99	

Table 8. Progression-Free Rates at 3, 6, 9, and 12 Months After Inclusion

	Non-GIST	
	Estimate (%)	SE (%)
Estimate, days		
Median	105	
95% CI	75 to 124	
3 months	52	5
6 months	29	5
9 months	20	4
12 months	17	4

Abbreviation: GIST, gastrointestinal stromal tumor.

any long-lasting treatment with these two drugs, even in responding patients.

Four treatment-related deaths with multiorgan failures occurred in the first patients included in the trial. A stringent and careful analysis of all severe toxicities (grade 3 to 4) observed in this group of patients has established a high correlation with (1) an abnormal ALP baseline value and (2) a rise of ALP and/or bilirubin in between cycles.[24] After the protocol amendment, the incidence of all serious toxicities was significantly reduced in patients consecutively included in this trial and in other trials worldwide.[25]

The median overall survival for patients receiving ET-743 as second- or third-line chemotherapy is unusually high ($>$ 9 months) in this cohort of heavily pretreated patients and could be explained by several parameters. First, there is favorable outcome of patients, even in patients receiving two previous chemotherapy regimens. The rates of objective regression and stable disease are similar in doxorubicin/ifosfamide chemosensitive and chemoresistant sarcomas, highlighting the results observed during the preclinical development of ET-743.[10,26] Second, there is a high proportion of patients receiving six or more cycles (30%), which is uncommon in screening studies testing new cytotoxic drugs. Third, there is the combination of the lack of ET-743 cumulative toxicities and the high median time to observe an objective regression (5.3 months), which emphasized the need to continue treatment even in patients with stable disease.[27] Fourth, there is a high rate of patients who clearly benefit from the drug not only in terms of the WHO criteria of responses but in terms of tumor control including tumor regressions (14 patients with a tumor shrinkage between 15% to 47% after an initial documented progression of disease),[28] prolonged stable disease (26% of patients), and locoregional treatments (complete resection of metastases in six patients).

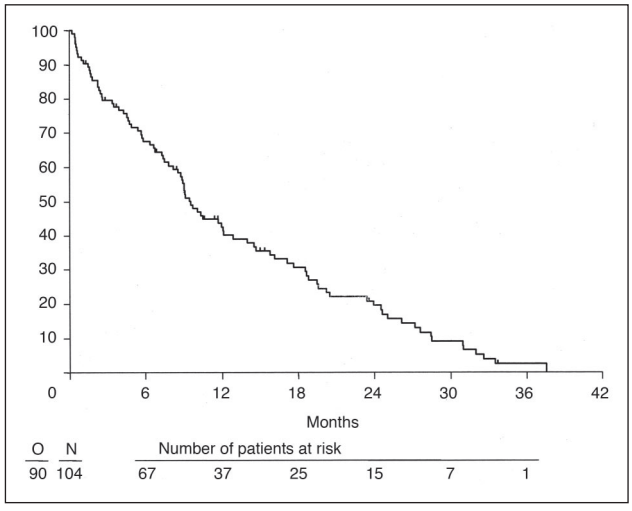

Fig 2. Overall survival of the 104 patients included in the trial.

The response rate is an easily measurable end point for phase II trials but does not take into account duration of the response and disease stabilization in patients with documented progressive disease before study entry. Disease stabilization seems to be a relevant achievement in advanced inoperable soft tissue sarcomas. Patients exhibiting a prolonged stable disease (after six cycles of chemotherapy) have an outcome similar to those who experienced a PR.[29] Since a high proportion (30% to 60%) of patients with metastatic soft tissue sarcomas experience this type of response, with tumor changes insufficient to enable classification into distinct response categories (CR, PR, and progressive disease), new end points or concepts have to be implemented in phase II trials. The progression-free rate incorporates the objective response rate, but also minor responses and prolonged stable diseases and evaluates the "tumor control" rate at predefined time points in patients with initial documented progressive disease, which is a requirement before study entry. The baseline values of progression-free rates have been recently estimated by a retrospective analysis of the database of the EORTC STBSG in second-line chemotherapy in different histologic subtypes with active drugs such as ifosfamide and dacarbazine and with inactive agents.[30] The 6-month progression-free rates are 14% and 8% for patients treated with active and inactive drugs, respectively. With this new definition of "success" or "failure" for an anticancer agent, the activity of ET-743 is higher than the two other active drugs in pretreated patients (29% *v* 14%). The 6-month PFR of 29% is the highest rate ever observed in all EORTC STBSG trials in pretreated patients with advanced sarcomas receiving a new cytotoxic agent.

