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European Journal of Cancer (2014) **50**, 388–396

Available at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Brostallicin versus doxorubicin as first-line chemotherapy in patients with advanced or metastatic soft tissue sarcoma: An European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group randomised phase II and pharmacogenetic study ☆

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Available online 8 November 2013

KEYWORDS
Randomised phase II study
GST
Brostallicin

Abstract ***Aim:*** Brostallicin is a DNA minor groove binder that has shown activity in patients with soft tissue sarcoma (STS) failing first-line therapy. The present study assessed the safety and efficacy of first-line brostallicin in patients with advanced or metastatic STS > 60 years or not fit enough to receive combination chemotherapy. A prospective explorative pharmacogenetic analysis was undertaken in parallel.

☆ This study was registered with ClinicalTrials.gov, number NCT00410462.

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0959-8049/$ - see front matter
http://dx.doi.org/10.1016/j.ejca.2013.10.002

Doxorubicin
Soft tissue sarcoma

Methods: Patients were randomised in a 2:1 ratio between IV brostallicin 10 mg/m^2 and doxorubicin 75 mg/m^2 once every 3 weeks for a maximum of six cycles. Disease stabilisation at 26 weeks (primary end-point) was considered a 'success'. Further testing of brostallicin was warranted if $\geqslant$35 'successes' were observed in the first 72 eligible patients treated with brostallicin. In addition, patients were genotyped for gluthatione S transferase (GST) polymorphisms.

Results: One hundred and eighteen patients were included (79 brostallicin and 39 doxorubicin). Brostallicin was well tolerated in comparison to doxorubicin with less grade 3–4 neutropenia (67% versus 95%), grade 2–3 systolic dysfunction (0% versus 11%), alopecia (17% versus 61%) and grade 2–3 mucositis (0% versus 18%). For brostallicin versus doxorubicin, 'successes' were observed in 5/77 versus 10/36, progression free survival at 1 year was 6.5% versus 15.6%, objective response rate was 3.9% versus 22.2% and overall survival at 1 year was 50.5% versus 57.9%, respectively. Only *GSTA1* genotype was significantly associated with success rate of doxorubicin treatment.

Conclusion: Brostallicin cannot be recommended at this dose and schedule in this patient population as first-line therapy. *GSTA1* genotype may be predictive for doxorubicin efficacy but warrants further study.

1. Introduction

Single-agent doxorubicin is generally still regarded as the standard first-line palliative systemic treatment for the majority of adult patients with advanced or metastatic non-gastrointestinal stromal tumour (GIST) soft tissue sarcoma (STS) [1]. Ifosfamide monotherapy yields similar outcomes but is characterised by a more unfavorable toxicity profile [2]. Although randomised studies have shown that combination chemotherapy of doxorubicin and ifosfamide provides higher response rates and progression free survival (PFS) than single-agent doxorubicin, this higher objective response rate is not translated into an improved overall survival (OS) [3]. Clearly, novel first-line approaches with higher anti-tumour activity are urgently needed.

Several novel agents with anti-tumour activity have been identified recently. Pazopanib and trabectedin are examples of such newer agents and have been shown to be active in subsets of pre-treated STS, although results of first-line studies are not yet available [4,5]. Another novel agent with anti-tumour activity in STS is brostallicin. Brostallicin is a synthetic α-bromoacrylic derivative of a distamycin-like structure having four pyrrolocarbamoyl units ending with a guanidino moiety [6]. It is an alkylating agent that exerts its activity through DNA minor groove binding, comparable to the mechanism of action of trabectedin. Preclinical studies suggest that brostallicin may be particularly active in drug resistance and in sarcoma, with both situations being mediated through high cellular levels of glutathione and gluthatione related enzymes [7]. Brostallicin was first investigated in STS in progressive pre-treated patients showing a 46% 3-month progression free survival (PFS) [8]. This is well above the minimum threshold for active agents in a second-line setting [9]. In the currently presented study we assessed the safety and efficacy of brostallicin compared to doxorubicin in a first-line setting in patients with advanced or metastatic intermediate to high-grade STS older than 60 years or not fit enough to receive combination chemotherapy. A prospective pharmacogenetic analysis was undertaken in parallel.

2. Patients and methods

2.1. Eligibility criteria

Patients with locally advanced or metastatic intermediate to high-grade STS not amenable to curative treatment with proven Response Evaluation Criteria in Solid Tumours (RECIST) progression in the 6 months before study entry were eligible. Other inclusion criteria were: no previous chemotherapy for metastatic disease, at least 60 years of age, or at least 18 years of age if non-amenable to intensive combination chemotherapy, World Health Organisation (WHO) performance status $<$2, clinically normal cardiovascular function, adequate bone marrow, hepatic and renal function and pathology material available for mandatory central review. Ethics approval was obtained and all patients gave written informed consent.

