available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.ejconline.com

# Steroid premedication markedly reduces liver and bone marrow toxicity of trabectedin in advanced sarcoma

F. Grosso[a,*], P. Dileo[a], R. Sanfilippo[a], S. Stacchiotti[a], R. Bertulli[a], C. Piovesan[a], J. Jimeno[b], M. D'Incalci[c], A. Gescher[d], P.G. Casali[a]

[a]Cancer Medicine Dept., Adult Sarcoma Medical Oncology Unit, Istituto Nazionale Tumori, Via G. Venezian 1, 20133 Milano, Italy
[b]PharmaMar, Madrid, Spain
[c]Oncology Department, Istituto Ricerche Farmacologiche Mario Negri, Milano, Italy
[d]Department of Cancer Studies, University of Leicester, Leicester UK

ARTICLE INFO

*Article history:*
Received 25 July 2005
Received in revised form
9 February 2006
Accepted 22 February 2006
Available online 5 June 2006

*Keywords:*
Advanced sarcoma
Trabectedin
Steroid premedication
Toxicity

ABSTRACT

Trabectedin is a marine-derived cytoxic alkaloid which has shown promising antitumour activity in a variety of human malignancies including sarcoma. Fifty-four patients with advanced sarcoma (age 43 yrs, range 18–70), all pretreated with prior chemotherapy, were enrolled on a named individual basis for treatment with trabectedin. Diagnosis was adult soft tissue sarcoma (STS) in 46 patients, Ewing's family tumour (EFT) in 4, and osteosarcoma (OS) in 4. The initial 23 patients (total number of courses administered: 68) did not receive premedication prior to trabectedin, while the other 31 patients (total number of courses administered: 134) received premedication with dexamethasone 4 mg po bid 24 hours before therapy. Incidence of toxicity (grade 3–4), expressed as percentage of courses, was as follows: in patients without dexamethasone, elevation of transaminases 34%, neutropenia 24% and thrombocytopenia 25%; in patients with prior dexamethasone, elevation of transaminases 2%, neutropenia 2% and no thrombocytopenia. The median received dose intensity of trabectedin was superimposable in the two groups (404 μg and 400 μg per week, respectively), as well as progression-free survival (19% at 6 months). Among STS patients, 9% had objective responses. In this unselected patient series, premedication with dexamethasone strongly reduced drug-induced hepatotoxicity and myelosuppression.



## 1. Introduction

Adult soft tissue sarcomas (STS) are a family of several malignant histological types of mesenchymal origin. Overall, they account for 1% of adult cancers, with an incidence around 2–3/100 000/year. Therefore, they constitute an important group of tumours but suffer from all difficulties generally posed by rare diseases. Approximately 50% of patients with STS develop distant metastases.[1] Current treatment for metastatic STS is surgery of lung metastases, if these are "isolated" and completely resectable, and/or chemotherapy.[2] Two agents are conventionally held to be active, doxorubicin (or epirubicin) and ifosfamide. However, the response rate to currently available chemotherapy in non-pretreated patients does not exceed 30–40%, and indeed was in the 20% range in large randomized clinical trials, which failed to demonstrate any substantial improvement with multi-agent as compared to single-agent chemotherapy.[3] After failure of conventional chemotherapy, no other drug has been proven of benefit. High-dose ifosfamide (12–15 g/sqm) is employed as second-line chemotherapy,

* *Corresponding author*: Tel.: +39 223902810; fax: +39 223902804.
E-mail address: federica.grosso@istitutotumori.mi.it (F. Grosso).
0959-8049/$ - see front matter 
doi:10.1016/j.ejca.2006.02.010

apparently with a response rate in the 10–20% range.[4–6] Dacarbazine has been held as another salvage option, with the same range of responses. Gemcitabine may be active in the subset of leiomyosarcomas, and taxanes in angiosarcoma.[7–11] No other medical option is currently available for patients with advanced STS. Indeed, their median survival is less than 1 year. Therefore, there is a clear need for new medical therapies in the advanced STS setting.

Trabectedin (Yondelis™) is a marine-derived cytoxic alkaloid, which covalently binds guanines at $N_2$ position in the DNA minor groove, thus affecting the regulation of transcription by inhibiting the interaction between DNA and transcription factors and other critical nuclear proteins.[12,13] In preclinical studies in human-derived STS cell lines trabectedin showed striking cytotoxicity against human STS cell lines.[14,15] Objective responses and disease stabilization in STS patients treated with trabectedin observed in Phase I studies led to Phase II studies.[16–19]

