EUROPEAN JOURNAL OF CANCER 48 (2012) 579–585

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

A phase 2 trial of trabectedin in children with recurrent rhabdomyosarcoma, Ewing sarcoma and non-rhab domyosarcoma soft tissue sarcomas: A report from the Children's Oncology Group

Sylvain Baruchel [a,*], *Alberto Pappo* [g], *Mark Krailo* [b,c], *K. Scott Baker* [d], *Bing Wu* [a], *Doojduen Villaluna* [b], *Michelle Lee-Scott* [a], *Peter C. Adamson* [f], *Susan M. Blaney* [e]

[a] *The Hospital for Sick Children, Toronto, ON, Canada*
[b] *COG Office, Arcadia, CA, United States*
[c] *University of Southern California, Los Angeles, CA, United States*
[d] *Seattle Children's Hospital and Fred Hustchison Cancer Research Center, Seattle, WA, United States*
[e] *Texas Children's Cancer Center, Houston, TX, United States*
[f] *Children's Hospital of Philadelphia, Philadelphia, PA, United States*
[g] *St. Jude Children's Research Hospital, Memphis, TN, United States*

ARTICLE INFO

Article history:
Available online 14 November 2011

Keywords:
Paediatrics
Sarcoma
Clinical trials
Phase 2

ABSTRACT

Purpose: To determine the toxicity, efficacy and pharmacokinetics of trabectedin given over 24 h every 3 weeks to children with recurrent rhabdomyosarcoma, Ewing sarcoma, or non-rhabdomyosarcoma soft tissue sarcomas.

Patients and methods: Trabectedin was administered as a 24-h intravenous infusion every 21 days. Two dose levels were evaluated (1.3 and 1.5 mg/m^2) for safety; efficacy was then evaluated using a traditional 2-stage design (10 + 10) at the 1.5 mg/m^2 dose level. Pharmacokinetics (day 1 and steady state) were performed during cycle 1.

Results: Fifty patients were enroled, eight patients at 1.3 mg/m^2 and 42 at 1.5 mg/m^2. Dose limiting toxicities (DLTs) in the dose finding component included fatigue and reversible GGT elevation in 1/6 evaluable patients at 1.3 mg/m^2 and 0/5 at 1.5 mg/m^2. Efficacy was evaluated in 42 patients enroled at the 1.5 mg/m^2 dose of whom 22% experienced reversible grade 3 or 4 toxicities that included AST, ALT, or GGT elevations, myelosuppression and deep venous thrombosis.

One patient with rhabdomyosarcoma had a partial response and one patient each with rhabdomyosarcoma, spindle cell sarcoma and Ewing sarcoma had stable disease for 2, 3 and 15 cycles, respectively.

Conclusion: Trabectedin is safe when administered over 24 h at 1.5 mg/m^2. Trabectedin did not demonstrate sufficient activity as a single agent for children with relapsed paediatric sarcomas.

* *Corresponding author:* Address: The Hospital for Sick Children, Division of Haematology/Oncology, 555 University Avenue, Toronto, ON, Canada M5G 1X8. Tel.: +1 416 813 8795; fax: +1 416 813 5327.
E-mail address: sylvain.baruchel@sickkids.ca (S. Baruchel).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.09.027

1. Introduction

Trabectedin (Yondelis; ET-743), is a synthetic alkaloid originally isolated from the marine ascidian *Ecteinascidia turbinate*.[1] Its complex mechanism involves binding to the minor groove of double-stranded DNA and subsequent bending of DNA towards the major groove,[2] resulting in inhibition of gene activation and of nucleotide excision repair and in induction of DNA strand breaks and cell cycle arrest in S and G2 phases.