2.2. Study design

Eligible patients were randomised to receive doxorubicin (standard treatment) or brostallicin, with a 1:2 ratio. Randomisation was done with stratification for institution and age ($<$60, $\geqslant$60 years). Brostallicin was administered at 10 mg/m^2 by 10-min IV infusion on day 1 of a 3 weekly cycle. An increased dose of 12.5 mg/m^2 was allowed from the second cycle, if cycle 1 was well tolerated (no toxicity higher than grade 1, except nausea, vomiting and alopecia). Doxorubicin

was administered at 75 mg/m^2 by IV bolus over 5–20 min on day 1, also of a 3 weekly cycle. Treatment was given for a maximum of six cycles, until disease progression, unacceptable toxicity or patient refusal.

Dose delay and reduction criteria were as used in the study by Leahy et al. [8].

2.3. Baseline and treatment assessments

Baseline studies included multiple-gated acquisition (MUGA)-scan or echocardiogram, ECG, full blood counts and biochemistry, and computed tomography (CT) or magnetic resonance imaging (MRI)-scan evaluation according to RECIST 1.0. Weekly full blood counts were performed during treatment. ECG and baseline blood tests were performed before each cycle and after the last cycle. A MUGA-scan or echocardiogram was repeated after the final cycle. Disease status was evaluated every second cycle (6-weekly) and at 26 weeks after start of treatment, unless disease progression had already been documented.

2.4. Statistical methods

The primary end-point was the PFS at week 26. A success was defined as patients who had no progression according to RECIST at week 26 after study entry. All others were coded as a failure. This primary end-point was assessed in all eligible patients who started treatment (activity population). A one-stage Fleming design was applied to the patients allocated to brostallicin treatment on the basis of the following hypotheses for the primary end-point: P0 was defined as the PFS at 26 weeks that would not warrant further investigation (null hypothesis; $P0 = 40\%$). P1 was defined as the PFS 26 weeks that would warrant further investigation (alternative hypothesis; $P1 = 55\%$) with a one-sided type I error rate of 0.05 and a power of 80%.These two reference values are based on a retrospective analysis of the European Organisation for Research and Treatment of Cancer (EORTC)-Soft Tissue and Bone Sarcoma Group (STBSG) database of patients treated with first-line therapy [9].

Under these hypotheses, a total of 72 eligible and treated patients would be needed to be recruited in the brostallicin arm (the doxorubicin arm was incorporated to check whether our a priori assumptions with respect to P0 were correct). Further testing of brostallicin would be warranted if 35 or more successes were observed. In total, 108 eligible patients starting protocol therapy were required (36 in the standard doxorubicin arm, 72 in the experimental brostallicin arm). An additional 10 patients were recruited to replace the expected number of patients who were considered non-evaluable for the primary end-point. Secondary activity end-points included overall PFS, objective tumour response, duration of response (for patients with complete or partial response), and OS.

No formal comparisons were made between the two arms. Statistical analyses were done with SAS (version 9.2).

2.5. Pharmacogenetic study

Blood samples for DNA collection were taken before the start of protocol therapy. Genetic variants of four glutathione S transferase encoding genes *GST-M*, *GST-P*, *GST-A* and *GST-T* were analysed (Methods online-only). The investigated end-points are two toxicity parameters during the first cycle (nadir/baseline ratio of neutrophils and severity of neutropenia according to CTCv3) and two activity parameters (the PFS status at the end of week 26 and OS). The correlations between polymorphisms and patients characteristics (all continuous variables were categorised) were tested using the Chi-square test or the Mantel–Haenzel test for trend. Comparison of safety and activity end-points between genotypes were performed by univariate analysis using the Chi-square test (for the $2 * 2$ tables), the Mantel–Haenzel test for trend (for ordered variables) for safety parameters and the PFS at 26 weeks or the Log-rank test or Wald test for OS.

3. Results

3.1. Trial patients

A total of 118 patients from 20 institutions were randomised in the study from October 2006 to August 2008. With three ineligible patients due to confirmed low-grade STS, and two patients who did not start their allocated protocol therapy, there were 77 evaluable patients in the brostallicin arm, and 36 in the doxorubicin arm for the activity analysis, and respectively, 78 and 38 patients for the safety analysis (Fig. 1). Only five patients below the age of 60 years were randomised (Table 1). Five of 36 doxorubicin- and 3 of 77 brostallicin-treated patients had locally advanced disease. All other patients had metastatic disease.