The main limiting toxicities in Phase I trials were severe thrombocytopenia and neutropenia. A moderate to severe, though reversible, acute elevation of transaminases, perhaps responsible for drug induced fatigue, was often reported. In Phase II studies, liver toxicity and myelotoxicity were confirmed to be the most critical side-effects. A multivariate analysis on clinical and pharmacokinetic data of 93 STS patients enrolled in Phase I studies revealed that baseline and inter-cycle increase of alkaline phosphatase and bilirubin levels predicted serious toxicity in the following courses. This observation led to the introduction of protocol amendments to ongoing studies recommending dose reductions in patients showing baseline or inter-cycle increased levels of alkaline phosphatase and/or bilirubin. In this way, the incidence of adverse events significantly decreased, though G3–G4 neutropenia and thrombocytopenia were still in the range of 10–15%, respectively, and G3–G4 elevation of transaminases in the range of 35–45%.[20,21] Recently, evidence in preclinical models has been presented which suggests that in rodents, which received trabectedin, pretreatment with dexamethasone dramatically ameliorated manifestations of hepatic toxicity.[22] In the light of the encouraging early clinical results observed with trabectedin, in April 2000 we commenced a treatment programme on "compassionate use" basis, in which patients with advanced STS, Ewing's family tumour (EFT) or osteosarcoma (OS) received trabectedin. Following the publication of toxicity protection afforded by dexamethasone in rodents,[23] we introduced premedication with dexamethasone prior to trabectedin into this treatment schedule from April 2002. Here we report the toxicity and activity results observed in these patients.

## 2. Patients and methods

### 2.1. Patient population

Since April 2000, advanced refractory sarcoma patients who were ineligible for ongoing Phase I and II studies were treated with trabectedin (supplied by Pharma Mar, Madrid, Spain), within a named-patient, "compassionate use" programme. Both Italian Ministry of Health's authorization and Pharma Mar approval, following an individual request by the treating physician, were needed for the patient to enter this programme. Patients were required to have unresectable advanced or metastatic, histologically proven STS, EFT or OS; to have been pretreated with at least both anthracyclines and ifosfamide; to have an expected survival of more than 3 months, and to give their written informed consent.

Overall 54 patients (32 females and 22 males) with advanced sarcoma received trabectedin. The first 23 patients (Group 1) received chemotherapy without steroid premedication, while the following 31 (Group 2) were administered dex 4 mg po bid 24-h before starting trabectedin infusion. Patient characteristics are summarized in Table 1. The median age of the whole cohort was 43 years (18–70), 38 years (18–59) in group 1 and 46 years (19–70) in group 2. ECOG/WHO Performance Status (PS) was 0 in 29 patients (54%; group 1: 18; group 2: 11); PS 1 in 22 patients (41%; group 1: 4; group 2: 18); and PS 2 in 3 patients (5%; group 1: 1; group 2: 2). Forty-six patients had a STS (15 in group 1, 31 in group 2) and histotypes were allocated as follows in group 1 and 2 respectively: synovial sarcoma, 4 and 11; leiomyosarcoma, 5 and 6; others high-grade sarcoma, 6 and 7; liposarcoma were all in group 2; 4 had a EFT, and 4 an OS all being in group 1. Extremities were the most common primary tumour site. Five patients had locally advanced disease (abdominal, 3; thoracic, 2), and 49 patients had metastatic disease, with a median of two involved sites (range: 1–5). The predominant sites of metastatic disease were lungs and pleura (94%), and soft parts (28%). Fifty-three percent of patients had received 2 or 3 prior chemotherapy regimens, and a similar proportion of patients had received prior radiotherapy. All patients had been previously treated with anthracyclines and ifosfamide, 96% of patients having received anthracyclines and ifosfamide in combination. All OS patients had received high-dose methotrexate as part of their first-line treatment, and one EFT patient had previously undergone high-dose chemotherapy with peripheral blood stem cell rescue. The median time from the diagnosis of sarcoma to trabectedin start was 34 months (range 7–177).

### 2.2. Treatment plan

Trabectedin was given every 21 days at different dose levels (1000–1650 mcg/sqm) with two different schedules as 3-hour infusion (15 patients) or as 24-hour c.i. (39 patients). The starting dose was selected considering alkaline phosphatase, bilirubin, creatinin, PS and previous treatments. Routine antiemetic premedication included both dexamethasone (8–20 mg i.v.) and a 5HT3 antagonist (ondansetron 16 mg po or i.v.). The first 23 patients (43%) received 68 cycles (34%) with the routine antiemetic prophylaxis alone, which did not include steroids on the day before therapy, but only on day 0 and possibly on day +1 (Group 1). Thirty-one (57%) patients received 134 cycles (66%) with steroid premedication (dex mg po bid) on the day before trabectedin infusion (Group 2). A complete blood count, liver and renal tests with serum electrolytes, serum protein electrophoresis, albumin/globulin ratio and creatinphosphokinase, were performed on day 4, 6, and 15. A complete blood count was also repeated on day 10 and 17. Each cycle was administered on day 21 if the patient had completely recovered to baseline values from hepatic and haematological toxicity (neutrophils $\geqslant 1500/mm^3$ and platelet

