Study ET-A-008-00 was a phase 1 open-label, non-randomised, dose-escalating multicenter study enrolling 12 patients with pediatric refractory solid tumours (data not shown). Definitive conclusions cannot be drawn given the relatively small sample size of paediatric patients in each dose group.

- Pharmacokinetic interaction studies

CYP3A4 is the main CYP enzyme responsible for the hepatic metabolism of trabectedin at clinically relevant concentrations. Therefore, co-administration with potent inducers or inhibitors of CYP3A4 is expected to reduce or increase, respectively, the plasma concentrations of trabectedin. Trabectedin metabolism was markedly diminished by chemical inhibitors of CYP3A4 (ketoconazole and troleandomycin) and selective inhibitory antibodies directed towards this enzyme in vitro.

Weekly administration of 0.3 to 0.65 mg/m2 of trabectedin as a 3-hour infusion (with dexamethasone prophylaxis) to patients with cancer had minimal impact on the *in vivo* activity of the CYP3A4 enzyme.

A pharmacokinetic study of liposomal doxorubicin and trabectedin has been conducted (data not shown).

Pharmacodynamics

- Mechanism of action

No clinical studies on the mechanism of action of trabectedin have been submitted.

- Primary and Secondary pharmacology

No clinical studies on the primary and secondary pharmacolgy of trabectedin have been submitted.

Discussion on Clinical Pharmacology

Systemic exposure after administration as a 24 hour constant rate intravenous infusion is dose proportional at doses up to and including 1.8 mg/m^2. Trabectedin pharmacokinetic profile is consistent with a multiple-compartment disposition model.

Following intravenous administration, trabectedin demonstrates a high apparent volume of distribution, consistent with extensive tissue and plasma protein binding (94 to 98% of trabectedin in plasma is protein bound). The distribution volume at steady state of trabectedin in human subjects exceeds 5000 l.

Clinically significant effects of race/ethnicity on the pharmacokinetics of trabectedin are not expected and, therefore, dose adjustments are not recommended at the moment. Nevertheless, the applicant commited to analyse the influence of race on pharmacokinetics when the data of the ongoing Phase 3 study ET743-OVA-301 in ovarian cancer be available.

Pharmacokinetics in children have not been established.

Cytochrome P450 3A4 is the major cytochrome P450 isozyme responsible for the oxidative metabolism of trabectedin at clinically relevant concentrations. Other P450 enzymes may contribute to metabolism. Trabectedin does not induce or inhibit major cytochrome P450 enzymes. Trabectedin metabolism was markedly diminished by chemical inhibitors of CYP3A4 (ketoconazole and troleandomycin) and selective inhibitory antibodies directed towards this enzyme. Chemical inhibitors and/or antibodies of other CYP enzymes had no effect.

Trabectedin was administered as a 1-, 3-, 24-, or 72-hour constant rate, intravenous infusion. Maximum concentrations of trabectedin in plasma were typically observed either during or immediately prior to the end of the infusion. The drug concentrations then declined in a multiexponential manner upon cessation of the intravenous infusion. Initially, a marked and rapid decline in plasma concentrations was observed which was followed by more prolonged distribution and terminal phases.

The pharmacokinetics of trabectedin, with respect to plasma Cmax and AUC, are dose-proportional when administered as a 24-hour or 3-hour intravenous infusion within the clinically relevant dose range.. Furthermore, it is agreed that assessments of dose-proportional pharmacokinetics for other time points are deemed to be inconclusive. It is considered likely that only little or no accumulation of

trabectedin in plasma will occur upon repeat administration of 1-hour or 3-hour infusions at 3-week intervals.

Little or no accumulation was apparent in the plasma concentrations of trabectedin when 1.5 mg/m2 was given as a 24-hour infusion every 3 weeks. In agreement with this, simulated plasma concentration-time profiles also predicted minimal accumulation of trabectedin following this dosing regimen

The clearance of trabectedin in whole blood is approximately 35 L/h. Thus, trabectedin may be classified as drug with a moderate extraction ratio. Variability in the pharmacokinetics of trabectedin was moderate to large. This can not be ascribed to one factor including gender, age body weight, body surface area, plasma clearance, or measures of hepatic function. The difference demonstrated in central volume in distribution associated to gender should be considered without clinical relevance

The distribution volume at steady state of trabectedin in human patients exceeds 5000. These results suggest trabectedin distributes extensively into peripheral tissues (outside the central compartment).

Trabectedin is extensively metabolized. Renal elimination of unchanged trabectedin in humans is low (less than 1%). The terminal half-life is long (population value of the terminal elimination phase: 180-hr). After a dose of radiolabelled trabectedin administered to cancer patients, faecal mean (SD) recovery of total radioactivity is 58% (17%), and urinary mean (SD) recovery is 5.8% (1.73%). Based on the population estimate for plasma clearance of trabectedin (31.5 l/h) and blood/plasma ratio (0.89), the clearance of trabectedin in whole blood is approximately 35 l/h. This value is approximately one-half the rate of human hepatic blood flow. Thus the trabectedin extraction ratio can be considered moderate. The inter-patient variability of the population estimate for plasma clearance of trabectedin was 51% and intra-patient variability was 28%.

A population pharmacokinetic analysis indicated that the plasma clearance of trabectedin is not influenced by age (range 19-83 years), or gender. The effects of race and ethnicity on trabectedin pharmacokinetics have not been studied.

There is no relevant influence of renal function measured by creatinine clearance on trabectedin pharmacokinetics within the range of values ($\geq$ 34.4 ml/min) present in the patients included in the clinical studies. No data are available in patients with a creatinine clearance of less than 34.4 ml/min. The low recovery (< 9% in all studied patients) of total radioactivity in the urine after a single dose of ^{14}C-labelled trabectedin indicates that renal impairment has little influence on the elimination of trabectedin or its metabolites.