3.2. Patient outcomes

The full protocol treatment (six cycles) was administered to 58% of the patients in the doxorubicin arm, but to only 19% of the patients in the brostallicin arm. In this latter arm, all patients stopped protocol therapy because of disease progression (except for one patient who discontinued treatment because of unrelated renal problems).

Dose was reduced in 9% of the patients (3% of the cycles) in the brostallicin arm, and in 11% of the patients (5% of the cycles) in the doxorubicin arm; treatment was

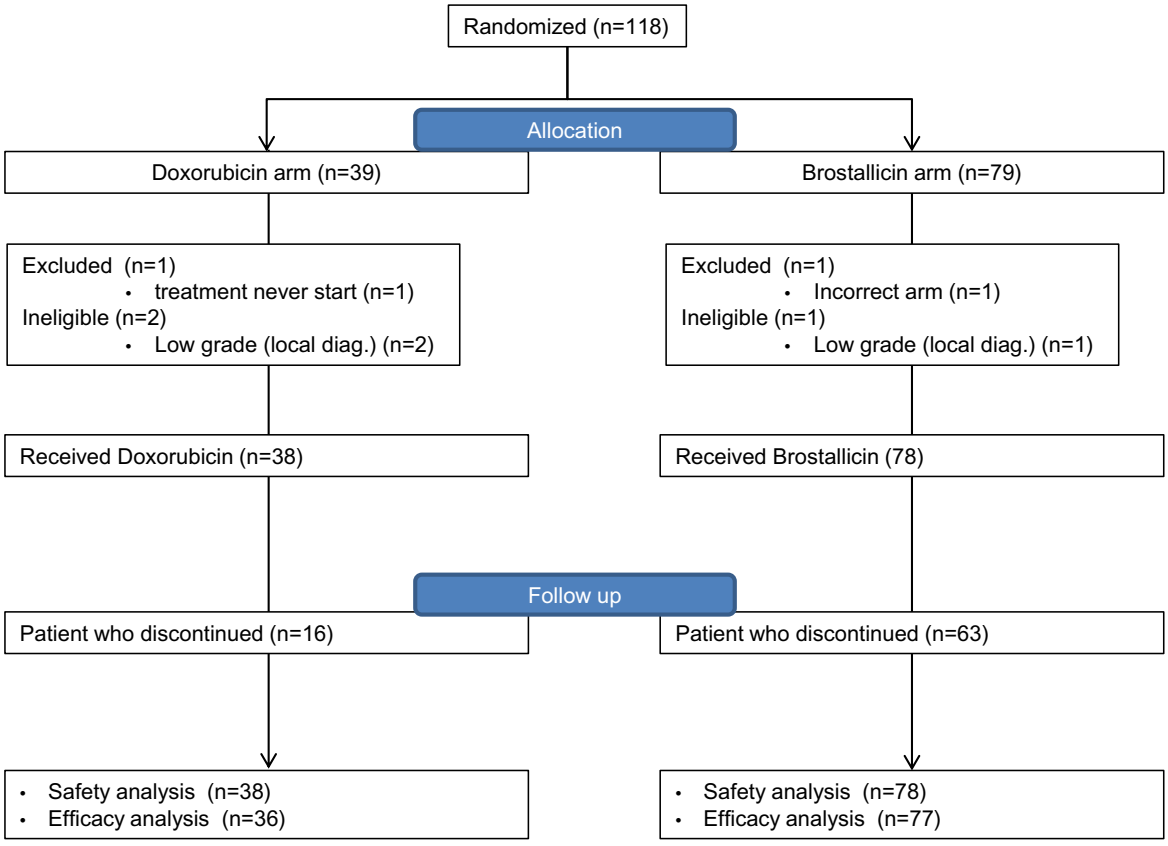

Fig. 1. CONSORT diagram. Two patients were excluded from both the safety and activity populations: one patient randomised to brostallicin was treated in error with doxorubicin, another patient did not start protocol therapy, because of rapid deterioration of performance status before the intended start of the therapy. In three cases, the reference and local pathologist agreed with the diagnosis of low grade, and those patients are therefore considered as ineligible for the trial and excluded from the activity population. For six other low-grade cases, there was disagreement between the local (diagnosed high-grade) and the review pathologist (diagnosed low grade). These patients are considered eligible as the patients were entered based on local pathology.

delayed in 36% of the patients (21% of the cycles) in the brostallicin arm, and in 45% of the patients (18% of the cycles) in the doxorubicin arm. Most dose and schedule modifications were due to neutropenia, in both treatment arms.