In phase II trials assessing the activity of new agents in soft tissue sarcomas, it would be simple to classify agents as inactive if two-thirds of patients progressed after two courses. In contrast, it is inconclusive to define as active a drug that produces objective response rates of between 5% and 15%, yet that is more or less the rate observed with the so-called "well known active drug" such as ifosfamide administered as second-line treatment.[21,31] The Progression Arrest Rate (PAR) is another interesting concept that

combines objective regression and stable disease together and calculates the proportion of patients who were not progressing immediately.[5] Only three drugs have demonstrated a PAR of ≥ 50% in studies including more than 40 patients: doxorubicin (70%), ET-743 (54%), and ifosfamide (52%). Using this definition, dacarbazine seems to be inactive (36%), and the relevant activity of taxotere/gemcitabine combination in leiomyosarcoma of all origins[32] could be explained by their PARs (47% and 39%, respectively), while these two agents have been considered inactive in previous trials including all histological subtypes of sarcoma and focusing exclusively on response rate.[23,33]

Since all the new drugs tested in the last 20 years failed to achieve high CR rates (presumably a requirement for improving survival)[19] and demonstrate a poor activity in terms of objective response rates, new end points need to be implemented in screening studies in order to discriminate reliably between potentially active drugs and definitively inactive agents in a small cohort of patients.

In a similar way, with the emergence of new molecular targets and genetic profiles in various histological subtypes of sarcomas, we have to modify our strategic approaches in the management of patients with advanced sarcomas.[34] The dramatic activity of Glivec in GIST,[35,36] the heterogeneous outcome of each histological subtypes of sarcomas as different diseases[37] and the high sensitivity of some histological subtypes of sarcoma to specific agents such as ifosfamide in synovial sarcomas,[38] taxol in angiosarcomas[39] and gemcitabine in leiomyosarcoma[40] clearly open a new era in the management of soft tissue sarcomas and designs of future clinical trials (ie, selected drugs or targeted therapy for specific histological subtypes of sarcoma).

The high efficacy of ET-743 in leiomyosarcoma (56% progression arrest rate), a histological subtype usually resistant to doxorubicin and/or ifosfamide regimens[29] and in synovial sarcoma (61%) in our study and in liposarcoma[41] in the US trial demands further evaluations of ET-743 in these specific histological subtypes.

In conclusion, ET-743 is undoubtedly one of the most promising cytotoxic agents tested in the last two decades in sarcomas. This drug could become a relevant therapeutic option in patient with anthracyclin/ifosfamide resistant sarcomas in the near future. The results observed in our trial have been corroborated by two other phase II studies, in even more heavily pretreated sarcomas[22] and in front-line chemotherapy regimen.[41] The pooled analysis of the three phase II studies, including 183 patients, demonstrated that the efficacy of ET-743, in terms of tumor control rate and overall survival (10 months), is both meaningful and consistent.[27] A potential patient selection factors which could contribute to the promising results in this present study can be highlighted and discussed but characteristics of patients included in this study are similar (same inclusion criterias) to those included in the prior EORTC STBSG trials testing active and inactive agents. However, validation of these results in a randomized trial would definitely confirm the place of ET-743 as a second-line agent and combination studies may lead to its incorporation into first-line therapy in future.[42]

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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