Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial

*Ian Judson, Jaap Verweij, Hans Gelderblom, Jörg T Hartmann, Patrick Schöffski, Jean-Yves Blay, J Martijn Kerst, Josef Sufliarsky, Jeremy Whelan, Peter Hohenberger, Anders Krarup-Hansen, Thierry Alcindor, Sandrine Marreaud, Saskia Litière, Catherine Hermans, Cyril Fisher, Pancras C W Hogendoorn, A Paolo dei Tos, Winette T A van der Graaf, for the European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group**

Summary

Background Effective targeted treatment is unavailable for most sarcomas and doxorubicin and ifosfamide—which have been used to treat soft-tissue sarcoma for more than 30 years—still have an important role. Whether doxorubicin alone or the combination of doxorubicin and ifosfamide should be used routinely is still controversial. We assessed whether dose intensification of doxorubicin with ifosfamide improves survival of patients with advanced soft-tissue sarcoma compared with doxorubicin alone.

Methods We did this phase 3 randomised controlled trial (EORTC 62012) at 38 hospitals in ten countries. We included patients with locally advanced, unresectable, or metastatic high-grade soft-tissue sarcoma, age 18–60 years with a WHO performance status of 0 or 1. They were randomly assigned (1:1) by the minimisation method to either doxorubicin (75 mg/m² by intravenous bolus on day 1 or 72 h continuous intravenous infusion) or intensified doxorubicin (75 mg/m²; 25 mg/m² per day, days 1–3) plus ifosfamide (10 g/m² over 4 days with mesna and pegfilgrastim) as first-line treatment. Randomisation was stratified by centre, performance status (0 *vs* 1), age (<50 *vs* ≥50 years), presence of liver metastases, and histopathological grade (2 *vs* 3). Patients were treated every 3 weeks till progression or unacceptable toxic effects for up to six cycles. The primary endpoint was overall survival in the intention-to-treat population. The trial is registered with ClinicalTrials.gov, number NCT00061984.

Findings Between April 30, 2003, and May 25, 2010, 228 patients were randomly assigned to receive doxorubicin and 227 to receive doxorubicin and ifosfamide. Median follow-up was 56 months (IQR 31–77) in the doxorubicin only group and 59 months (36–72) in the combination group. There was no significant difference in overall survival between groups (median overall survival 12·8 months [95·5% CI 10·5–14·3] in the doxorubicin group *vs* 14·3 months [12·5–16·5] in the doxorubicin and ifosfamide group; hazard ratio [HR] 0·83 [95·5% CI 0·67–1·03]; stratified log-rank test p=0·076). Median progression-free survival was significantly higher for the doxorubicin and ifosfamide group (7·4 months [95% CI 6·6–8·3]) than for the doxorubicin group (4·6 months [2·9–5·6]; HR 0·74 [95% CI 0·60–0·90], stratified log-rank test p=0·003). More patients in the doxorubicin and ifosfamide group than in the doxorubicin group had an overall response (60 [26%] of 227 patients *vs* 31 [14%] of 228; p<0·0006). The most common grade 3 and 4 toxic effects—which were all more common with doxorubicin and ifosfamide than with doxorubicin alone—were leucopenia (97 [43%] of 224 patients *vs* 40 [18%] of 223 patients), neutropenia (93 [42%] *vs* 83 [37%]), febrile neutropenia (103 (46%) *vs* 30 [13%]), anaemia (78 [35%] *vs* 10 [5%]), and thrombocytopenia (75 [33%]) *vs* one [<1%]).

Interpretation Our results do not support the use of intensified doxorubicin and ifosfamide for palliation of advanced soft-tissue sarcoma unless the specific goal is tumour shrinkage. These findings should help individualise the care of patients with this disease.

Funding Cancer Research UK, EORTC Charitable Trust, UK NHS, Canadian Cancer Society Research Institute, Amgen.

Introduction

The term soft-tissue sarcoma encompasses a broad diversity of tumours. For a few sarcomas—notably, gastrointestinal stromal tumours—effective targeted treatment is available.[1] However, although translocations or amplifications have been associated with an increasing number of sarcoma subtypes, these findings have led to innovative treatment for only a minority of cases.[2–4] For most advanced sarcomas, clinicians rely on conventional chemotherapy for palliation, which is somewhat effective, but few patients achieve an objective response.[5] Histological diagnosis can be used to guide treatment for some sarcomas—eg, taxanes for angiosarcoma,[6,7] or gemcitabine-containing treatment for leiomyosarcoma and undifferentiated pleomorphic sarcoma.[8,9] Nevertheless, doxorubicin and ifosfamide—which have been used to treat soft-tissue sarcoma for more than 30 years—still have an important role. Whether doxorubicin alone or the