**Table 1 – Patients characteristics**

| Characteristics | Group1 | Group 2 | Total |
|---|---|---|---|
| | w/out DEX | w/ DEX | |
| Age, years | | | |
| Median | 38 | 46 | 43 |
| Range | (18–59) | (19–70) | (18–70) |
| *Sex* | | | |
| Female | 11 | 21 | 32 |
| Male | 12 | 10 | 22 |
| *PS (ECOG)* | | | |
| 0 | 18 | 11 | 29 |
| 1 | 4 | 18 | 22 |
| 2 | 1 | 2 | 3 |
| STS | 15 | 31 | 46 |
| LMS | 5 | 6 | 11 |
| Nonuterine | 3 | 1 | 4 |
| Uterine | 2 | 5 | 7 |
| Liposarcoma | 0 | 7 | 7 |
| Synovial sarcoma | 4 | 11 | 15 |
| STS, Others | 6 | 7 | 11 |
| EFT | 4 | – | 4 |
| Osteosarcoma | 4 | – | 4 |
| *Site of primary disease* | | | |
| Trunk, face, neck | 2 | 5 | 7 |
| Extremity | 6 | 19 | 25 |
| Retroperitoneum | 1 | 5 | 6 |
| Uterine | 3 | 2 | 5 |
| Visceral | 4 | 2 | 6 |
| Skeletal, extremity | 4 | – | 4 |
| Skeletal, axial | 1 | – | 1 |
| *Number of sites involved* | | | |
| Median | 1,5 | 2 | 2 |
| Range | 1–3 | 1–5 | 1–5 |
| Bulky/Locally advanced disease[a] | 1 | 4 | 5 |
| *Disease localization* | | | |
| Lung or pleura | 22 | 29 | 51 |
| Soft Tissue | 6 | 9 | 15 |
| Liver | 2 | 3 | 5 |
| Peritoneum | 3 | 1 | 4 |
| Abdomino-pelvic cavity | 1 | 5 | 6 |
| Bone | 3 | 2 | 5 |
| Other | 1 | 9 | 10 |
| *Time since initial diagnosis (mos)* | | | |
| Median | 27 | 36 | 34 |
| Range | 8–177 | 7–125 | 7–177 |
| *Time between last CT and first cycle of ET743* | | | |
| Median | 3,5 | 4,3 | 4 |
| Range | (1–39) | (1–51) | (1–51) |
| *Number of prior chemotherapy regimen* | | | |
| 1 | 11 | 8 | 19 |
| 2 | 7 | 13 | 20 |
| 3 | 7 | 2 | 9 |
| 4–6 | 2 | 3 | 5 |
| *Prior chemotherapy* | | | |
| Anthracyclines | 23 | 31 | 54 |
| Ifosfamide | 23 | 31 | 54 |
| Both | | | 52 |
| HD chemotherapy with PBSC | 1 | – | 1 |
| HD MTX | 4 | – | 4 |
| Prior radiotherapy | 14 | 17 | 31 |
| Surgery for the primary tumor | 20 | 30 | 50 |

**Table 1 – continued**

Abbreviations: DEX, dexamethasone; PS, performance status; ECOG, Eastern Cooperative Oncology Group; STS, soft tissue sarcomas; LMS, leiomyosarcoma; EFT, Ewing's family tumour; HD, high dose; PBSC, peripheral blood stem cells; MTX, methotrexate.
a Unidimensionally measured lesion: diameter $\geqslant$10 cm.

count $\geqslant$100000/mm$^3$), and had recovered from non-haematological toxicity to at least Grade I. If these criteria were not met on day 21, next cycle was post-poned by 1 week. A maximum of 3-week delay was allowed: in the lack of recovery from toxicity after the 3-week delay, the patient was taken off the programme, unless a clinical benefit was evident.

Table 2 enlists patient assignment to the various dose levels and infusion modalities, split according to whether steroid premedication with dex on the day −1 was given or not.

Trabectedin was supplied by Pharma Mar as a lyophilized powder in glass vials containing 250 mcg or 1000 mcg of the drug. It was reconstituted in 5 ml or 20 ml of sterile water for injection and further diluted in 1000 ml of 0.9% sodium chloride solution and administered as a 3-hour infusion or as a 24-hour continuous infusion via a central venous access using an electric pump.

### 2.3. *Assessments*

Toxicity was evaluated according to National Cancer Institute Common Toxicity Criteria.

Best tumour response assessment was based on WHO criteria. Tumour evaluation through an appropriate clinical and/or radiological method was performed every 2 cycles. Specifically, a "minor response" (MR) was defined as a 25–50% decrease of measurable target lesions, whatever its duration. Duration of response was calculated from treatment start.

Progression free survival (PFS) was defined as the time between the start of the treatment with trabectedin and disease progression or patient's death. PFS was calculated with Kaplan-Meyer method.

Statistical analysis was performed by using the chi-square test and the Fisher exact test, when appropriate. The level of significance was set to $P < 0.05$. The software SPSS version 11 for Windows was used.