Although the population analysis showed no relationship between the serum liver enzymes concentrations and the plasma clearance of trabectedin, systemic exposure to trabectedin may be increased in patients with hepatic impairment; therefore close monitoring of toxicity is warranted.

Clinical efficacy

- Dose response study(ies)

In the first application, four phase I studies in patients with solid tumours were provided (ET-A.001, PMA-002-95, ET-A-003-95 and ET-A-004-97). These studies evaluated different schedules (1, 3, 24 and 72 hour infusions weekly, every 21 days and 1 hour infusion for 5 days in a 21 day cycle). Doses evaluated ranged from 50 to 1800 $\mu g/m^2$ every three weeks. DLT were thrombocytopenia, pancytopenia, fatigue, lethargy, emesis, rhabdomyolysis and hepatotoxicity. MTD for both 3h and 24 hour infusions were 1.8 mg. The 1h and 72h infusional regimes were considered less appropriate for further phase II studies. In this application, an additional study (ET-A-005-99) was provided. This study tested 3 hour infusions weekly for three weeks in four week cycles at doses ranging from 300 to 650 $\mu g/m^2$ weekly, in 31 patients. DLT were neutropenia, hepatotoxicity and rhabdomyolysis and the MTD was 650 $\mu g/m^2$. Antitumour activity was only evaluated in study ET-A-004-97 (72 h infusion) and ET-A-005-99.

- Main study(ies)

A randomized, multicenter, open-label study of Yondelis (ET-743 Ecteinascidin) administered by 2 different schedules (weekly for 3 of 4 weeks vs. q3 weeks) in subjects with locally advanced or

metastatic liposarcoma or leiomyosarcoma following treatment with an anthracycline and ifosfamide (ET743-STS-201).

METHODS

Study Participants

Treatments

Objectives

The study was originally designed to select the most appropriate schedule for further testing. Following protocol amendment, the objective was to compare the time to progression (TTP) after treatment with trabectedin, administered on two different treatment schedules in patients with liposarcoma or leiomyosarcoma (L-sarcomas) who had been previously treated with an anthracycline and ifosfamide.

Outcomes/endpoints

The initial primary efficacy endpoint was the point estimate (95% CI) for clinical benefit, a composite rate of confirmed CR or PR or SD lasting for at least 24 weeks. If the true clinical benefit rate was less than 20% (14 or fewer patients achieving clinical benefit), this would lead to not recommending further evaluation of the dose regimen. Alternatively, further development would have been recommended if 15 or more patients achieved clinical benefit.

Promising preliminary descriptive data were publicly disclosed during an oral presentation at the 2004 annual meeting of the American Society of Clinical Oncology (ASCO). These early descriptive data in 80 evaluable patients suggested that the q3wk 24-h regimen might be more efficacious than the qwk 3-h schedule. Moreover, these early data also suggested that the qwk 3-h schedule was active in this clinical setting. This led to extension of the study expanding the sample size in order to allow a formal comparison between the two trabectedin schedules, changing the endpoint to time to progression (TTP). Crossover from one treatment schedule to the alternate was allowed in patients after progressive disease to the treatment assigned by randomization.

Secondary endpoints included to estimate the rate and duration of best overall objective response, to compare progression-free survival (PFS) and overall survival (OS), to characterize the safety profile, and to estimate the pharmacokinetics of trabectedin.

TTP was calculated as time between date of randomization (in ET743-STS-201 randomized study) or first dose (in the single-arm studies) and date of disease progression. Patients who were progression-free at the time of data cut-off or died without disease progression in each study were censored at the date of the last tumor assessment. TTP was assessed by independent review.

PFS was calculated as time between date of randomization (in ET743-STS-201 randomized study) or first dose (in non-randomized initial studies) and date of disease progression or death. Patients who were progression-free at the time of data cut-off in each study were censored at the date of the last tumor assessment. PFS was assessed by independent review. OS was calculated between date of randomization (in ET743-STS-201 randomized study) or first dose (in the initial studies) and date of death. All patients who died, regardless of the cause of death, were considered to have had an event.

Objective response was graded according to RECIST.

Sample size

The initial sample size of the original study was 45 patients in each study arm. The sample size was recalculated with the protocol amendment. With 260 evaluable patients and the observation of 217 TTP events (final analysis), the study would have greater than 90% power to detect a minimum of 60% improvement in median TTP at a 2-sided 5% significance level.

Randomisation

Subjects were centrally assigned to either arm in a 1:1 ratio by permuted-block randomisation and were stratified according to ECOG status (0-1).

Blinding (masking)

It was an open-label study, although a blinded independent radiological review panel of tumour assessments and an IDMC were instituted.