Trabectedin induces tumour regression in histologic subsets of adult soft tissue sarcomas including myxoid liposarcoma and leiomyosarcoma, suggesting that this drug is an effective therapeutic option for adults with these subtypes of soft tissue sarcomas.[3–7] The different mechanisms of action and efficacy of this agent in adults with soft tissue sarcomas prompted us to further explore its efficacy in children with recurrent or refractory sarcomas. A prior Children's Oncology Group phase 1 trial of trabectedin evaluated a 3-h infusion schedule at doses of 1.5 and 1.3 mg/m^2 in a total of twelve children with refractory solid tumours. Reversible neutropenia and hepatic toxicity were the primary toxicities; the recommended phase 2 dose on this administration schedule was 1.1 mg/m^2 every 21 days.[8] One of three patients with Ewing sarcoma had a complete response that was sustained for 10 months. Following the initial assessment of trabectedin in children, results from adult trials suggested that administration of trabectedin as a 24-h infusion at a dose of 1.5 mg/m^2 every 3 weeks would be associated with superior disease control rates.[4–6] Therefore in this trial, we initially evaluated the safety of administering trabectedin as a 24-h (rather than a 3-h infusion) at two dose levels, to ensure the safety of this schedule prior to proceeding with the phase 2 trial in children with recurrent rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) or Ewing sarcoma.

2. Patients and methods

2.1. Eligibility criteria

Eligibility criteria included: age $\geqslant$12 months and $\leqslant$21 years when initially diagnosed, weight $\geqslant$15 kgs, histologic diagnosis of rhabdomyosarcoma, Ewing sarcoma or non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), measurable disease according to RECIST criteria, performance score by Karnofsky or Lansky of $\geqslant$50%, and normal organ function (normal creatinine for age; ALT, AST and GGT $\leqslant$2.5 times the institutional normal; albumin $\geqslant$2.5 g/dL; serum bilirubin and alkaline phosphatase $\leqslant$ the institutional upper limits of normal; shortening fraction $\geqslant$27% or ejection fraction $\geqslant$50%; ANC $\geqslant$1500 μL; platelet count $\geqslant$100,000 μL and haemoglobin $\geqslant$8 g/dL). In addition, patients had to have fully recovered from the toxic effects of prior chemotherapy, immunotherapy and radiotherapy. They must not have received growth factor support or platelets within 1 week of study entry, must not have received enzyme inducing anticonvulsants within 14 days of study entry, and must have been receiving medications that interfere with CYP3A4. Prior to drug administration, patients were required to have a central venous line. Exclusion criteria included active uncontrolled infection, preexisting liver disease, history of congestive heart failure, prior history of allogeneic stem cell transplant and TBI, and pregnancy or lactation.

The study protocol was approved by the institutional review board of each institution from which patients were enroled. Informed consent was obtained from the patient or their parent or guardian, and assent was obtained as appropriate, prior to enrolment.

2.2. Drug administration

Trabectedin was administered as a 24-h intravenous infusion every 21 days at two dose levels: 1.3 mg/m^2 and 1.5 mg/m^2. Dexamethasone, 2.5 mg/m^2, was administered orally the evening before trabectedin and every 12 h on days 1, 2 and 3 of each cycle.

2.3. Statistical considerations

2.3.1. Dose finding phase

A limited dose escalation was performed to evaluate two trabectedin dose levels utilising the 24-h infusion schedule. The initial dose level was the recommended phase 2 dose from the paediatric phase 1 trial using a 3-h infusion schedule, 1.3 mg/m^2. The second dose level, 1.5 mg/m^2, was the recommend phase 2 adult dose on the 24-h infusion schedule. Patients were enroled in cohorts of six. If less than two patients experienced dose limiting toxicity (DLT) during the first cycle, the 1.3 mg/m^2 dose level was considered tolerable and the dose was escalated to 1.5 mg/m^2. If two or more patients experience DLT during the first cycle, the dose was to be reduced to 1.1 mg/m^2. If the dose was escalated to 1.5 mg/m^2 and one or fewer of these patients experience DLT during the first cycle, the 1.5 mg/m^2 dose level was considered the recommended dose and patients would be enroled to complete the two-stage design described below. Only patients treated at the recommended dose of 1.5 mg/m^2 were considered for response and efficacy evaluation, which included all patients enroled on the phase II portion of the study and patients enroled on the phase 1 portion of the study at the recommended dose ('response cohort'). All response cohort patients who were evaluable for DLT were included in the characterisation of toxicity of the recommended dose.