Lancet Oncol 2014

Published **Online** March 5, 2014 http://dx.doi.org/10.1016/S1470-2045(14)70063-4

*Members listed in acknowledgments

Royal Marsden Hospital, London, UK (Prof I Judson MD, Prof C Fisher DSc); **Erasmus MC Cancer Institute, Rotterdam, Netherlands** (Prof J Verweij PhD); **Leiden University Medical Center, Leiden, Netherlands** (Prof H Gelderblom PhD, Prof P C W Hogendoorn PhD); **Eberhard Karls Universitaet Tübingen, Tübingen, Germany** (Prof J T Hartmann MD); **Christian-Albrechts-University, Kiel, Germany** (Prof J T Hartmann); **Catholic Hospital, Consortium, Bielefeld, Germany** (Prof J T Hartmann); **Department of General Medical Oncology, University Hospitals Leuven, KU Leuven, Leuven, Belgium** (Prof P Schöffski MPH); **Department of Medicine, NetSARC and LYRIC, Centre Leon Berard, Lyon, France** (Prof J-Y Blay PhD); **University Centre Leon Berard, Lyon, France** (Prof J-Y Blay); **Netherlands Cancer Institute, Amsterdam, Netherlands** (J M Kerst PhD); **National Cancer Institute, Bratislava, Slovakia** (Prof J Sufliarsky MD); **The London Sarcoma Service, University College Hospital, London, UK** (Prof J Whelan MD); **Mannheim University Medical Center, Mannheim, Germany** (Prof P Hohenberger MD); **Department of Oncology, Herlev Hospital—University Copenhagen, Herlev, Denmark** (A Krarup-Hansen MD); **Department of Oncology, McGill University Montreal, QC, Canada** (Prof T Alcindor MD); **Montreal General Hospital,**

Montreal, QC, Canada (Prof T Alcindor)**; EORTC, Brussels, Belgium** (S Marreaud MD, S Litière PhD, C Hermans)**; Azienda ULSS 9 Treviso, Treviso, Italy** (Prof A P dei Tos MD)**; and Department of Medical Oncology, Radboud University Medical Center Nijmegen, Netherlands** (Prof W T A van der Graaf PhD)

Correspondence to: Prof Ian Judson, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK
ian.judson@icr.ac.uk

combination of doxorubicin and ifosfamide should be used routinely is still controversial. Few studies have directly addressed this question and none have shown that overall survival is improved by dose intensification or combination treatment compared with doxorubicin alone. Ifosfamide has a clear dose–response relationship, with 9 g/m² fractionated over 3 days producing a higher proportion of responses than 5 g/m² given as a 24 h infusion.[10] Responses in as many as 50–60% of patients have been reported for various regimens of anthracycline plus ifosfamide[11–13] but these findings have not been replicated in randomised trials. In the palliative setting, disease control can delay deterioration of symptoms, therefore progression-free survival might be equally important as overall survival, although improved overall survival is still a key goal of treatment.[14]

We assessed whether the addition of ifosfamide to doxorubicin improved the survival of patients with locally advanced unresectable or metastatic soft-tissue sarcoma. To establish the true value of the combination, we used a dose of ifosfamide used in previous phase 2 trials to enable direct comparison and the doxorubicin dose was identical in the two groups both to maximise dose intensification and to test the effect of adding ifosfamide.

For the **study protocol** see http://www.eortc.be/services/download/Protocols/62012.pdf