**Table 2 – Patient assignment to the various dose levels and infusion modalities and split according to whether steroid premedication with dex on the day −1 was given or not**

| Dose level mcg/sqm | 3-hour | | | | 24-hour | | | |
|---|---|---|---|---|---|---|---|---|
| | DEX | | w/o DEX | | DEX | | w/o DEX | |
| | No. pts | (%) | No. pts | (%) | No. pts | (%) | No. pts | (%) |
| 1650 | 1 | (2) | 3 | (6) | | | | |
| 1500 | | | 4 | (7) | 7 | (13) | 5 | (9) |
| 1300 | | | 6 | (11) | 10 | (18) | | |
| 1200 | | | 1 | (2) | 11 | (20) | 2 | (4) |
| 1100 | | | 1 | (2) | 1 | (2) | | |
| 1000 | | | | | 1 | (2) | 1 | (2) |

## 3. Results

A total of 202 cycles (group 1, 68 cycles; group 2, 134) were administered, with a median of 3 cycles per patient (range 1–20). Twelve patients (22%) received at least 5 cycles. Eleven patients, 7 receiving trabectedin as a 3-h infusion (all in group 1) and 4 as a 24-h c.i, (1 in group 1 and 3 in group 2), needed some dose reduction for the following reasons: inter-cycles elevation of ALP, 4 (group 1: 3, group 2: 1); thrombocytopenia, 3 (group 1: 3); prolonged elevation of transaminases, 1 (group 1: 1); febrile neutropenia, 1 (group 2: 1); inter-cycle elevation of bilirubin, 1 (group 1: 1); unreported reasons, 1 (group 2: 1). In all but the last 2 patients, cycles needed to be delayed as well. Six other patients had at least one cycle delayed: 3 due to prolonged neutropenia (group 1: 2, group 2: 1), 1 for patient decision (group 2: 1), 2 for unreported reasons (group 1: 1, group 2: 1).

Data about haematological and hepatic toxicities were available for all patients. Main toxicities both in the whole cohort and split according to whether steroid premedication with dex on the day −1 was given or not (group 2 and group 1, respectively) are listed in Table 3. Grade 3–4 elevation of transaminases occurred in 31% of patients and 12% of cycles. In all but one patient, liver toxicity was reversible to baseline within 15 days and was not clinically significant. Overall, neutropenia occurred in 31% of patients and 24% of cycles (G1–2, 15%, and G 3–4, 9%). Only one patient had febrile neutropenia. Grade 3–4 thrombocytopenia was encountered in 15% of

**Table 3 – Main toxicities "per patients" and "per No of cycles" in the whole cohort and split according to whether steroid premedication with dex on the day −1 was given or not**

| G3–G4 Toxicities | Patients | | | Cycles | | |
|---|---|---|---|---|---|---|
| | Group 1 No (%) | Group 2 No (%) | Whole cohort No (%) | Group 1 No (%) | Group 2 No (%) | Whole cohort No (%) |
| AST-ALT ↑ | 16 (70) | 1 (3) | 17 (31) | 23 (34) | 1 (<1) | 24 (12) |
| Neutropenia | 9 (39) | 3 (10) | 12 (22) | 16 (23) | 3 (2) | 19 (9) |
| Thrombocytopenia | 8 (35) | 0 (0) | 8 (15) | 17 (25) | 0 (0) | 17 (8) |

Group 1: not premedicated with dexamethasone; Group 2: premedicated with dexamethasone.

**Table 4 – Planned Dose Intensity and Received Dose Intensity in the whole cohort and split according to whether premedication was given or not**

| | Group 1 | Group 2 | Whole cohort |
|---|---|---|---|
| Planned Dose Intensity (mcg pw)/(range) | 500 (333–550) | 433 (333–550) | 433 (333–550) |
| Received Dose Intensity (mcg pw)/(range) | 404 (266–550) | 400 (276–550) | 424 (266–550) |

Abbreviations: pw, per week. Group 1 not premedicated with dexamethasone; Group 2: premedicated with dexamethasone.