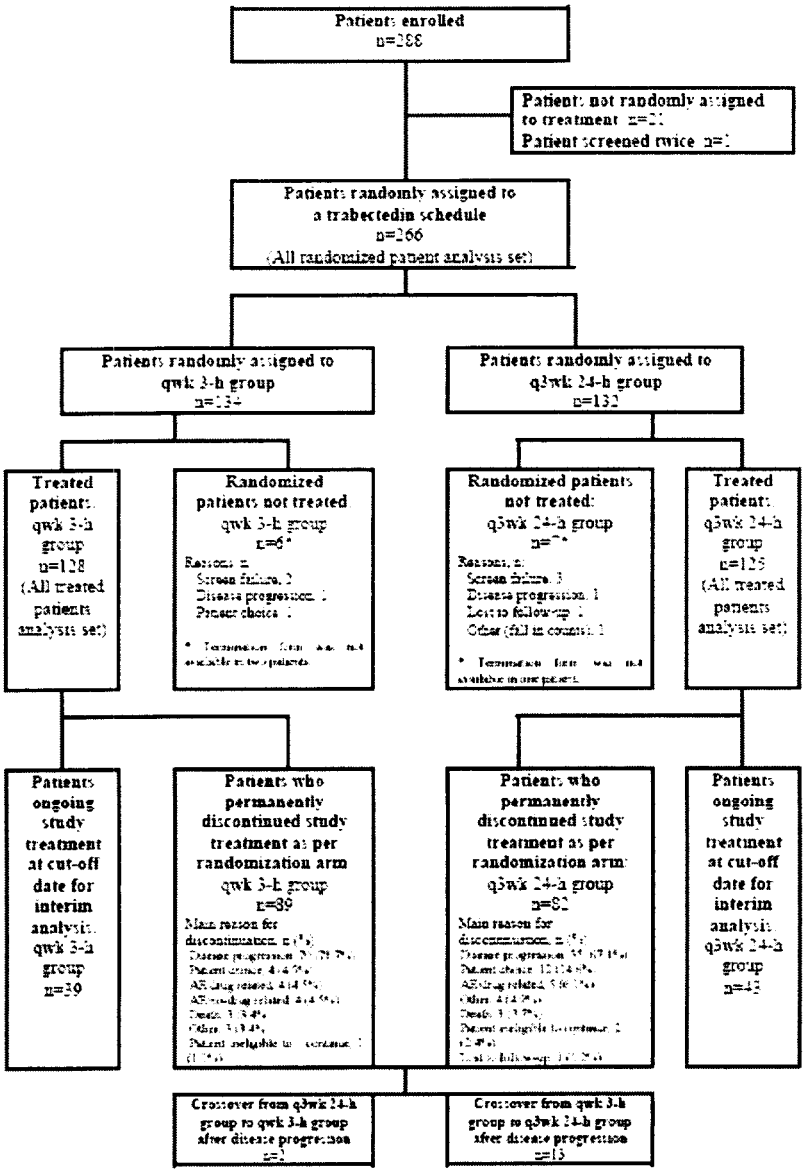
Statistical methods

The final version of the SAP is dated February 3rd, 2006. Apparently, the database for the interim analysis (locked after cut-off date the 31 May 2005) was planned to be made available to the sponsor on 13 February 2006. In August 05, the IDMC conducted an analysis on the interim data and recommended to advise patients still under treatment and progression-free, to cross over from the qwk to the q3wk arm. The efficacy evidence is based on the prospectively planned interim analysis of the amended study, which was to happen when 150 TTP events had taken place. The final analysis is to be performed when 217 events take place, with alpha 0.25 for each analysis. TTP was to be compared using a 2-sided un-stratified log-rank test. The Kaplan-Meier method would be used to estimate the distribution functions for each treatment arm. The effect of baseline prognostic factors on time-to-event endpoints was to be analysed using Cox regression models. The primary analysis was to be based on tumour assessment from the independent radiological review on the "all randomised set".

The date of progression was to be assigned based on the time of the first evidence of progression. Subjects who were lost to follow-up or who were still being treated without documented DP were to be censored at the time of the last tumour assessment. Apparently, no imputation of missing data was performed for the primary analysis. A patient was considered to have a missing tumour assessment if an assessment was not performed within 1.5 weeks of the scheduled assessment. However, the impact of potential missing tumour assessment on the TTP analysis was to be examined by 2 imputation analyses. In the first one, the midpoint of the last 2 assessment dates on or prior to the documented disease progression were to be used to impute the date of DP. In the second one, a predetermined schedule would be used. A TTP analysis based on the imputed data was to be performed. In this analysis, all progression and censoring dates were to be imputed by their corresponding scheduled tumour assessment dates.

RESULTS

Participant flow



Recruitment

Recruitment started on 12 May 2003. By August 2004 (when the major amendment was performed), 146 patients had already been recruited, and by cut-off date (May 2005) 266 patients had been randomized.

Conduct of the study

Eligibility exceptions were noted in 22 patients (16.4%) in qwk 3-h and in 13 (9.8%) in the q3wk 24-h arm. Deviations regarding efficacy assessments were detected in a similar number of patients in each treatment arm (approximately 9%).

Baseline data

Demographic baseline data, including age, seem to be evenly distributed among treatment arms. In general, there were no evident imbalances regarding EOCG status, time from initial diagnosis, histology or histopathological grade, tumour size, liver or lung metastasis, or previous treatments. Virtually all patients had received both anthracyclines and ifosfamide. Information regarding next line therapy has not been provided.