Dose-limiting toxicity was defined as: (1) grade 3 or 4 non-hematological toxicity considered possibly, probably or likely related to trabectedin with the exception of grade 3 nausea or vomiting, grade 3 ALT or AST that returned to grade 1 or baseline prior to the next treatment cycle, grade 3 fever or infection or alopecia; or (2) grade 4 neutropenia >7 days duration, grade 4 thrombocytopenia of >7 days which required transfusion on more than two occasions in 7 days or which caused a delay of >14 days in the start of the next treatment cycle. Grade 3 and 4 GGT elevation were considered as a DLT. Only DLTs that occurred in the first cycle were considered for dose escalation.

Clinical and laboratory adverse events were graded according to the NCI Common Terminology Criteria for Adverse Events version 3 (http://ctep.info.nih.gov).

2.3.2. Phase 2 component

A two-stage design was employed for evaluating efficacy of trabectedin at the 1.5 mg/m^2 dose level. Ten response-evaluable patients were enroled in the first stage in each of the disease strata defined as: (1) non-rhabdomyosarcomatous soft tissue sarcoma, (2) Ewing sarcoma and (3) rhabodmyosarcoma. If none of the patients in the first stage demonstrated a complete or partial response, as determined by RECIST version 1.0, enrolment to that stratum was closed with the conclusion that trabectedin did not demonstrate sufficient activity for further investigation. If six or more objective responses were observed in the first stage, the enrolment to that stratum was closed with the conclusion that trabectedin demonstrated sufficient activity for further investigation. Otherwise, enrolment was continued to enrol a total of 20 response-evaluable patients. If three or more of the 20 patients demonstrated an objective response, then trabectedin activity was deemed of sufficient interest for further investigation; otherwise, it was concluded that trabectedin did not demonstrate sufficient activity for further investigation. With this design, if trabectedin was associated with a true response rate of 5%, the probability that trabectedin was considered active was 0.10. If the true response rate was 25%, the probability that trabectedin was considered active in a stratum would be 0.92. Confidence intervals were to be constructed using the method of Chang and O'Brien.[9] All patients who had two consecutive evaluations of stable disease, complete remission (CR) or partial response (PR) were considered 'responders' for the purposes of the two-stage design. Responses as determined by the institutional radiologist were confirmed by central expert radiologist review.

2.4. Pharmacokinetics

During the first cycle of therapy, heparinised blood samples (3 mL) for pharmacokinetic studies were obtained from consenting patients prior to the start of the trabectedin infusion and at 1.5, 4, 8, 23.5, 24 and 26.5 h after the start of the infusion. Plasma was obtained by centrifugation (2500*g* for 10 min at 4 °C) within 15 min after collection and stored at –70 °C until assayed. Trabectedin plasma concentrations were measured using a previously validated HPLC/MS/MS assay[4] with a lower limit quantification of 0.05 ng/mL. The trabectedin plasma concentration–time data were analysed using non-compartmental methods. Day one peak trabectedin concentration (C_{max}) and time to peak concentration (T_{max}) were determined from the time–concentration plots. Exposure ($AUC_{0-24\ h}$) was calculated using the linear trapezoidal method.

3. Results

ADVL0221 (Fig. 2) was open for enrolment from January 2008 through April 2010. A total of fifty patients were enroled and all were considered eligible for this study (Table 1). The clinical characteristics are depicted in Table 1.

3.1. Dose finding phase

Fourteen patients were enroled in the dose-finding phase of the trial (phase 1). Eight patients received the 1.3 mg/m^2 dose and six received the 1.5 mg/m^2 dose. Amongst these 14 patients, three were not fully evaluable for toxicity due to

Table 1 – Patient characteristics (*n* = 50).