**Table 5 – Responses, response duration and characteristics of responding patients**

| Best Resp | Pts No. (%) | Sex | Age | Histotype | Disease sites | RDI (μg pw) | DEX (Y/N) | No. cycles | Resp. duration (mos) | Comment |
|---|---|---|---|---|---|---|---|---|---|---|
| CR | 1 (2%) | F | 25 | Pleomorphic sarcoma | Lung | 414 | Y | 6 | 24 | Surgery for lung mets (confirmed pCR) |
| PR | 3 (6%) | F* | 57 | Liposarcoma | Lung, pleura, soft part | 291 | Y | 20 | 23 | Treatment stopped for shared decision |
| | | F | 57 | Uterine leiomyosarcoma | Lung, liver | 352 | N | 5 | 5 | |
| | | F | 27 | Synovialsarcoma | Lung, soft part | 433 | N | 1 | NV | Treatment stopped due to severe adverse event |
| MR | 7 (13%) | F | 37 | EFT | Lung, pleura | 404 | N | 3 | 3 | |
| | | M | 27 | Osteo | Lung | 266 | N | 2 | 3 | |
| | | F | 24 | Synovialsarcoma | Lung | 417 | N | 7 | 8 | |
| | | M | 22 | Epithelioid sarcoma | Lung, soft part | 390 | N | 4 | 3 | |
| | | M | 24 | EFT | Lung, Bone | 525 | N | 2 | 2 | |
| | | M | 58 | Chondrosarcoma | Lung | 292 | N | 4 | 4 | |
| | | M | 57 | Synovialsarcoma | Lung, pleura, bone | 443 | N | 4 | 3 | |

Abbreviations: RDI, received dose intensity; DEX, dexamethasone; CR, disappearance of all known lesions on radiological grounds; pCR, pathological complete response, no cancer was present in the tissue removed after treatment; PR, partial response (⩾50% decrease); MR, minor response (⩾25% and <50% decrease); EFT, Ewing's family tumour.

patients and 8% of cycles. No unexpected reduction in haemoglobin level was reported. Nausea and vomiting were generally mild and manageable. One patient discontinued her treatment because of G4 neutropenia and thrombocytopenia, with a major septic event. Fatigue was reported by 32 patients (60%). G3–G4 elevation of transaminases occurred in 34% of cycles without steroid premedication and in 1% of cycles with steroid premedication ($\chi^2$ $P < 0.0001$). G3–G4 neutropenia was seen in 24% of cycles without steroid premedication and in 2% of premedicated cycles ($\chi^2$ $P < 0.0001$). G3–G4 thrombocytopenia occurred only in non-premedicated cycles.

The median planned dose intensity (PDI) for the whole cohort of patients was 433 mcg per week (pw) (range: 333 – 550), while the median received dose intensity (RDI) was 424 mcg pw (range: 266–550). The PDI for patients in group 1 was 500 mcg per week (range: 333–550), while of patients in group 2 was 433 mcg pw (range: 333–550). The RDI were 404 mcg pw (range: 266–550) and 400 mcg pw (range: 276–550), respectively. Table 4 summarizes data about PDI and RDI in the whole cohort and in the two groups.

All patients were assessable for response. Responses, response duration and characteristics of responding patients are listed in Table 5. Overall, 1 complete response (CR), 3 partial response (PR) and 7 minor response (MR) were reported. The median duration of response was 3.5 months (range 2–24). The median progression-free survival (PFS) was 2.6 months (range 2.1–3.0). The progression-free rate at 4 and 6 months (PFR-4m, PFR-6m) was, respectively, 27% and 19%.

**Table 6 – Progression free survival rate at 4 and 6 months according to the histological type**

| Histotype | PFR-4m | PFR-6m | Median PFS (range) |
|---|---|---|---|
| **ALL** | 27% | 19% | 2.6 (2.1 – 3.0) |
| **STS, other** | 17% | 11% | 2.8 (1.6 – 4.0) |
| **LIPOSARCOMA** | 28% | 28% | 1.6 (0.5 – 1.8) |
| **LEIOMYOSARCOMA** | 45% | 18% | 2.8 (0.5 – 5.1) |
| **SYNOVIAL** | 24% | 24% | 2.3 (1.5 – 3.0) |

Abbreviations: PFR, progression free rate; STS, soft tissue sarcoma.

