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# Safety and efficacy of ET-743: The French experience

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**Initial evidence of clinical benefit with ecteinascidin-743 (ET-743) in patients with sarcoma was provided during a Phase I pharmacokinetic study in which 52 patients received ET-743 at doses of 50–1800 μg/m² as a 24 h continuous infusion every 3 weeks. Neutropenia and thrombocytopenia were the dose-limiting toxicities; liver toxicity (a severe but transient and reversible increase in transaminase concentrations) was not treatment limiting. In conjunction with results obtained with ET-743 in a compassionate-use program, these indications of activity in heavily pretreated patients with sarcoma prompted initiation of a French multicenter Phase II study of ET-743 in this population. From February 1999 to January 2001, 54 patients with advanced anthracycline-pretreated soft-tissue sarcoma (STS) received ET-743 at a dose of 1500 μg/m² every 3 weeks by continuous 24 h infusion. The main histological subtype was leiomyosarcoma (37%); the majority of primary tumors were visceral (24%) or uterine (19%) sarcomas. In this Phase II population (≥25% negative prognostic or predictive factors of response to chemotherapy; ≥50% anthracycline- and ifosfamide-resistant), safety data were comparable to those obtained in the Phase I and compassionate-use studies. Asymptomatic and reversible neutropenia and transaminitis (grade 3/4) were the most frequent toxicities (~60% of patients); febrile neutropenia was infrequent (<10%). No mucositis, alopecia, cardiac or neurotoxicity was observed. Two severe cases of rhabdomyolysis occurred. Side effects were non-cumulative, reversible and manageable. Of 52 evaluable patients, three (6%) achieved a long-lasting (8–13 months) partial response, four (8%) achieved a minor response (25–50% tumor reduction) and 22 (42%) achieved disease stabilization. With a 13-month median follow-up, median survival was almost 11 months. Progression-free survival at 6 months was 26.5% and the overall survival rate at 12 months was almost 50%. The response rate was uninfluenced by tumor metastatic site, size or anthracycline sensitivity status. These results, combined with the lack of cumulative toxicity, confirm the role of ET-743 in the treatment of advanced STS. [© 2002 Lippincott Williams & Wilkins.]**

*Key words*: Ecteinascidin-743, soft-tissue sarcoma, chemotherapy.

## Introduction

Adult soft-tissue sarcomas (STS) represent fewer than 1% of all adult tumors; however, in France alone, approximately 1000 new cases are diagnosed annually.[1] Locally advanced STS is not amenable to surgery, and few agents achieve response rates better than 15% against advanced disease.[2] Current treatment relies primarily on chemotherapy with agents such as doxorubicin (the reference agent for first-line therapy) and ifosfamide; in many cases, however, these two agents fail to modify dramatically the natural history of advanced disease. Survival rates associated with chemotherapy tend to be disappointing, with a median survival after diagnosis of metastasis of typically less than 1 year.[3,4] Furthermore, few other drugs have shown meaningful activity against these tumors, underlining the need for new treatments.

Ecteinascidin-743 (ET-743) is a marine-derived antitumor agent that binds to the DNA minor groove bending the DNA towards the major groove. ET-743 has a unique triple mode of action, including promoter-selective inhibition of transcriptional activation of key genes such as *c-fos*, *c-jun*, *p21* and *MDR1* (multidrug resistant 1), inhibition of transcription-dependent nucleotide excision repair pathways, and inhibition of cell cycle progression, leading to p53-independent apoptosis.[5]

## Preclinical studies of ET-743

Preclinical studies have shown low or no cross-resistance between ET-743 and many standard anti-cancer compounds.[6] ET-743 has shown activity at nanomolar concen-

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**Table 1.** Characteristics of patients in the Phase II trial

| Characteristic | Group I ($n$ = 24) | Group II ($n$ = 30) | All patients ($n$ = 54) |
|---|---|---|---|
| Age (years) | 51 (22–6) | 43 (23–62) | 48 (22–66) |
| Men:women (%) | 50:50 | 40:60 | 44:56 |
| Histology (%) | | | |
| Leiomyosarcoma | 33 | 40 | 37 |
| Liposarcoma | 21 | 3 | 11 |
| Fibrosarcoma | 4 | 10 | 7 |
| GIST | 8 | 3 | 6 |
| Primary (%) | | | |
| Visceral | 38 | 13 | 24 |
| Uterine | 13 | 23 | 19 |
| Retroperitoneal | 21 | 7 | 13 |
| Lower limb | 4 | 13 | 9 |
| Median time to diagnosis (months) | 24 (4–182) | 25 (5–122) | 25 (4–182) |
| Lesion >10 cm or 50 $cm^2$ (%) | 25 | 38 | 31 |
| No. sites involved† | 1.5 (1–4) | 2 (1–3) | 2 (1–4) |
| Localization (%) | | | |
| Lung – pleura | 46 | 83 | 67 |
| Soft tissue | 54 | 47 | 50 |
| Liver | 38 | 27 | 31 |
| Lymph node | 17 | 20 | 19 |
| Bone | 8 | 10 | 9 |
| Pretreatment (%) | | | |
| Radiotherapy | 29 | 57 | 44 |
| Chemotherapy | | | |
| Anthracyclines | 96 | 100 | 98 |
| Alkylators/HDI | 88/– | 93/32 | 91/17 |
| Platinum/HD | 12/– | 39/21 | 26/11 |
| Anthracycline resistance (%) | 53 | 67 | 61 |
| Ifosfamide resistance (%) | 53 | 70 | 63 |