Demographic characteristics

		qwk 3-h (n=134)	q3wk 24-h (n=132)	Total (n=266)	p-value*
Gender	Female	78 (58.2%)	90 (68.2%)	168 (63.2%)	0.0997
	Male	56 (41.8%)	42 (31.8%)	98 (36.8%)	
Race	Asian	3 (2.2%)	3 (2.3%)	6 (2.3%)	0.5145
	Black	4 (3.0%)	9 (6.8%)	13 (4.9%)	
	Other**	2 (1.5%)	3 (2.3%)	5 (1.9%)	
	White	125 (93.3%)	117 (88.6%)	242 (91.0%)	
Age (years)	Median	54	53	53	0.5578
	Range	23-77	20-80	20-80	
	18-65	114 (85.1%)	117 (88.6%)	231 (86.8%)	0.4690
	≥65	20 (14.9%)	15 (11.4%)	35 (13.2%)	
ECOG performance status***	0	65 (48.5%)	67 (50.8%)	132 (49.6%)	0.8063
	1	68 (50.7%)	65 (49.2%)	133 (50.0%)	
	2	1 (0.7%)		1 (0.4%)	
Body Mass Index (kg/m²)	Median	25.8	26.3	26.1	0.6997
	Range	16.7-44.3	15.8-47.8	15.8-47.8	
	<30	100 (74.6%)	91 (68.9%)	191 (71.8%)	0.3410
	≥30	34 (25.4%)	41 (31.1%)	75 (28.2%)	
Height (cm)	Median	168	168	168	0.4892
	Range	151-189	137-193	137-193	
Weight (kg)	Median	73.5	75.8	75	0.8166
	Range	42.3-133.6	41-148.2	41-148.2	
Body surface area (m²)	Median	1.8	1.8****	1.8	0.7963
	Range	1.3-2.5	1.4-2.7	1.3-2.7	
Age at initial diagnosis (years)	Median	51	49.5	50	0.7323
	Range	20-74	17-76	17-76	0.394
Time from initial diagnosis to randomization (months)	Median	31	30.1	30.5	0.5119
	Range	4.4-171.8	1.6-175.7	1.6-175.7	
	<24	58 (43.3 %)	55 (41.7 %)	113 (42.5%)	0.8052
	≥24	76 (56.7 %)	77 (58.3 %)	153 (57.5%)	
Time from diagnosis to first metastasis (months)	≤12	71 (53.4 %)	68 (51.9 %)	139 (52.7%)	0.9019
	>12	62 (46.6 %)	63 (48.1 %)	125 (47.3%)	
Time from PD in last prior treatment to randomization (months)	Median	1.3	1.3	1.3	0.9975
	Range	0.1-38.8	0.1-42.8	0.1-42.8	0.1846
	<3	98 (73.1 %)	86 (65.2 %)	184 (69.2%)	
	≥3	36 (26.9 %)	46 (34.8 %)	82 (30.8%)	

Data shown are n (%) except for median and range.
* Fisher's exact test (for categorical variables) and Wilcoxon's test (for continuous variables) qwk 3-h *vs.* q3wk 24-h.
**Three Hispanic, one Lebanese, and one from the Maghreb.
***P-value for two categories (0 and 1: one patient with PS=2 was included in PS=1 category).
****Data on 131 patients.

Primary tumour location and histology

		qwk 3-h (n=134)	q3wk 24-h (n=132)	Total (n=266)	p-value*
Diagnosis	Soft Tissue Sarcoma	134 (100.0%)	132 (100.0%)	266 (100.0%)	
Histology	Leiomyosarcoma	85 (63.4%)	90 (68.2%)	175 (65.8%)	0.4399
	Liposarcoma	49 (36.6%)	42 (31.8%)	91 (34.2%)	
Histopathological grade**	G1: Well differentiated	13 (9.7%)	8 (6.1%)	21 (7.8%)	0.4007
	G2: Moderately differentiated	21 (15.7%)	28 (21.2%)	49 (18.4%)	
	G3: Poorly differentiated	53 (39.6%)	45 (34.1%)	98 (36.9%)	
	Unknown***	47 (35.1%)	51 (38.6%)	98 (36.9%)	
Primary tumor site at initial diagnosis	Abdomen/pelvis, other	13 (9.7%)	19 (14.4%)	32 (12.0%)	0.8896 (Extremities vs. other)
	Abdominal pelvic wall	8 (6.0%)	7 (5.3%)	15 (5.6%)	
	Chest wall	2 (1.5%)	3 (2.3%)	5 (1.9%)	
	Chest, other	3 (2.2%)	2 (1.5%)	5 (1.9%)	
	Face	3 (2.2%)	3 (2.3%)	6 (2.3%)	
	Gastrointestinal tract	3 (2.2%)	5 (3.8%)	8 (3.0%)	
	Intrathoracic	4 (3.0%)		4 (1.5%)	
	Lower extremity	28 (20.9%)	29 (22%)	57 (21.4%)	
	Neck	1 (0.7%)		1 (0.4%)	
	Retroperitoneal	33 (24.6%)	27 (20.5%)	60 (22.6%)	
	Upper extremity	8 (6.0%)	5 (3.8%)	13 (4.9%)	
	Uterus	28 (20.9%)	32 (24.2%)	60 (22.6%)	

Data shown are n (%)
* Fisher's exact test (for categorical variables) and Wilcoxon's test (for continuous variables) qwk 3-h vs. q3wk 24-h
**Histological grade was not collected on the CRF. The grades reported here correspond to available data from the ongoing independent review.
***Including 67 no yet reviewed cases by the central pathology review.

Patients were enrolled in the US (n=181), Russia (n=26), Canada (n=24), France (n=17), Italy (n=8), Australia (n=4), Belgium (n=3) and Spain (n=3).

Numbers analysed

The "all-randomised" set was used for the primary analysis (n=266).

Outcomes and estimation

Results for the primary and main efficacy secondary endpoints are shown in the following tables and figures. For visual comparison, the data on L-sarcoma population treated with 24-h regimen q3wk for the initial phase II studies (ET-B-005—98, ET-B-008-98, ET-B-017-99) are also provided (N=100, see Supportive Studies in the section on Clinical Efficacy).