Characteristic	*n* (%)
No of eligible patients	50 (100%)
Age (years)	15.5 (range, 4–24)
Diagnosis	
Rhabdomyosarcoma	23 (46%)
Ewing sarcoma	16 (32%)
Non-rhabdomyosarcoma soft tissue sarcoma (NRSTS)	11 (22%)
Sarcoma NOS	1
Alveolar soft part sarcoma	2
Spindle cell sarcoma	2
Undifferentiated sarcoma	2
Desmoplastic small round cell tumour	1
Synovial sarcoma	2
Sex	
Male	31 (62%)
Female	19 (38%)
Race	
White	38 (76%)
African American	7 (14%)
Asian	2 (4%)
Other	2 (4%)
Unknown	1 (2%)

Table 2 – Number of evaluable patients and dose-limiting toxicities observed among patients in the dose-finding phase of the trial (*n* = 14).

Dose level (mg/m^2)	No. patients	No. evaluable patients	No. dose limiting toxicities (DLTs)	Type
1.3	8	6	1	Fatigue GGT elevation
1.5	6	5	0	None

disease progression prior to completing cycle 1. Amongst the 11 evaluable patients, one of six evaluable patients at the 1.3 mg/m^2 dose had dose limiting grade 3 elevation of GGT and fatigue. No DLTs were seen in the five enroled at the 1.5 mg/m^2 dose level (Table 2). Reversible grade 3 myelosuppression and reversible grade 3 elevation of AST/ALT were reported in seven patients. The recommended dose for this phase of the study was 1.5 mg/m^2 dose.

3.2. *Phase 2 component*

3.2.1. *Response*

Forty-two patients were available for the efficacy evaluation component of this trial (six were from those administered the 1.5 mg/m^2 dose in the phase 1 part of this study and 36 patients were enroled in the phase 2 portion). Forty patients were fully evaluable for response. Reasons for inevaluability included withdrawal of consent by one patient with rhabdomyosarcoma and non-compliance in one patient with Ewing sarcoma (Table 3). One patient with rhabdomyosarcoma achieved a partial response after six cycles; three patients achieved stable disease (one rhabdomyosarcoma after 15 cycles, one spindle cell sarcoma after two cycles and one Ewing sarcoma after four cycles). The median number of cycles administered was four (range 1–15).

3.2.2. *Toxicity*

Forty-one patients were fully evaluable for toxicity of whom nine (22%) experienced a DLT (Tables 4 and 5). Eight of the DLTs occurred during the first cycle of treatment. Two patients were removed from the study because of prolonged myelosuppression with failure to recover their ANC counts to eligibility criteria within 14 days. Two patients, both of whom had central venous catheters, experienced a deep venous thrombosis, one patient required that line be removed and treatment with anticoagulant.

3.2.3. *Pharmacokinetics*

Plasma samples for pharmacokinetic analysis were obtained from 10 patients (Fig. 1). Significant inter-patient variability in drug disposition was observed. Trough drug concentrations exceeded concentrations associated with anti-tumour activity within preclinical model systems.[10–13]

4. Discussion

Trabectedin, (ecteinascidin-74, ET-743), is a natural marine compound derived from the Caribbean tunicate *Ecteinascidia turbinata* that is currently approved in Europe for the treatment of advanced recurrent soft tissue sarcomas and ovarian cancer.[3–6] Trabectedin has produced objective responses in

Table 3 – Responses to trabectedin among evaluable patients in the phase 2 component (*n* = 40).

Stratum	PR[a]	SD[b]	PD[c]	Not evaluable
Rhabdomyosarcoma	1	1	18	1
Non-rhabdomyosarcoma soft tissue sarcoma (NRSTS)	0	1	9	1
Ewing sarcoma	0	1	9	1
Overall	1	3	36	2

[a] PR, partial response.
[b] SD, stable disease.
[c] PD, progressive disease.