Methods

Study design and participants

We did this phase 3, randomised controlled trial (EORTC 62012) at 38 hospitals in ten countries (Belgium, Canada, Denmark, France, Germany, Netherlands, Slovakia, Spain, Switzerland, UK; appendix). Patients had to have histological evidence of high-grade soft-tissue sarcoma (grades 2–3) according to the Federation Nationale des Centres de Lutte Contre le Cancer grading system[15] when applicable and radiological evidence of measurable unresectable or metastatic disease progression within 6 weeks before treatment according to RECIST (version 1.0).[16] We included patients with the following tumour types: undifferentiated pleomorphic sarcoma, myxoid or round cell liposarcoma, pleomorphic liposarcoma and dedifferentiated liposarcoma, pleomorphic rhabdomyosarcoma, synovial sarcoma, myxofibrosarcoma, fibrosarcoma, leiomyosarcoma, angiosarcoma, malignant peripheral nerve sheath tumour, epithelioid sarcoma, unclassified high-grade sarcoma (not otherwise specified). A panel of specialist sarcoma pathologists did a mandatory central pathology review but patients were enrolled on the basis of local diagnosis. Patients had to be age 18–60 years, with a WHO performance status[17] of 0 or 1, absolute neutrophil count more than 2×10^9 cells per L, more than 100×10^9 platelets per L, serum creatinine of 120 µmol/L or less or calculated creatinine clearance (Cockroft and Gault method) more than 65 mL/min, two functioning kidneys, bilirubin 30 µmol/L or less, and albumin more than 25 g/L. Patients also had to have a normal (according to local assessments) left ventricular ejection fraction by multiple gated acquisition scan or echocardiogram. Women of child-bearing potential had to take adequate contraceptive measures and have a negative pregnancy test within 7 days of study entry. Any psychological or other disorder that could hamper compliance was discussed with the patient before registration. We excluded patients with: gastrointestinal stromal tumour, mixed mesodermal tumour, chondrosarcoma, malignant mesothelioma, neuroblastoma, osteosarcoma, Ewing's sarcoma, desmoplastic small round cell tumour, embryonal rhabdomyosarcoma, and alveolar soft part sarcoma. Additional exclusion criteria were other severe illness (eg, psychosis or previous history of cardiovascular disease), symptomatic or known CNS metastases, previous or concurrent second primary malignant tumours (except adequately treated in-situ carcinoma of cervix or basal cell carcinoma). We also excluded patients who had had radiotherapy to the sole available index lesion or those who had received chemotherapy for advanced disease, although previous adjuvant chemotherapy (preoperative or postoperative) was allowed if disease progression had not occurred within 6 months of completion.

The study protocol is available online. The trial was approved by national and institutional research ethics committees at all participating centres. Patients provided written informed consent.

See Online for appendix

Randomisation and masking

Eligible patients were randomly assigned (1:1) to either doxorubicin alone or intensified doxorubicin and ifosfamide. The randomisation sequence was generated by an online randomised trial access system based on the minimisation method. Randomisation was stratified by centre, performance status (0 *vs* 1), age (<50 years *vs* ≥50 years), liver metastases (present *vs* absent), and histological grade (2 *vs* 3). Neither patients nor investigators were masked to treatment allocation.

Procedures

Patients assigned to receive doxorubicin alone were given doxorubicin 75 mg/m² by intravenous bolus on day 1 or 72 h continuous intravenous infusion. Those assigned to receive intensified doxorubicin and ifosfamide received doxorubicin 25 mg/m² per day on days 1–3 and ifosfamide (2·5 g/m² per day, days 1–4) plus mesna (0·5 g/m² by intravenous bolus before ifosfamide, 1·5 g/m² concurrent with ifosfamide, and 1 g/m² orally 2 h and 6 h after completion of ifosfamide infusion), followed by pegfilgrastim (6 mg subcutaneously, day 5; appendix). Treatment was repeated every 3 weeks until disease progression or unacceptable toxic effects, up to a maximum of six cycles. Patients who discontinued in the first 6 weeks because of overt disease progression were deemed to have early progression and analysed for response as treatment failures.

Side-effects of treatment were graded according to International Common Toxicity Criteria (version 2.0).[18] Dose modifications for adverse events were done

according to the protocol. Clinical assessments of safety, including physical examination, performance status, blood chemistry, and urinalysis (with dipstick) were done at baseline and before each cycle of treatment. Expected side-effects were myelotoxicity, nausea, fatigue, anorexia, dysgeusia, gastrointestinal disturbances, and mouth ulceration. Doxorubicin causes cumulative cardiotoxicity and ifosfamide can cause cumulative renal impairment, bladder toxic effects, and central encephalopathy.

Disease was assessed after every two cycles of treatment with chest radiography and either CT or MRI scans. For patients with complete response, partial response, or stable disease at the end of treatment (assessed with RECIST 1.0), assessments were continued every 6 weeks. After treatment progression, patients were followed up every 12 weeks for survival; follow-up for survival is still ongoing.

Outcomes

The primary endpoint was overall survival. Secondary endpoints were progression-free survival, best overall response, and toxic effects. For the assessment of best overall response, local response assessment was used; no central review of response was done. Complete response or partial response had to be confirmed by a repeat measurement at least 4 weeks after response criteria were first met. For stable disease, a minimum of 6 weeks was specified.