Neutropenia was the most frequently observed toxicity, in both arms, and reached grade 3–4 in 95% of the patients in the doxorubicin arm versus 67% in the brostallicin arm; other haematological toxicities were observed with a similar profile (but less severe). No grade 3 or 4 non-haematological events were observed, except for one grade 3 ASAT (aspartate aminotransferase) elevation with brostallicin. The following drug related adverse events were observed in at least 10% of the patients in both arms, except where stated: fatigue, weight loss, alopecia (doxorubicin), anorexia, constipation, diarrhoea, mucositis (doxorubicin), nausea, vomiting and febrile neutropenia. They were generally more frequent in the doxorubicin arm, but it should be noted that treatment exposure was also longer in this arm.

Brostallicin was well tolerated when compared with doxorubicin with less grade 2–3 systolic dysfunction (0% versus 11%), alopecia (17% versus 61%) and grade 2–3 mucositis (0% versus 18%). However, grade 3–4 tumour pain was worse (14% versus 3%) in patients receiving brostallicin.

The efficacy analysis was performed at a median follow-up of 623 days. Fifteen 'successes' were observed in this study, 5/77 (6%) in the brostallicin arm, and 10/36 (28%) in the doxorubicin arm (Table 2). Amongst the failures, seven patients (three brostallicin, four doxorubicin) were recorded with progression between weeks 28 and 31, whilst they were not progressive at the previous evaluation (week 23 or before). Compliance to the week 26 evaluation required by the protocol could have increased the success rate, but even then brostallicin would have not met the pre-specified criteria for further evaluation in this setting. Additionally, six patients (four brostallicin, two doxorubicin) were reported as 'clinical progression' without radiological documentation before week 26. New anticancer therapy was given before week 26 in six cases (three brostallicin, three doxorubicin), also these patients were considered as failures. Median PFS was shorter in the brostallicin arm (7 weeks) when compared with doxorubicin (6 months) (Fig. 2). The response rate given by the primary end-point success

Table 1
Baseline and tumour characteristics of all randomised patients. MPNST, malignant peripheral nerve sheath tumour; NOS, not otherwise specified.

	Treatment arm		Total ($N = 118$)
	Doxorubicin ($N = 39$) *N* (%)	Brostallicin ($N = 79$) *N* (%)	*N* (%)
Histology of soft tissue sarcoma			
Adipocytic	9 (23.1)	10 (12.7)	19 (16.1)
Dedifferentiated	6	7	13
Myxoid	2	3	5
Round cell	1	0	1
Fibroblastic	3 (7.7)	9 (11.4)	12 (10.2)
Adult fibrosarcoma	0	5	5
Myxofibrosarcoma	3	3	6
Sclerosing epitheliod fibrosarcoma	0	1	1
Fibrohistiocytic	4 (10.3)	7 (8.9)	11 (9.3)
Pleomorphic MFH*	4	5	9
Giant cell MFH*	0	1	1
Inflammatory MFH*	0	1	1
Smooth muscles Leiomyosarcoma (excl skin)	15 (38.5)	29 (36.7)	44 (37.3)
Skeletal muscle Pleomorphic rhabdomyosarcoma	1 (2.6)	2 (2.5)	3 (2.5)
Vascular Haemangioendothelioma	0 (0.0)	3 (3.8)	3 (2.5)
Uncertain different	1 (2.6)	4 (5.1)	5 (4.2)
Synovial sarcoma	1	2	3
Clear cell carcinoma	0	1	1
Neoplasms with perivascular epithelioid cell differentiation (PEComa)	0	1	1
MPNST	1 (2.6)	4 (5.1)	5 (4.2)
Malignant solitary fibrous	0 (0.0)	2 (2.5)	2 (1.7)
Undifferentiated NOS	3 (7.7)	6 (7.6)	9 (7.6)
Other	2 (5.1)	2 (2.5)	4 (3.4)
Unknown	0 (0.0)	1 (1.3)	1 (0.8)

* MFH: Malignant Fibrous Histiocytoma

Table 2
Progression free survival status at 26 weeks from randomisation and best overall response.