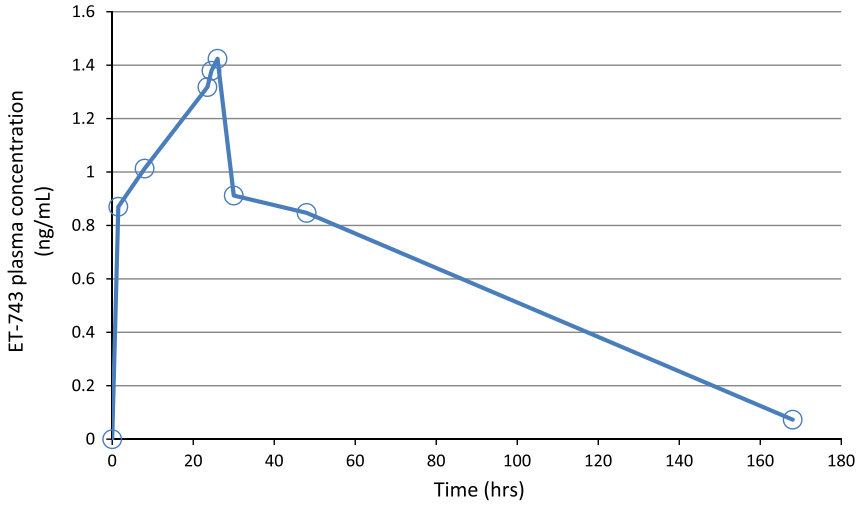
Table 4 – Dose-limiting toxicities observed among nine patients in the phase 2 component of the trial (*n* = 41).

Toxicity	Attribution	Grade 3	Grade 4
Fatigue	Definitely	1	0
GGT[a]	Probably	7	0
AST	Definitely	2	0
ALT	Definitely	2	0
ANC	Definitely		1
Deep venous thrombosis	Definitely	1	

[a] Gamma-g transpeptidase.

Table 5 – Toxicities observed in 5% or more of patients at doses of 1.5 mg/m^2 (n = 41).

Toxicity type	Number	Percent
Haemoglobin	3	7
Leucocytes (total WBC)	11	27
Lymphopenia	7	17
ANC	14	34
Platelets	5	12
Fatigue	2	5
ALT, SGPT	13	32
AST, SGOT	10	24
GGT	6	15
Hypokalemia	2	5
Thrombosis/embolism (vascular access-related)	2	5



n	Dose (mg/m^2)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng/mL×h)	CL (L/h/m^2)	$t_{½}$ (h)	MRT (h)
10	1.5	2.49 ±2.25	112.6± 132.5	24.3 ± 16.2	52.6±18.4	55.7±16.9

Fig. 1 – Plasma phamacokinetic.

less than 10% of adult patients with recurrent sarcomas but progression-free rates at 6 months have been higher than those observed with other conventional chemotherapeutic agents.[2–8,14–18] The histologic subgroups that have benefitted the most from this agent include leiomyosarcoma, liposarcoma, and synovial sarcoma.[14,19] In a recent open-label multicentre randomised study of adults with liposarcoma and leiomyosarcoma, superior disease control rates were documented using a 24-h continuous infusion schedule.[19]

Preclinical studies using sarcoma cell lines found that trabectedin is a very active drug at low concentrations readily achievable under clinical conditions, and indicate that sarcoma cell lines such as fibrosarcoma, malignant fibrous histiocytoma, mesenchymal chondrosarcoma, liposarcoma, malignant hemangiopericytoma and malignant mesenchymoma are particularly sensitive to trabectedin.[10–13] In *in vitro* paediatric tumour models, IC_{50} values ranged from 0.3 to 1 nM (72–96 h exposure) in 12/13 osteosarcoma and 6/6 Ewing sarcoma cell lines.[11,12]

Our paediatric trial did not meet the required response rates to justify further development of this drug as a single agent in relapsed paediatric sarcomas. Although our study was not designed to analyse progression free survival as a primary end-point, only four patients across disease cohorts, including one patient with a PR, experienced stable disease, which does not suggest a meaningful signal of disease stabilisation for trabectedin in these relapsed sarcomas.