Values are median (range), %, or †number (range). HD = high-dose chemotherapy; HDI = high-dose ifosfamide; GIST = gastrointestinal stromal tissue.

trations *in vitro* against a variety of human cancer cell lines[7] and surgically-derived human tumor cells growing in primary cultures,[6] and *in vivo* against human tumor xenografts.[8] The duration of exposure of the tumor to ET-743 is of potential clinical relevance, with *in vitro* studies showing a direct relationship between anti-tumor activity and exposure time.[9]

## Phase I study and compassionate-use program

On the basis of the preclinical data, a Phase I pharmacokinetic study of ET-743 was initiated in 1996. Cancer patients meeting the standard Phase I eligibility criteria, with normal baseline biology and no exposure to radio-, chemo- or immunotherapy in the previous 4 weeks, were included. Patients ($n$ = 52) received ET-743 doses ranging from 50 to 1800 $\mu g/m^2$ as a 24 h continuous infusion every 3 weeks, with standard anti-emetic premedication.[10] The maximum tolerated dose was established as 1800 $\mu g/m^2$ and a dose of 1500 $\mu g/m^2$ was selected for future trials.

The dose-limiting toxicities were neutropenia and thrombocytopenia. Thus, at the maximum tolerated dose, grade 3/4 neutropenia occurred in almost 100% of patients ($n$ = 4) and cycles ($n$ = 16) and platelet transfusion was required in 50% and 25% of patients and cycles, respectively. Notably, the incidence of febrile neutropenia was low. Liver toxicity, as indicated by a severe but transient and reversible increase in transaminase concentrations, occurred in 68% of patients and 38% of cycles with the dose of 1500 $\mu g/m^2$, but was never treatment limiting. Importantly, anti-tumor activity was observed in this trial in patients with sarcoma (and also in those with breast tumors). When these Phase I data were combined with those from the use of ET-743 1500 $\mu g/m^2$ every 3 weeks on a compassionate-use basis, results were available for 29 patients with advanced sarcoma.[11] The incidences of hematological and liver toxicities per patient and per cycle were similar to those reported with 1500 $\mu g/m^2$ doses in the Phase I trial. Similarly, pooling of efficacy data for these 29 patients showed an encouraging 14% partial response rate, including two partial responses in patients with osteosarcoma, with a 55% disease control rate (partial responses

plus minor responses and stable disease for a period of more than 2 months).[11] Notably, the median response (partial response plus minor response) duration was 10.5 months. These pooled data strengthened the rationale for a continuing French multicenter Phase II trial in patients with advanced, heavily pretreated STS.[12]

## Phase II trial of ET-743

### Patients and trial design

From February 1999 to January 2001, 54 patients with advanced STS who fulfilled the standard Phase II eligibility criteria were enrolled into the trial. Patients were allocated to one of two groups according to their level of pretreatment: group I ($n$ = 24) had been pretreated with no more than two single agents or one combination regimen; group II ($n$ = 30) consisted of more heavily pretreated patients, who had received more than two single agents or more than one combination regimen. ET-743 treatment comprised the same schedule as in the Phase I trial/compassionate-use program, namely 1500 μg/m$^2$ given every 3 weeks by continuous 24 h infusion. The primary endpoint was the tumor response rate; secondary endpoints were response duration, progression-free survival and survival time.

The patients' characteristics are summarized in Table 1. The main histological subtype was leiomyosarcoma (37%), followed by liposarcoma (11%), and the majority of primary tumors were visceral (24%) or uterine (19%) sarcomas; almost 33% of patients had liver metastases, which are recognized as negative prognostic factors for response to chemotherapy. Furthermore, more than 60% of patients were resistant to anthracyclines or ifosfamide, the reference agents for STS. Resistance to these agents was defined as progressive disease while under treatment, irrespective of the best response achieved previously. The more heavily pretreated patients in group II had more negative prognostic factors, such as bulky disease (38% in group II compared with 25% in group I).