	Treatment arm	
	Doxorubicin ($N = 36$) *N* (%)	Brostallicin ($N = 77$) *N* (%)
Week 26 evaluation		
Alive, no PD*	10 (27.8)	5 (6.5)
Documented PD* < week 26	13 (36.1)	60 (77.9)
Documented PD* on week 26	3 (8.3)	1 (1.3)
Not assessed, PD* > week 26	4 (11.1)	3 (3.9)
Clinical PD* < week 26	2 (5.6)	4 (5.2)
Early death due to PD*	1 (2.8)	2 (2.6)
New treatment before PD*	3 (8.3)	2 (2.6)
Best overall response		
Complete response	0 (0.0)	1 (1.3)
Partial response	8 (22.2)	2 (2.6)
No change	16 (44.4)	27 (35.1)
Progression disease	12 (33.3)	45 (58.4)
Non-evaluable	0 (0.0)	2 (2.6)

* PD: Progression disease

rate and by the Kaplan–Meier (KM) method was different. The difference can be explained by the small sample size used, the definition of response (the non-evaluable response is a failure but not in the KM method). The 3-months PFS for brostallicin and doxorubicin was 18% and 69%, respectively. Best objective responses

PFS duration					
Treatment arm	Patients	Observed Events	Hazard Ratio	Median (Years)	% at 1 Year
Doxorubicin	36	33	1.00	0.51	15.63
Brostallicin	77	74	2.01	0.13	6.49

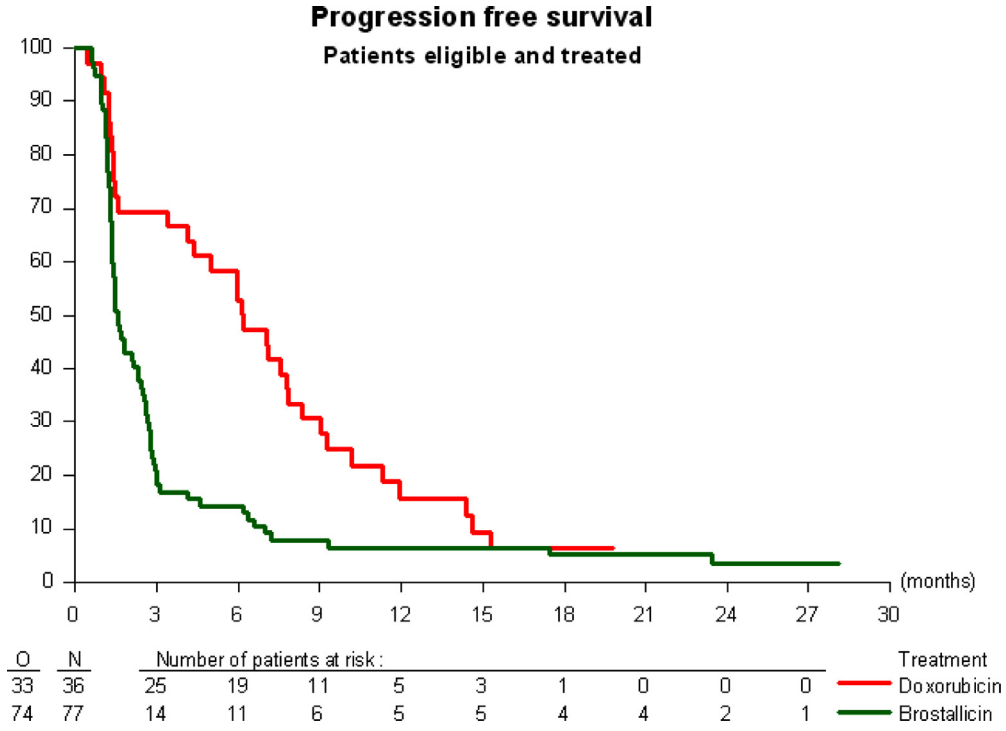

Fig. 2. Progression free survival Kaplan–Meier curve of first-line doxorubicin versus brostallicin in locally advanced or metastatic intermediate to high-grade soft tissue sarcoma.

are also shown in Table 2 with more responses (partial response (PR) and complete response (CR)) seen in those receiving doxorubicin than brostallicin (22.2% versus 3.9%, respectively). The responses were observed in two patients with extrapulmonary metastases, in seven patients with lung metastases only and in two patients with combined lung and extrapulmonary metastases. There was one CR in the brostallicin arm: this patient had an intermediate grade unclassified soft tissue sarcoma with high oestrogen and progesterone expression suggestive of a tumour with uterine origin. A follow-up scan after six cycles of brostallicin confirmed the complete remission of the lung metastases, which was maintained during further follow-up.

No difference was observed in OS between the two arms (Fig. 3).