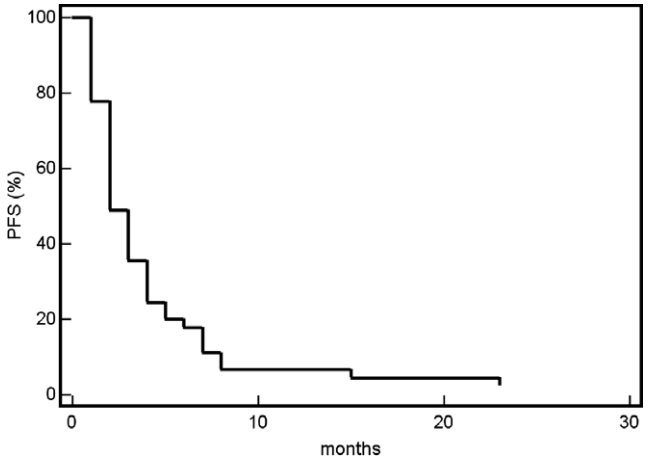


**Fig. 1 – PFS curve for patients with a STS histology.**

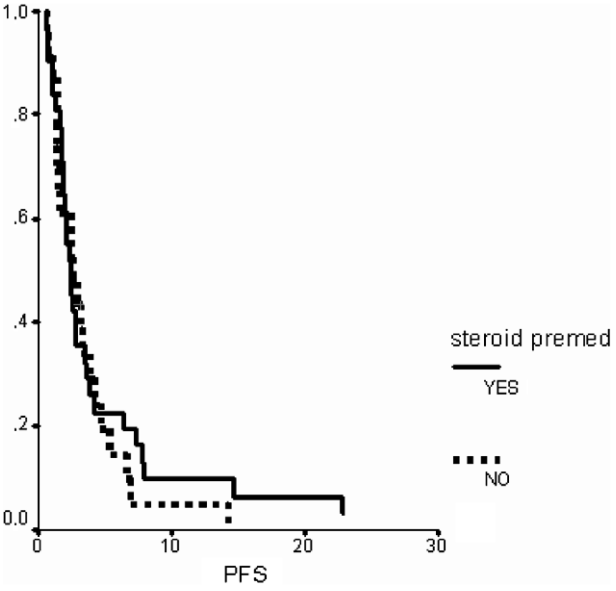


**Fig. 2 – Progression Free Survival of patients who received steroid premedication and those who did not.**

The histological types of patients reaching a PFS longer than 4 months were: leiomyosarcoma (5), synovial sarcoma (3), liposarcoma (2), pleomorphic sarcoma (2), EFT (1), alveolar sarcoma (1). Data about median PFS and PFR at 4 and 6 months broken down according to the histological type are summarized in Table 6. Fig. 1 shows the PFS curve for patients with a STS histology.

The data shown in Fig. 2 suggest there is no difference in PFS between patients who received steroid premedication and those who did not.

## 4. Discussion

In 54 advanced sarcoma patients, who had received prior chemotherapy, trabectedin showed an average response rate of 10% and a PFS-6m ranging from 11% to 28% across histological types. Almost all responses and long-term stabilizations were observed in liposarcomas and leiomyosarcomas, but also in synovial sarcomas and EFT. Most importantly, in this series, the toxicity profile of the drug markedly improved after introducing premedication with dexamethasone on the day before chemotherapy.

Overall, more than 200 courses of trabectedin were administered. In 32 patients who received dexamethasone (8 mg) 24 hours before starting trabectedin, both liver and bone marrow toxicities were markedly reduced as compared to 22 patients who did not receive dexamethasone. Incidence of toxicity manifestations in non-pretreated versus pretreated patients, respectively, were 34% vs. 2% for G3–G4 elevation of transaminases, 24% vs 2% for G3–G4 leukopenia, and 25% vs none for G3–G4 thrombocytopenia. Received dose intensity in the two groups as well as PFS were superimposable. Therefore, steroid premedication would not seem to confound efficacy, though the number of patients is too low as to allow any comparison and no conclusion can be drawn on this point. In addition, it has to be borne in mind that the two patient treatment modes

were just sequential, so that patients were not randomised in a pre-planned manner. However, the difference in toxicity between the steroid-pre-treated and non-pretreated groups seems sufficiently striking to indicate clinical relevance. On the other hand, confirmatory studies are needed in order to rule out the theoretical possibility that efficacy may be affected by steroid premedication.

We introduced steroid premedication following experiments in preclinical models, which demonstrated that pretreatment with high-dose dexamethasone effectively protected female rats from hepatic damage (female rats are the animal species which is most susceptible to the adverse liver side-effects of trabectedin). The timing of dexamethasone administration in relation to trabectedin was shown to be crucial, a 24-h pre-treatment interval being the most effective.[22] One may speculate that such decreased liver toxicity translates in decreased bone marrow toxicity as well. In fact, the clinical observation reported here was a dramatic decrease in both liver and bone marrow toxicity. Any relationship between the two toxicities remains to be elucidated. In rodents, trabectedin caused an up-regulation of genes involved in the cell cycle regulation, as well as of ABC transport genes, and a down-regulation of several genes including P450 genes *Cyp1a1, Cyp2E1* and *Cyp 3a25*.[23,24] Pretreatment with dexamethasone abrogated all these changes. It is therefore conceivable that pretreatment with dexamethasone modifies the expression of genes involved in trabectedin-induced liver toxicity. On the other hand, the finding that liver concentrations of trabectedin in rats pretreated with dexamethasone were lower than in controls suggests the possibility that the protection is related to an increased hepatic clearance of the drug. It is worth noting that in the rodent the changes in liver levels of trabectedin did not influence the systemic pharmacokinetic properties or plasma AUC of trabectedin, findings which are consistent with the lack of attenuation of antitumour activity.

It has already been reported that Dexamethasone co-treatment in human may decrease the incidence of severe toxicities as well as the AUC of the drug. But a significant relationship between the most severe grade of toxicities and the AUC of the drug could not be identified.[25] Thus, it seems likely that, in human too, the protective effect of Dexamethasone premedication from trabectedin's adverse effects cannot be simply related to an increased elimination of the drug but may be due to a more complex interference on the metabolizing process of the drug.