In adults, most common ($\geqslant$5%) grade 3–4 AEs in the q3wk 24-h dose group were increased ALT (12%), neutropenia (12%), increased AST (8%) and dysponea, fatigue, nausea and vomiting (7%). Haematological toxicity was substantially and consistently higher in the q3wk 24-h group compared to the qwk 3-h group: four percent of patients developed febrile neutropenia in the q3wk 24-h regimen compared to less than 1% in the qwk 3-h group. In our study, trabectedin was well tolerated with transient and self-resolving AEs. The incidence of grade 3–4 AEs in our series is lower than reported in adults. Hepatic toxicity was mainly transaminase elevation (ALT

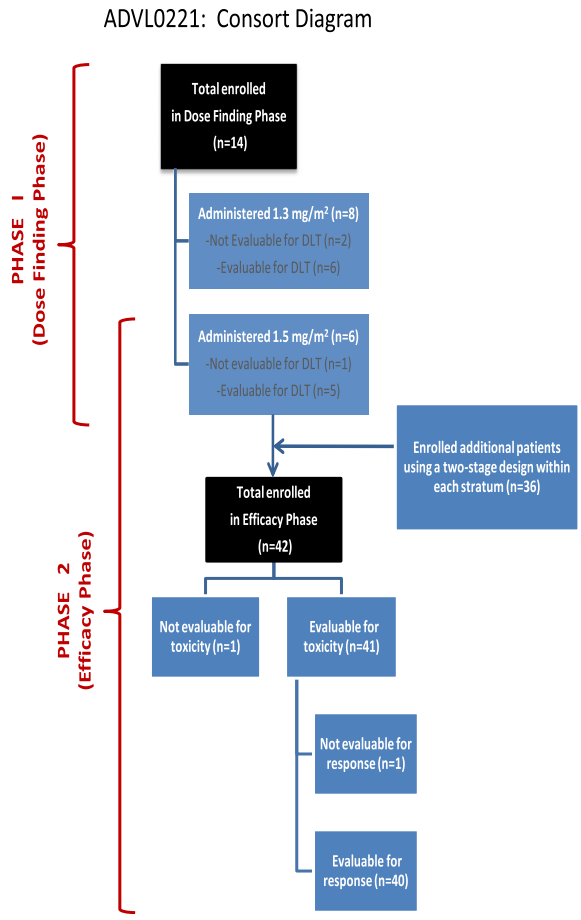


Fig. 2 – ADVL0221 diagram.

and AST, 32% and 24%, respectively). GGT elevations were also common (15%) and were not always correlated with transaminitis. In line with prior experience, transaminase increases were reversible and non-cumulative, and no patients showed any symptoms or signs of liver failure due to treatment. While neutropenia was the most common overall toxicity (34%), the incidence of grade 3–4 neutropenia and febrile neutropenia was extremely low (0.02%) and treatment delays or therapy discontinuation was infrequent (<2%).

Rhabdomyolysis has been reported in adults, and associated with death in ~0.5% of patients, prior to routine use of adjuvant corticosteroid therapy.[20,21] Rhabdomyolysis has never been reported in children receiving trabectedin and did not occur in this trial. Of note are two patients that developed deep venous thrombosis despite the use of a central line and one patient requiring usage of anticoagulant and removal of the central line. One additional patient developed a myelodysplastic syndrome 13 months after having completed protocol treatment and had received regimen containing other myelotoxic drugs such as temozolomide and etoposide.

The results of this paediatric pharmacokinetics are generally similar to those observed in adults.[4–6] Following intravenous administration, trabectedin demonstrates a high apparent volume of distribution, consistent with extensive tissue and plasma protein binding (94–98% of trabectedin in plasma is protein bound). Plasma clearance was high (24.3 ± 16.2 L/h/m^2) and consistent with previously published adult studies (21.2–53.7 L/h/m^2). The trough concentrations were within the range associated with activity in preclinical models.[12]

In conclusion, despite adult benefits to patients with specific subsets of sarcomas, especially leiomyosarcomas, synovial cell sarcoma and liposarcomas, this trial did not demonstrate any significant evidence of activity for trabectedin in children with relapsed sarcomas.

Conflict of interest statement

Following acceptance of the paper for publication, Dr. Baruchel signed an agreement to act as a consultant for Pharmamar for a PIP EMA submission. No honorarium had been paid to Dr. Baruchel at the time the manuscript was submitted.