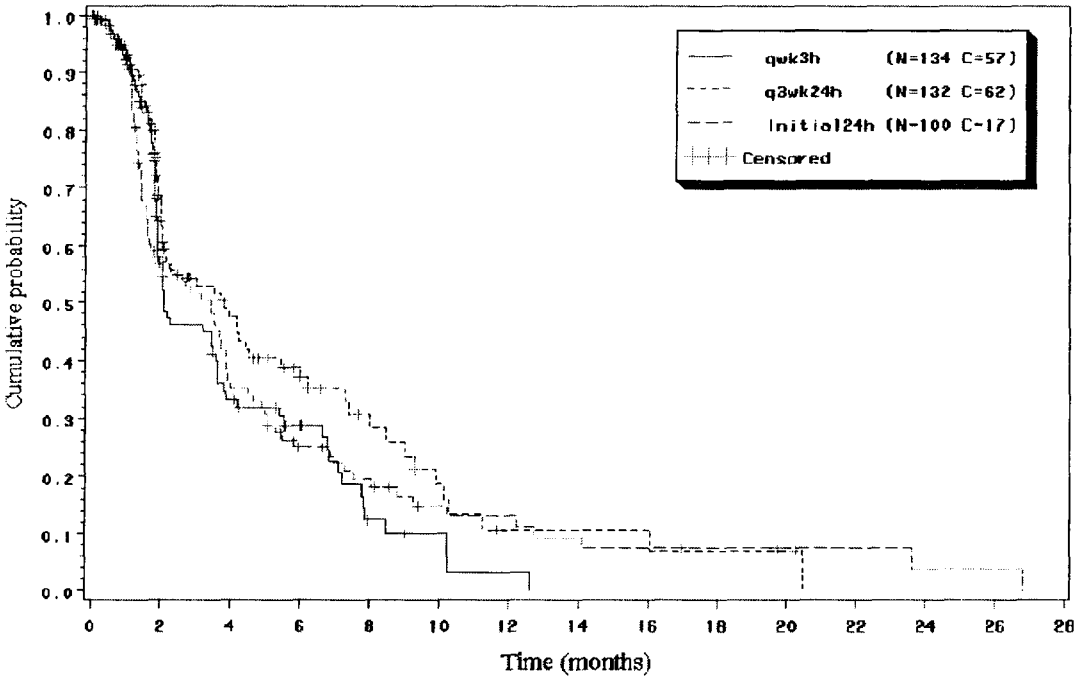
Time to Progression

Time to Progression (Integrated L-sarcoma Population)

Descriptive	qwk 3-h (N=134)	q3wk 24-h (N=132)	Initial 24-h (N=100)
Events	77 (57.5%)	70 (53.0%)	83 (83.0%)
Censored	57 (42.5%)	62 (47.0%)	17 (17.0%)
Median	2.1 95% CI (1.9-3.6)	3.8 95% CI (2.1-5.4)	3.4 95% CI (1.7-3.9)
No PD at 3 months	46.1% 95% CI (35.9-56.4)	53.1% 95% CI (42.9-63.3)	51.7% 95% CI (41.6-61.8)
No PD at 6 months	28.9% 95% CI (19.0-38.7)	37.1% 95% CI (26.4-47.8)	25.0% 95% CI (16.1-33.9)
No PD at 12 months	3.3% 95% CI (0-9.2)	10.6% 95% CI (1.5-19.8)	12.9% 95% CI (5.2-20.6)

log rank test (p-value=0.1711)

Kaplan-Meier of Time to Progression (Integrated L-sarcoma Population)



Progression-Free Survival (Integrated L-sarcoma Population)

Descriptive	qwk 3-h (N=134)	q3wk 24-h (N=132)	Initial 24-h (N=100)
Events	84 (62.7%)	78 (59.1%)	87 (87.0%)
Censored	50 (37.3%)	54 (40.9%)	13 (13.0%)
Median	2.1 95% CI (1.9-3.4)	3.5 95% CI (2.0-4.5)	2.7 95% CI (1.7-3.7)
PFS at 3 months	45.1% 95% CI (35.2-55.0)	50.2% 95% CI (40.3-60.1)	48.8% 95% CI (38.8-58.7)
PFS at 6 months	26.9% 95% CI (17.6-36.2)	34.6% 95% CI (24.5-44.7)	23.6% 95% CI (15.1-32.1)
PFS at 12 months	5.2% 95% CI (0-11.6)	11.5% 95% CI (2.8-20.2)	12.2% 95% CI (4.9-19.5)

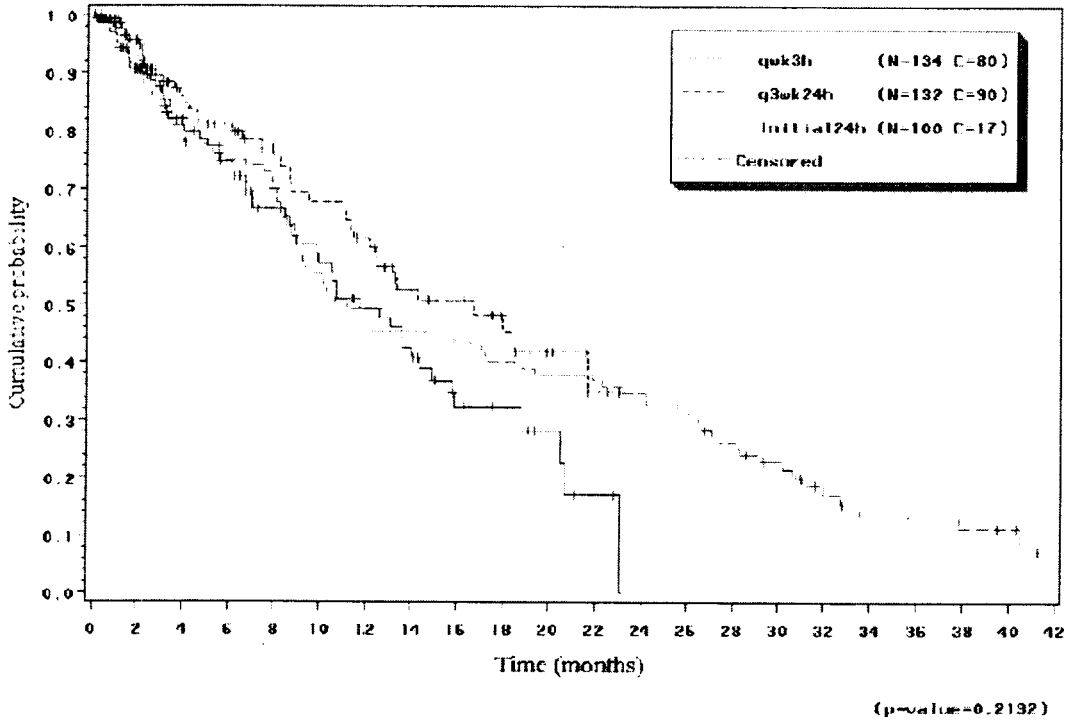
log rank test (p-value=0.2438)