The most frequent first post-protocol therapy in the brostallicin arm was doxorubicin-based treatment (55%), followed by local therapy (16%), and other drugs (8%): 20% of the patients did not receive any further therapy. In the doxorubicin arm 24% of the patients went on to receive ifosfamide (or trofosfamide), other drugs (28%) and local therapy (21%): 33% of the patients did not receive any further therapy.

3.3. Pharmacogenetic study

Sixteen centres provided analysable blood samples for 90 out of the 118 patients registered in the study (76%). (Table 3).

In the brostallicin-treated patients, no significant correlation between GST variants and efficacy endpoints were found. Also, no correlation was found between polymorphisms and neutropenia, in either treatment arm (data not shown).

In the doxorubicin arm, the PFS at 26 weeks success rate was significantly higher for the GSTA1 T/T genotype (success rate 62.5%; 95% confidence interval (CI) [24.49–91.48]) (as compared with C/C 12.5 [0.32–52.65]; and C/T12.5 [1.55–38.35]) ($P = 0.023$) (Table 4).

4. Discussion

This randomised phase II study was performed to establish the activity of brostallicin in first-line treatment of advanced or metastatic STS. The basis of this study was formed by the success of a preceding phase II study where we observed a 46% progression free rate at

OS duration					
Treatment arm	Patients	Observed Events	Hazard Ratio	Median (Years)	% at 1 Year
Doxorubicin	36	24	1.00	1.10	57.94
Brostallicin	77	54	1.16	1.06	50.45

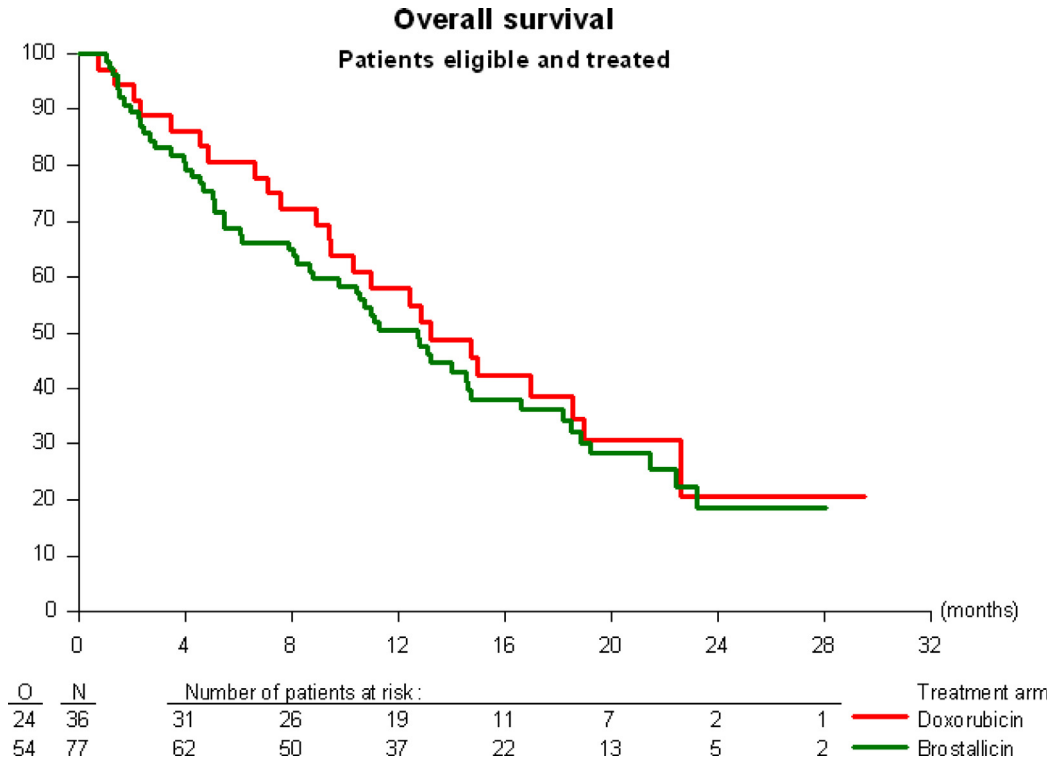

Fig. 3. Overall survival Kaplan–Meier curve of first-line doxorubicin versus brostallicin in locally advanced or metastatic intermediate to high-grade soft tissue sarcoma.

Table 3
Genotype frequency by randomised treatment arm.