### Safety of ET-743

Asymptomatic and reversible neutropenia and transaminitis (grade 3/4) were the most frequent toxicities, occurring in almost 60% of patients (Table 2). Febrile neutropenia was infrequent (fewer than 10% of patients) and fewer than 10% of cycles were complicated by grade 3/4 thrombocytopenia. Nausea and vomiting were easily controlled with a standard anti-emetic premedication, asthenia was seldom severe, and grade 3/4 thrombocytopenia always occurred concurrently with severe neutropenia. Importantly, transaminitis, which occurred at some level in all patients during treatment, was never dose-limiting; it typically started on day 2, peaked during week 1 and returned to baseline at day 15. There were two severe cases of rhabdomyolysis in group I, with toxic death as a result of cirrhosis decompensation ($n$ = 1) and refusal of dialysis ($n$ = 1). Nausea/vomiting and asthenia were reported in 35% and 63% of patients, respectively, with no difference of distribution between the two groups. No mucositis, alopecia, cardiotoxicity or neurotoxicity was observed.

**Table 2.** Safety of ET-743 in patients with sarcoma in the Phase II trial

| | Patients (%) | | Cycles (%) | |
|---|---|---|---|---|
| Grade 3/4 toxicity | Group I ($n$ = 24) | Group II ($n$ = 30) | Group I ($n$ = 89) | Group II ($n$ = 123) |
| Neutropenia | 67 | 53 | 40 | 41 |
| Febrile neutropenia | 13 | 3 | 3 | 1 |
| Thrombocytopenia | 21 | 17 | 9 | 7 |
| Anemia | 17† | 27 | 6† | 8 |
| Transaminitis | 63 | 53 | 35 | 24 |
| Rhabdomyolysis | 8 | 0 | 2 | 0 |
| Nausea/vomiting‡ | 35 | | 20 | |
| Asthenia§ | 63 | | 4 | |

†No grade 4 toxicity reported; ‡grade 2/3/4 toxicity; §grade 2/3 toxicity.

Overall, more than 50% of cycles were delayed by 1 week, with a median of one cycle delayed per patient. Hematological toxicity was responsible for about 70% of delays; however, 20–30% of delays were not treatment-related and for delayed cycles fewer than 20% required dose reductions. Moreover, the relative dose intensity (amount of drug delivered per unit of time relative to the theoretical planned dose) was 98% and 86% for groups I and II, respectively.

### Clinical response and survival

Of 52 patients in whom the response was evaluable, three achieved a partial response, all in uterine sarcomas, and four achieved a minor response. When these responses were combined with those of the 22 patients with stable disease for a period of more than 2 months, the clinically relevant disease control rate increased to 55.8%. After a median follow-up of 13 months, the duration of response was 8.6 months. The progression-free survival at 6 months was 26.5% and the median survival was almost 11 months, with an overall survival rate at 12 months of almost 50% (Figure 1). The response rate was not influenced by tumor metastatic site, size or anthracycline sensitivity status. Thus benefits with respect to progression-free survival (23.2% in group I compared with 29.2% in group II at 6 months) and overall survival (57.6% in group I and 41.2% in group II at 12 months) were observed in patients in both group I and group II.

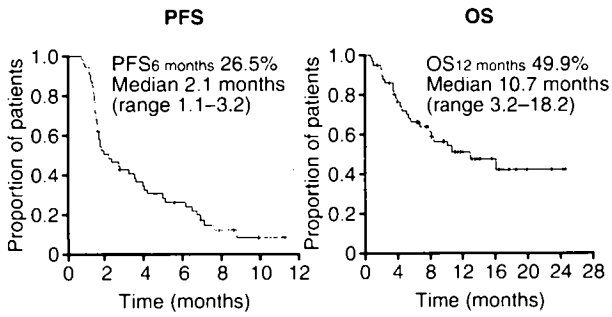


**Figure 1.** Progression-free survival (PFS) and overall survival (OS) of patients with sarcoma in the Phase II trial of ET-743.

## Conclusions

On the basis of the results of the French Phase I trial, compassionate-use program and Phase II trial, ET-743 shows a consistently mild toxicity – chiefly neutropenia and liver toxicity (transaminitis) – in patients with sarcoma. In these trials, the overall response rate ranged from 6 to 14%, with a 55.8% disease control rate. Moreover, survival data from the Phase II trial show a very promising 6-month progression-free survival rate exceeding 25%, clearly challenging historical experience with currently approved and commonly used second-line agents for sarcomas. The duration of response ranged from 8.6 to 10.5 months. This experience with ET-743 in France confirms its activity in the treatment of advanced STS. Because of the low toxicity of ET-743 (it does not cause alopecia, mucositis, cardiotoxicity or neurotoxicity), it is currently being investigated in combination regimens.

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