Overall Survival

Descriptive	qwk 3-h (N=134)	q3wk 24-h (N=132)	Initial 24-h (N=100)
Events	54 (40.3%)	42 (31.8%)	83 (83.0%)
Censored	80 (59.7%)	90 (68.2%)	17 (17.0%)
Median	11.8 95% CI (8.9-14.9)	16.7 95% CI (12.2-n.r.)	11.2 95% CI (9.1-17.2)
OS at 6 months	74.8% 95% CI (65.9-83.7)	81.2% 95% CI (73.4-89.0)	75.0% 95% CI (66.5-83.5)
OS at 12 months	49.4% 95% CI (37.9-60.9)	61.6% 95% CI (50.5-72.6)	49.3% 95% CI (39.5-59.2)
OS at 24 months	-	-	34.7% 95% CI (25.3-44.2)

n.r. - upper limit not reached
log rank test (p-value=0.2132)

Kaplan-Meier of Overall Survival (Integrated L-sarcoma Population)



Overall Response Rate

There were no complete responses according to the independent review. Overall response rates were low whereas the SD rates were in the 30% - 50% range. The rate of PD as best response was consistently below 50% in all three set of patients. Of note, 95% confidence intervals for PR, SD and PD overlap.

Best Overall Response (Integrated L-sarcoma Population)

Response	Number of patients (%)		
	qwk 3-h (N=134)	q3wk 24-h (N=132)	Initial 24-h (N=100)
Partial response	1 (0.7%) 95% CI (0-4.1)	4 (3.0%) 95% CI (0.8-7.6)	12 (12.0%) 95% CI (6.4-20)
Stable disease	46 (34.3%) 95% CI (26.3-43.0)	55 (41.7%) 95% CI (33.2-50.6)	42 (42.0%) 95% CI (32.2-52.3)
Progressive disease	53 (39.6%) 95% CI (31.2-48.4)	42 (31.8%) 95% CI (24.0-40.5)	43 (43.0%) 95% CI (33.1-53.3)
Not evaluable	34 (25.4%) 95% CI (18.3-33.6)	31 (23.5%) 95% CI (16.5-31.6)	3 (3.0%) 95% CI (0.6-8.5)
PR+SD	47 (35.1%) 95% CI (27.0-43.8)	59 (44.7%) 95% CI (36.0-53.6)	54 (54.0%) 95% CI (43.7-64.0)

Ancillary analyses

An Updated Clinical Study Report was submitted including a number of new statistical analyses. The key efficacy result of the ET743-STS-201 study, i.e., the final TTP primary analysis per independent review, assessed at **cut-off date 31 May 2006**, shows statistically significant differences favouring the q3wk 24-h regime (log-rank p=0.0302; significance level for 206 progression events after alpha spending adjustment foreseen in the Statistical Analysis Plan, p=0.0340). The results are summarised in Table XXX. Different TTP sensitivity analyses were conducted to assess the impact of different methods of adjudication of progression in case of missing evaluations (data not shown). These sensitivity analyses consistently showed similar relative risk reductions in each assessment for patients treated in the q3wk 24-h arm. The results were statistically significant in the primary, protocol-specified analysis of TTP as well as in the majority of sensitivity analyses.

Summary of final results for the primary efficacy endpoint: time to progression as per independent review (ET743-STS-201 study)

Efficacy variables	**qwk 3-h** (n=134)	**q3wk 24-h** (n=136)	**LR* (p-value) HR* (p-value)**
TTP, months (independent review) Number of events, n (%) Median (95% CI) No PD at 3 months, % (95% CI) No PD at 6 months, % (95% CI)	102 (76.1%) 2.3 (2.0-3.5) 45.1% (36.3-53.9%) 27.3% (19.0-35.6%)	104 (76.5%) 3.7 (2.1-5.4) 53.4% (44.6-62.2%) 37.2% (28.4-46.0%)	. LR: 4.698 (p=0.0302)** HR: 0.734 (p=0.0320) . .

Data for TTP are shown for all randomised patients. *Log rank and HR q3wk 24-h vs. qwk 3-h group. ** The level of significance (log-rank) to be reached for 206 events after alpha spending adjustment was =0.0340. CI, confidence interval; HR, hazard ratio; LR, log-rank; PD, progressive disease; TTP, time to progression.

In a multivariate analysis including all available variables, the known prognostic factors for metastatic STS emerged as independent prognostic factors. In a multivariate model, the statistically significant treatment effect was confirmed (HR=0.680; p=0.0174).