	Treatment arm		Total ($N = 90$)	P
	Doxorubicin ($N = 32$) N (%)	Brostallicin ($N = 58$) N (%)	N (%)	
GSTA1				0.139
C/C	8 (25.0)	26 (44.8)	34 (37.8)	
C/T	16 (50.0)	24 (41.4)	40 (44.4)	
T/T	8 (25.0)	8 (13.8)	16 (17.8)	
GSTP1				0.870
AA	14 (43.8)	27 (46.6)	41 (45.6)	
AG	14 (43.8)	22 (37.9)	36 (40.0)	
GG	4 (12.5)	9 (15.5)	13 (14.4)	
GSTM1				0.776
Mutant	17 (53.1)	29 (50.0)	46 (51.1)	
Wildtype	15 (46.9)	29 (50.0)	44 (48.9)	
GSTT1				1.000
Mutant	4 (12.5)	8 (13.8)	12 (13.3)	
Wildtype	28 (87.5)	50 (86.2)	78 (86.7)	

Table 4
Germline GSTA1 genotypes related to success rate of brostallicin or doxorubicin in first-line treatment of advanced or metastatic soft tissue sarcoma.

GSTA1	Brostallicin				Doxorubicin			
	C/C ($N = 26$) *N* (%)	C/T ($N = 24$) *N* (%)	T/T ($N = 8$) *N* (%)	*P*	C/C ($N = 8$) *N* (%)	C/T ($N = 16$) *N* (%)	T/T ($N = 8$) *N* (%)	*P*
PFS rate at 26 weeks				0.418				0.023
Success: alive, no PD*	3 (11.5)	1 (4.2)	0 (0.0)		1 (12.5)	2 (12.5)	5 (62.5)	
Failure: alive, PD*	16 (61.5)	13 (54.2)	4 (50.0)		5 (62.5)	5 (31.3)	2 (25.0)	
Failure: dead, no PD*	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	1 (6.3)	0 (0.0)	
Failure: dead, PD*	7 (26.9)	7 (29.2)	4 (50.0)		0 (0.0)	4 (25.0)	1 (12.5)	
Failure: missing eval.	0 (0.0)	3 (12.5)	0 (0.0)		2 (25.0)	4 (25.0)	0 (0.0)	
Success rate	11.54	4.17	NA		12.5%	12.5%	62.5%	
95% confidence interval (CI)	[2.45–30.15]	[0.11–21.12]	NA		[0.32–52.65]	[1.55–38.35]	[24.49–91.48]	

* PD: Progression disease

3-months, which was well above the 40% threshold as defined by van Glabbeke et al. [8,9]. In this study we doubled the number of patients in the experimental arm to increase the power to test the PFS and the OS as secondary end-points. However in the current study the success rate for brostallicin was below the minimum threshold as defined by the protocol, such that further study of brostallicin in this patient population is not justified. Potential reasons for the discrepancy between the previous study and the present one could be the observed different distribution of STS subtypes between both studies, differential activity of brostallicin in first versus further lines of therapy, or the factor of chance in these relatively limited sized studies.

In addition to the lack of activity of brostallicin in first-line treatment, several important issues become apparent from this study.

Firstly, this study confirms that doxorubicin is indeed an active drug in this indication in terms of prolonging progression free survival, provided that patients in the brostallicin arm did not fare worse than no treatment. It is important to note that doxorubicin was initially adopted as standard first-line therapy for STS based on studies without randomisation against best supportive care. And there was only one other prior study showing that doxorubicin improved PFS over another therapy [10].

Secondly, although the study was not designed to compare outcomes between both arms, overall survival seems not to be different between both arms. This is likely to be the result of the activity of subsequent post-study treatments. Given the strong impact of performance score on prognosis in advanced disease [11], this suggests that the time when an effective therapy is given in regards to the probability of survival does not seem that important in unresectable metastatic disease as long as patients are intensively followed during treatment as happened during this trial, and an effective treatment is initiated prior to clinical deterioration. Thirdly, the pharmacogenetic study was not able to identify patients who derived benefit from brostallicin. One reason might be that there were just too few successes in the brostallicin arm to detect such a relationship, although another reason is of course that such an association does not exist. Finally, there was a relationship between *GSTA*1 TT genotype and efficacy of doxorubicin. This is not unexpected as the low expression variant TT genotype was associated with reduced risk of death after treatment with various alkylating agents in various tumour types [12,13]. The rationale for this lies in the GSTA1 mediated conjugation of glutathione to alkylating agents [14]. However, it should be stated that this observation in our study is explorative, and therefore needs confirmation in other studies.