Trabectedin is one of the first marine-derived agents to be available in the clinic. Its peculiar mechanism of action and patterns of resistance, along with demonstrations of activity in sarcomas and ovarian cancer, render this drug highly interesting from the clinical standpoint.[26,27] Clearly, the value of the drug in the advanced setting will depend on the efficacy to toxicity ratio. The toxicity profile of trabectedin is consistent with a main effect on liver and bone marrow. Although in all clinical trabectedin studies liver toxicity has proven to be manageable and therefore of minor concern, thrombocytopenia was a major adverse effect in some patients that is in a small but definite proportion of patients.[16] Therefore, the risk of thrombocytopenia may become a relevant factor in the clinical decision-making on whether to administer this agent as further-line chemotherapy in an advanced sarcoma patient population. From this perspective, the ability of dexamethasone to prevent thrombocytopenia may be of major clinical importance and determine the future use of this agent.

In regard to antitumour activity in this series, liposarcomas and leiomyosarcomas proved sensitive as in all published studies. Currently, it is widely assumed that, amongst sarcomas, liposarcomas and leiomyosarcomas may mainly gain a benefit from trabectedin.[28] In addition to conventional histological assessment, biologic and biomolecular characterization may further help predict the tumour sensitivity to trabectedin. It has been recently reported that low *BRCA1* mRNA expression correlates with higher PFS and median overall survival.[29,30] All this is exceedingly important, because on one side there is an acute, unmet need for new medical options to offer to patients with metastatic STS failing anthracyclines and ifosfamide. On the other side, it is crucial to effectively select candidates in the context of an advanced disease setting. Thus, the combination of classical histologic selection with biomolecular analysis might improve our ability to select those sarcoma patients who are more likely to benefit from this new agent.

Potential biases of "compassionate use" programmes are obvious, and results should always be interpreted with caution. Under another perspective, however, they might also be viewed as a kind of "unselected" Phase II studies, so that, in a sense, they may be even closer to real clinical practice. Therefore, we maintain that our results support the available evidence pointing to some antitumour activity of trabectedin in advanced STS. Most importantly, these results suggest that premedication with dexamethasone on the day before chemotherapy may substantially improve the tolerability profile of trabectedin. This is all the more significant, because it is backed by evidence accrued in rodent models.

Clinically, this might help maximize the therapeutic index of trabectedin, and thus strengthen its role as a viable treatment option in advanced sarcomas.

## Conflict of interest statement

Drs Casali P.G, D'Incalci M and Gescher A received honoraria for speaker and advisory role. Drs Grosso F, Dileo P and Stacchiotti S received travel coverage for scientific meetings. Dr Jimeno J is currently a PharmaMar employee (VP, Scientific Development) and holds shares of Zeltia, the holding corporation. Drs Sanfilippo R, Bertulli R and Piovesan C do not have conflict of interests.

## Acknowledgements

29th European Society for Medical Oncology Congress, Vienna, 29 October–2 November 2004.