The results of the different time-to-event analyses (TTP, PFS and OS) conducted in the all randomised, all treated and confirmed L-sarcoma data sets demonstrated a consistent pattern of treatment benefit favouring the q3wk 24-h trabectedin regimen (data not shown).

There were no statistically significant differences in TTP outcomes pre-vs. post-amendment. The HRs reflecting the greater benefit associated with the q3wk 24-h regime over the qwk 3-h regime were virtually identical in both cohorts (0.729 vs. 0.738) and consistent with the HR of 0.734 obtained in the intention-to-treat (ITT) population of 270 randomised patients.

Tumour shrinkage of any magnitude assessed by independent review was achieved by 50.5% of patients treated with the trabectedin q3wk 24-h regime as compared to 32.4% of patients treated with trabectedin qwk 3-h.

The sponsor was asked to submit an updated exploratory survival analysis (including an analysis censoring patients at time of cross-over to the alternative regimen). At the most recent **cut-off date (25 May 2007),** a total of 206 deaths had been reported in all randomised patients (last death recorded on 19 April 2007): 106 deaths in the qwk 3-h arm and 100 deaths in the q3wk 24-h arm. The median follow-up was 30.0 months (95% CI, 25.0-36.6 months) in the q3wk 24-h arm and 27.9 months (95% CI, 23.6-37.3 months) in the qwk 3-h arm (p=0.7838). Forty-three patients (32.1%) crossed over from the qwk 3-h to the q3wk 24-h arm, most of them (29 patients) after progression of the disease. Only six patients (4.4%) crossed over from the q3wk 24-h to the qwk 3-h arm, all of them after disease progression. Additional OS analyses have been done by censoring patients at the time of crossover to the alternative trabectedin regime. Censoring of patients at time of crossover to the alternative regime increased the difference in overall survival between treatment arms (data not shown). The survival at 12 months was in the range of 48.5-51.4% in the qwk 3-h arm and in the range of 60.2-66.7% in the q3wk 24-h arm. In this exploratory analyses, an improvement in one year survival with trabectedin q3wk 24-h was observed in the "all randomised" population and the most important effect was found in the "all treated" and "confirmed L-sarcoma" populations (data not shown).

- Analysis performed across trials (pooled analyses and meta-analysis)

The applicant provided a separate analysis, for patients with liposarcoma or leyomiosarcoma compared to patients with other kinds of STS. Comparison of efficacy data obtained in the ET743-STS-201 study *vs.* pooled data from three previous phase II trials with the q3wk 24-h trabectedin regime

	ET743-STS-201 (interim data 31-05-2006)			Pooled data previous phase II studies q3wk 24-h		
	qwk 3-h	q3wk 24-h	Total	L-sarcomas	Non-L-sarcomas	Total
n	134	132	266	100	83	183
TTP						
Median (months)	2.1	3.8	3.0	3.4	1.9	2.7
	(1.9-3.6)	(2.1-5.4)	(2.1-3.8)	(1.7-3.9)	(1.6-3.0)	(1.7-3.5)
No PD at 3 months (%)	46.1	53.1	49.7	51.7	40.0	46.5
	(35.9-56.4)	(42.9-63.3)	(42.5-56.9)	(41.6-61.8)	(29.0-51.0)	(39.0-53.9)
No PD at 6 months (%)	28.9	37.1	32.9	25.0	19.1	22.4
	(19.0-38.7)	(26.4-47.8)	(25.6-40.2)	(16.1-33.9)	(9.7-28.4)	(15.9-28.8)
PFS						
Median (months)	2.1	3.5	2.5	2.7	1.8	2.3
	(1.9-3.4)	(2.0-4.5)	(2.0-3.6)	(1.7-3.7)	(1.5-2.9)	(1.6-3.2)
PFS >3 months (%)	45.1	50.2	47.7	48.8	38.3	44.0
	(35.2-55.0)	(40.3-60.1)	(40.7-54.7)	(38.8-58.7)	(27.8-48.8)	(36.8-51.3)
PFS >6 months (%)	26.9	34.6	30.6	23.6	19.0	21.5
	(17.6-36.2)	(24.5-44.7)	(23.7-37.5)	(15.1-32.1)	(10.1-28.0)	(15.3-27.7)
OS						
Median (months)	11.8	16.7	13.4	11.2	8.7	10.3
	(8.9-14.9)	(12.2-nr)	(11.1-15.9)	(9.1-17.2)	(5.7-13.9)	(8.7-13.9)
% Alive at 12 months	49.4	61.6	55.4	49.3	45.2	47.5
	(37.9-60.9)	(50.5-72.6)	(47.4-63.5)	(39.5-59.2)	(34.4-56.0)	(40.2-54.8)
% Alive at 24 months	NA	NA	NA	34.7	22.8	29.3
				(25.3-44.2)	13.6-31.9	22.6-36.0
RR (%)	1.0	4.0	2.5	12.0	2.4	7.7
	(0.0-5.5)	(1.1-9.9)	(0.8-5.8)	(6.4-20.0)	(0.3-8.4)	(4.3-12.5)

Data shown are per independent review. In brackets, 95% confidence intervals (CI). nr, upper limit not reached. L-sarcomas, liposarcoma or leiomyosarcoma; NA, not available; RR, objective response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

- Clinical studies in special populations

No specific studies have been performed in special populations. Children were not included in the pivotal study. Twelve patients aged ≤ 16 were enrolled within two phase II studies.

Thirty-five (13.2%) patients over 65 were included in the pivotal trial. In the SPC it is stated that plasma clearance and distribution volume is not influenced by age, so the same initial dose should be recommended in elderly patients.