Inevitably, this study has some drawbacks. PFS rate at 6 months as a primary end-point in a first-line trial is potentially problematic, as this can only reliably be assessed in patients with proven progression prior to trial entry. Patients thus might need a second scan showing disease progression in order to fulfill the entry criteria. Clearly, this could cause a dilemma for both patients and treating physicians who might be reluctant to wait to document disease progression before initiating treatment. This potential to compromise study accrual led to a protocol amendment allowing patients to be entered in whom objective progression within 6 months before study entry was not required. In fact, after the amendment, the number of patients not showing disease progression prior to therapy was very low and was equally distributed between the two arms, such that it had no significant impact on the results of the study.

Our study does not show a difference in survival. With the increase in survival of metastatic STS in the recent years because of the availability of more systemic treatment options than in the past, OS difference is less meaningful for judging efficacy of drugs in the first-line setting than in the past. Also more than half of the patients in the brostallicin arm were treated with doxorubicin after progression, although not vice versa as brostallicin is not available outside clinical trials, so

there was in effect crossover to doxorubicin. One could therefore speculate that further line doxorubicin treatment in the brostallicin arm obscured the expected survival advantage of the doxorubicin arm.

In summary, this study shows that brostallicin at this dose and schedule is not effective in first-line treatment of locally advanced or metastatic STS. This study also shows that doxorubicin is indeed an effective drug for this indication, and that *GSTA1* TT germline genotype might predict efficacy of doxorubicin, although the latter observation clearly needs further confirmation.

Funding

This study was funded through a grant of SML to the EORTC-STBSG.

Conflict of interest statement

All authors have no COI, except S.D.W. who was a consultant to SML at the time of the conduct of the study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2013.10.002.

References

[1] The ESMO/European Sarcoma Networking Group. Soft tissue and visceral sarcoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(Suppl. 7):S92–9.

[2] Lorigan P, Verweij J, Papai Z, et al. Phase III trial of 2 investigational schedules of ifosfamide compared with standard-dose doxorubicin in patients with advanced or metastatic soft tissue sarcoma, a European Organisation of Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group study. J Clin Oncol 2007;25:3144–50.

[3] Judson I, Verweij J, Gelderblom H, et al. Results of a randomized phase III trial (EORTC 62012) of single agent doxorubicin versus doxorubicin plus ifosfamide as first line chemotherapy for patients with advanced or metastatic soft tissue sarcoma: a survival study by the EORTC Soft Tissue and Bone Sarcoma Group. ESMO 2012:LBA07.

[4] 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 2 different schedules. J Clin Oncol 2009;27:4188–96.

[5] Van der Graaf WTA, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft tissue sarcoma (PALETTE): a randomized, double-blind, placebo-controlled fase 3 trial. Lancet 2012;379:1879–86.

[6] Broggini M, Marchini S, Fontana E, et al. Brostallicin: a new concept in minor groove DNA binder development. Anticancer Drugs 2004;15:1–6.

[7] Geroni C, Marchini S, Cozzi P, et al. Brostallicin, a novel anticancer agent whose activity is enhanced upon binding to glutathione. Cancer Res 2002;15:2332–6.

[8] Leahy M, Ray-Coquard I, Verweij J, et al. Brostallicin, an agent with potential activity in metastatic soft tissue sarcoma, a phase II study from the European Organisation of Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Eur J Cancer 2007;43:208–15.

[9] Van Glabbeke M, Verweij J, Judson I, et al. Progression-free rate as the principal end-point for phase II trials in soft tissue sarcomas. Eur J Cancer 2002;38:543–9.

[10] Verweij J, Lee SM, Ruka W, et al. Randomized phase II study of docetaxel versus doxorubicin in first- and second-line therapy in patients with locally advanced and metastatic soft tissue sarcoma in adults: a study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol 2000;18:2081–6.

[11] Penel N, Van Glabbeke M, Mathoulin-Pelissier S, et al. Performance status is the most powerful risk factor for early death amongst patients with soft tissue sarcoma: a study of the European Organisation of Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (STBSG) and the French Sarcoma Group (FSG) study. Br J Cancer 2011;104:1544–50.

[12] Sweeney C, Ambrosone CB, Joseph L, et al. Association between a glutathione S-transferase A1 promotor polymorphism and survival after breast cancer treatment. Int J Cancer 2003;103:810–4.

[13] Khrunin AV, Moisseev A, Gorbunova V, Limborska S. Genetic polymorphisms and the efficacy and toxicity of cisplatin based chemotherapy in ovarian cancer patients. Pharmacogenomics J 2010;10:54–61.

[14] Dirven HA, van Ommen B, van Bladeren P. Involvement of human glutathione S-transferase isoenzymes in the conjugation cyclophosfamide metabolites with glutathione. Cancer Res 1994;54:2615–20.