## REFERENCES

1. Brennan MF, Alektiar KM, Maki RG. Soft tissue sarcoma. In: DeVita Jr VT, Hellman S, Rosenberg SA, editors. *Cancer:*

*Principles and Practice of Oncology*. Sixth ed. Philadelphia, PA: springer. p. 841–1980.
2. Singer S, Demetri GD, Baldini EH, et al. Management of soft-tissue sarcomas: an overview and update. *Lancet Oncol* 2000;**1**:75–85.
3. Keohan ML, Taub RN. Chemotherapy for advanced sarcoma: Therapeutic decisions and modalities. *Semin Oncol* 1997;**24**:572–9.
4. Patel SR, Vadhan-Raj S, Papadopolous N, et al. High-dose ifosfamide in bone and soft tissue sarcomas: Results of phase II and pilot studies—Dose-response and schedule dependence. *J Clin Oncol* 1997;**15**:2378–84.
5. Le Cesne A, Antoine E, Spielmann M, et al. High-dose ifosfamide: circumvention of resistance to standard-dose ifosfamide in advanced soft tissue sarcomas. *J Clin Oncol* 1995;**13**:1600–8.
6. Nielsen OS, Judson I, van Hoesel Q, et al. Effect of high-dose ifosfamide in advanced soft tissue sarcomas. A multicentre phase II study of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2000;**36**:61–7.
7. Antman KH. Chemotherapy of advanced sarcomas of bone and soft tissue. *Semin Oncol* 1992;**19**:13–20.
8. Okuno S, Ryan LM, Edmonson JH, et al. Phase II trial of gemcitabine in patients with advanced sarcomas (E1797): a trial of the Eastern Cooperative. *Oncology Group Cancer* 2003;**97**:1969–73.
9. Svancarova L, Blay JY, Judson IR, et al. Gemcitabine in advanced adult soft-tissue sarcomas. A phase II study of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2002;**38**:556–9.
10. Fata F, O'Reilly E, Ilson D, et al. Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. *Cancer* 1999;**86**:2034–7.
11. Casper ES, Waltzman RJ, Schwartz GK, et al. Phase II trial of paclitaxel in patients with soft-tissue sarcoma. *Cancer Invest* 1998;**16**:442–6.
12. Bonfanti M, La Valle E, Fernandez Sousa Faro JM, et al. Effect of ecteinascidin-743 on the interaction between DNA binding proteins and DNA. *Anticancer Drug Des* 1999;**14**:179–86.
13. Izbicka E, Lawrence R, Raymond E, et al. In vitro antitumor activity of the novel marine agent, ecteinascidin-743 (ET-743, NSC-648766) against human tumors explanted from patients. *Ann Oncol* 1998;**9**:981–7.
14. Li WW, Takahashi N, Jhanwar S, et al. Sensitivity of soft tissue sarcoma cell lines to chemotherapeutic agents: identification of ecteinascidin-743 as a potent cytotoxic agent. *Clin Cancer Res* 2001;**7**:2908–11.
15. D'Incalci M, Jimeno J. Preclinical and clinical results with the natural marine product ET-743. *Expert Opin Investig Drugs* 2003;**12**:1843–53.
16. Taamma A, Misset JL, Riofrio M, et al. Phase I and pharmacokinetic study of ecteinascidin-743, a new marine compound, administered as a 24-hour continuous infusion in patients with solid tumors. *J Clin Oncol* 2001;**19**(5):1256–65.
17. Yovine A, Riofrio M, Blay JY, et al. Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. *J Clin Oncol* 2004;**22**:890–9.
18. Delaloge S, Yovine A, Taamma A, et al. Ecteinascidin-743: a marine-derived compound in advanced, pretreated sarcoma patients-preliminary evidence of activity. *J Clin Oncol* 2001;**19**:1248–55.
19. Garcia-Carbonero R, Supko JG, Manola J, et al. Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy. *J Clin Oncol* 2004;**22**:1480–90.
20. Le Cesne A, Misset JL, Demetri G, et al. Consistent evidence of activity of ecteinascidin (ET-743) in pretreated, advanced soft tissue sarcoma (ASTS): results from a pooled analysis of three pivotal phase II clinical trials (p2ct) and safety profile of a 24-h infusion schedule. *Proc ECCO 11, Eur Journal of Cancer* 2001;**37**:34.
21. Gomez J, Lopez-Lazaro L, Guzman C, et al. Identification of biochemical parameters that predict the onset of severe toxicities in patients treated with ET-743. *Proc Am Soc Clin Oncol* 2000;**19**:187a.
22. Donald S, Verschoyle RD, Greaves P, et al. Complete protection by high-dose dexamethasone against the hepatotoxicity of the novel antitumor drug yondelis (ET-743) in the rat. *Cancer Res* 2003;**63**:5902–8.
23. Donald S, Verschoyle RD, Edwards R, et al. Hepatobiliary damage and changes in hepatic gene expression caused by the antitumor drug ecteinascidin-743 (ET-743) in the female rat. *Cancer Res* 2002;**62**:4256–62.
24. Donald S, Verschoyle RD, Greaves P, et al. Comparison of four modulators of drug metabolism as protectants against the hepatotoxicity of the novel antitumor drug yondelis (ET-743) in the female rat and in hepatocytes in vitro. *Cancer Chemother Pharmacol* 2004;**53**:305–12.
25. Puchalski TA, Ryan DP, Garcia-Carbonero R, et al. Pharmacokinetics of ecteinascidin 743 administered as a 24-h continuous intravenous infusion to adult patients with soft tissue sarcomas: associations with clinical characteristics, pathophysiological variables and toxicity. *Cancer Chemother Pharmacol* 2002;**50**:309–19.
26. Le Cesne A, Blay JY, Judson I, et al. 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. *J Clin Oncol* 2005;**23**:576–84.
27. Sessa C, De Braud F, Perotti A, et al. Trabectedin for women with ovarian carcinoma after treatment with platinum and taxanes fails. *J Clin Oncol* 2005;**23**:1867–74.
28. Samuels BL, Rushing D, Chawla SP, et al. Randomized phase II study of trabectedin (ET-743) given by two different dosing schedules in patients (pts) with leiomyosarcomas (LMS) or liposarcomas (LPS) refractory to conventional doxorubicin and ifosfamide chemotherapy. *Proc Am Soc Clin Oncol* 2004;**22**:9000.
29. Van Oosterom A, Maki R, Taron M, et al. Correlation between the pattern of DNA repair efficiency and the natural history of patients with advanced sarcoma treated with ET-743 (Yondelis). *Proc Eu Soc Med Oncology* 2004;**15**:7450.
30. Van Oosterom A, Maki R, Taron M, et al. Impact of the DNA repair efficiency in the outcome of sarcoma patients treated with ET-743 (Yondelis). *Proc 16th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics*, 2004; abstr 479.