Conventional restrictions of liver function parameters were used in the pivotal trial. In addition, patients with active viral hepatitis, chronic liver disease or creatinine above the ULN were excluded

from the pivotal trial. Approximately 15% of patients in each treatment arm had hepatic metastasis at baseline.

- Supportive study(ies)

Results from phase II, non-comparative studies ET-B-005-98, ET-B-008-98 and ET-B-017-99 are provided as supportive evidence. These studies included STS patients with up to 2 prior treatments, measurable disease, WHO PS <2, adequate hematologic, hepatic and renal function. Trabectedin was administered with the same q3wk 24-h dose and regime and the population was similar in these three studies (patients with STS after failure of previous chemotherapy), although for study 017, PD was not a formal requirement for eligibility. Evaluations were performed every 6 weeks. The primary endpoint was RR according to the WHO criteria. In the provided analysis, patients with GIST and Ewing's sarcoma were excluded (6 patients). Results are summarised in the following table.

Results of phase II uncontrolled studies

	ET-B-005-98 (Group A)	ET-B-005-98 (Group C)	ET-B-008-98 (Group 1)	ET-B-008-98 (Group 2)	ET-B-017-99	Total (pooled data)
n	44	55	23	27	34	183
RR (%)	9.1	10.9	0	3.7	8.8	7.7
	(2.5-21.7)	(4.1-22.3)	(0-14.8)	(0.9-19.0)	(1.9-23.7)	(4.3-12.5)
TTP						
Median (months)	3.1	2.9	1.9	2.2	1.6	2.7
	(2.0-3.9)	(1.8-4.6)	(1.5-3.9)	(1.3-5.0)	(1.3-3.5)	(1.7-3.5)
No PD at 3 months (%)	52.6	49.7	47.6	44.4	34.6	46.5
	(36.8-68.5)	(36.3-63.1)	(26.1-69.2)	(25.7-63.2)	(18.0-51.3)	(39.0-53.9)
No PD at 6 months (%)	20.5	23.7	26.5	25.9	16.2	22.4
	(7.4-33.5)	(11.5-36.0)	(6.9-46.0)	(9.4-42.5)	(2.5-29.8)	(15.9-28.8)
PFS						
Median (months)	2.6	2.9	1.9	2.2	1.6	2.3
	(1.4-3.7)	(1.8-4.6)	(1.5-3.9)	(1.3-5.0)	(1.3-2.8)	(1.6-3.2)
PFS >3 months (%)	45.5	49.7	41.4	44.4	33.8	44.0
	(30.7-60.2)	(36.3-63.1)	(20.8-62.0)	(25.7-63.2)	(17.6-50.0)	(36.8-51.3)
PFS >6 months (%)	17.7	23.7	23.0	25.9	17.6	21.5
	(6.2-29.1)	(11.5-36.0)	(5.4-40.7)	(9.4-42.5)	(4.2-30.9)	(15.3-27.7)
OS						
Median (months)	8.7	13.9	12.9	10.7	12.6	10.3
	(5.5-11.7)	(8.9-19.4)	(6.9-26.6)	(4.2-17.2)	(8.1-24.2)	(8.7-13.9)
% Alive at 12 months	34.1	53.8	52.2	42.4	55.9	47.5
	(20.1-48.1)	(40.5-67.1)	(31.8-72.6)	(23.1-61.6)	(39.2-72.6)	(40.2-54.8)
% Alive at 24 months	18.2	32.5	39.1	25.4	35.3	29.3
	(6.8-29.6)	(19.8-45.2)	(19.2-59.1)	(8.1-42.7)	(19.2-51.4)	(22.6-36.0)

Data shown are per independent review. In brackets, 95% confidence intervals (CI). **005-A:** first cohort or pretreated STS patients in ET-B-005-98 study. **005-C:** second cohort or pretreated STS patients in the ET-B-005-98 study. **008(1):** moderately pre-treated STS patients (≤2 single agents or one combination regime) in ET-B-008-98 study. **008(2):** extensively pre-treated STS patients (≥3 different single agents or >1 combination regime, or one combination and one or more single agents) in ET-B-008-98 study. The final reports of these three phase II trials had a total of 189 patients. For the current analysis, six patients were excluded: four with GIST in ET-B-008-98 study (3 in arm 008(1) and one in arm 008(2), and 2 patients with Ewing's sarcoma in ET-B-017-99 study. RR, objective response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

- Discussion on clinical efficacy

The main study evaluated the efficacy and safety of trabectedin, administered by two 2 different treatment regimens in 266 patients with locally advanced or metastatic leiomyosarcoma or liposarcoma (L-sarcoma) whose disease had relapsed or become refractory after treatment with an anthracycline and ifosfamide that had been given either in combination or in sequence. The distributions of demographic characteristics were well balanced in the two study groups. The two study groups were well balanced regarding important prognostic variables e.g. age, ECOG performance status (PS score of 0 or 1), histology (liposarcoma or leimyosarcoma), histopathological tumor grade, presence of liver metastases, bulky disease and time from diagnosis to treatment.

The interim analysis presented showed a median TTP (according to the independent review) of 2.1 months (95% CI, 1.9-3.6 months) in the qwk 3-h group and 3.8 months (95% CI, 2.1-5.4 months) in the q3wk 24-h group (log-rank p=0.0382), which represents a clinically significant difference. These results were not statistically significant at the 5% level after considering the alpha spending adjustement. However, consistent trends were observed for other time-dependent variables (PFS and OS).

The updated analyses provided further evidence to support the existence of a significant difference in terms of TTP and PFS. The further analyses did not suggest significant effects on OS but this might be