Acknowledgements

We thank Elizabeth O'Connor, Biljana Georgievska, Nicole Stewart and Smita Subramanian from the COG Operations Center for outstanding data management and administrative support throughout the development and conduct of this trial.

Funding sources: Research is supported by U10 CA98543-09 and U10 CA98413-09 of the Children's Oncology Group from the National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NCI or the NIH.

REFERENCES

1. D'Incalci M, Galmarini CM. A review of trabectedin (ET-743): a unique mechanism of action. *Mol Cancer Ther* 2010;**9**:2157–63.
2. Guan Y, Sakai R, Rinehart KL, Wang AH. Molecular and crystal structures of ecteinascidins: potent antitumor compounds from the Caribbean tunicate *Ecteinascidia turbinata*. *J Biomol Struct Dyn* 1993;**10**:793–818.
3. 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.
4. 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.
5. Garcia-Carbonero R, Supko JG, Maki RG, et al. Ecteinascidin-743 (ET-743) for chemotherapy-naive patients with advanced soft tissue sarcomas: multicenter phase II and pharmacokinetic study. *J Clin Oncol* 2005;**23**:5484–92.
6. Perez-Ruixo JJ, Zannikos P, Hirankarn S, et al. Population pharmacokinetic meta-analysis of trabectedin (ET-743, Yondelis®) in cancer patients. *Clin Pharmacokinet* 2007;**46**:867–84.
7. Demetri GD, Chawla SP, von Mehren M, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior

anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. *J Clin Oncol* 2009;**27**:4188–96.
8. Lau L, Supko JG, Blaney S, et al. A phase I and pharmacokinetic study of ecteinascidin-743 (Yondelis) in children with refractory solid tumors. A Children's Oncology Group study. *Clin Cancer Res* 2005;**11**:672–7.
9. Chang MN, O'Brien PC. Confidence intervals following group sequential tests. *Control Clin Trials* 1986;**7**:18–26.
10. Borden EC, Baker LH, Bell RS, et al. Soft tissue sarcomas of adults: state of the translational science. *Clin Cancer Res* 2003;**9**:1941–56.
11. Forni C, Minuzzo M, Virdis E, et al. Trabectedin (ET-743) promotes differentiation in myxoid liposarcoma tumors. *Mol Cancer Ther* 2009;**8**:449–57.
12. Li W, Jhanwar S, Elisseyeff Y, Bertino JR. Potent antitumor activity of ET-743 against human soft tissue sarcoma cell lines. *Clin Cancer Res* 1999;**5**:3790s.
13. Hornicek FJ, Weissbach L, Nielsen G, et al. In vitro effect of the tetrahydroisoquinoline alkaloid–ecteinascidin-743 (ET-743) on chondrosarcoma cell. *Clin Cancer Res* 1999;**5**:3790s.
14. Casali PG, Sanfilippo R, D'Incalci M. Trabectedin therapy for sarcomas. *Curr Opin Oncol* 2010;**22**:342–6.
15. 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.
16. Blay JY, van Glabbeke M, Verweij J, et al. Advanced soft-tissue sarcoma: a disease that is potentially curable for a subset of patients treated with chemotherapy. *Eur J Cancer* 2003;**39**:64–9.
17. 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.
18. Thornton KA. Trabectedin: the evidence for its place in therapy in the treatment of soft tissue sarcoma. *Core Evid* 2009;**4**:191–8.
19. Paz-Ares L, López-Pousa A, Poveda A, et al. Trabectedin in pre-treated patients with advanced or metastatic soft tissue sarcoma: a phase II study evaluating co-treatment with dexamethasone. *Invest New Drugs* 2010. doi:10.1007/s10637-010-9561-9.
20. Demetri GD, Chawla SP, von Mehren M, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. *J Clin Oncol* 2009;**27**:4188–96.
21. Fetterly GJ, Owen JS, Stuyckens K, et al. Semimechanistic pharmacokinetic/pharmacodynamic model for hepatoprotective effect of dexamethasone on transient transaminitis after trabectedin (ET-743) treatment. *Cancer Chemother Pharmacol* 2008;**62**:135–47.