Statistical analysis

The trial was powered to detect a hazard ratio (HR) of 0·737 at most. Under the proportional hazards hypothesis, this corresponds to a 10% difference in 1-year survival (60% *vs* 50%). The choice of 50% as comparator was based on an analysis of more than 2000 patients with sarcoma treated with first-line anthracycline-containing chemotherapy, for whom median survival was 12 months.[19] 366 events were needed to detect such a difference with a two-sided stratified log-rank test (α=0·05, power=80%). With 450 patients recruited over a 4-year period, we expected 366 events to have occurred after roughly 1·5 years of additional follow-up. We did two interim analyses: one futility analysis after 52 events (progression or death) to assess if progression-free survival at 6 months was significantly greater in the doxorubicin and ifosfamide group than in the doxorubicin group (target HR 0·5, α=0·05) and one based on overall survival after 188 deaths (using an error spending function with a boundary parameter of 0·2). We used a stopping rule for toxic effects, with ongoing analyses once every 6 months, such that if febrile neutropenia occurred in more than 30% of cycles of treatment with doxorubicin and ifosfamide, the study would be stopped.

Overall survival was computed from the date of randomisation to the date of death from any cause. Patients alive at the time of the analysis were censored at their last follow-up date. Progression-free survival was computed from the date of randomisation to the first recorded date of progression or death. Patients alive and progression-free at the time of analysis were censored at the date of last follow-up.

We estimated overall survival and progression-free survival with the Kaplan-Meier method and compared treatment groups with a two-sided log-rank test. We compared best overall response between the two groups with a Mantel-Haenszel χ^2 test for trend (classifying early death and not evaluable as progressive disease). We used a significance level of 0·0451 (adjusted for interim analysis, associated CIs are 95·5%) for the analysis of overall survival, whereas we used 0·05 for the other endpoints.

We did the primary efficacy analyses for the intention-to-treat population—ie, all randomly assigned patients (including those retrospectively found to be ineligible) according to their allocated treatment. We assessed safety for the safety population—ie, all patients who started their allocated treatment. We did sensitivity efficacy analyses for the per-protocol population—ie, all randomly assigned patients who satisfied the eligibility criteria and started their allocated treatment.

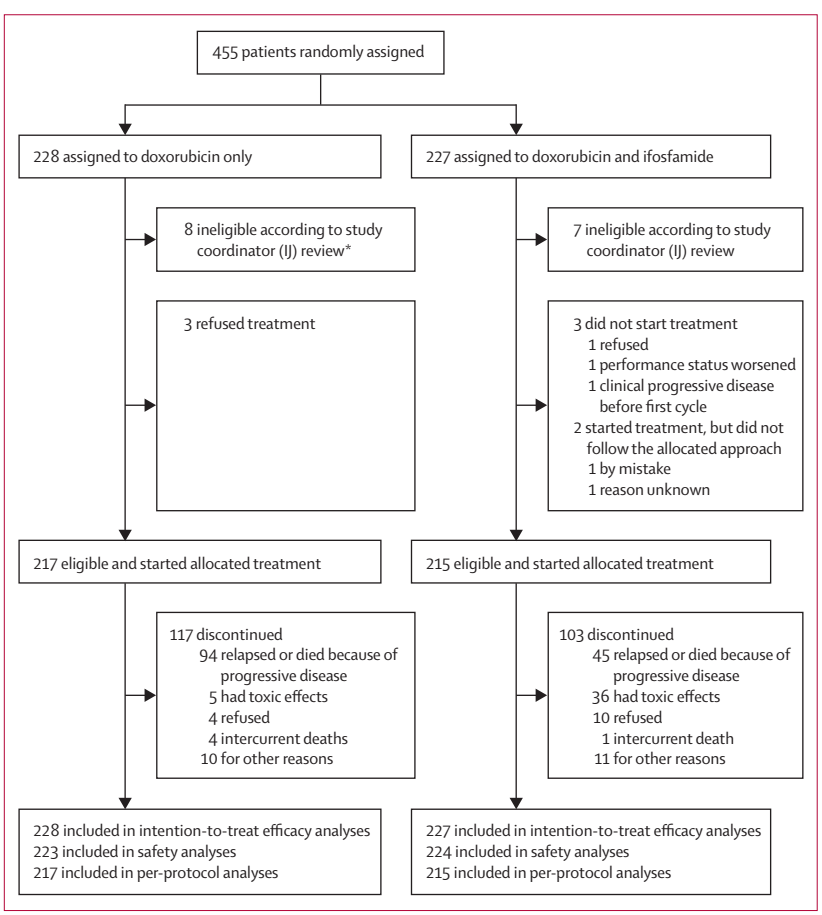

Figure 1: **Trial profile**
*One of whom started treatment but did not follow the allocated approach.

The clinical cutoff date was July 5, 2012. East (version 5) was used to calculate sample size and stopping boundaries; we did all other statistical analyses with SAS (version 9.3). This trial is registered with ClinicalTrials.gov, number NCT00061984.

Role of the funding source

EORTC designed and coordinated the trial. The funders had no role in the design of the study; collection, analysis, or interpretation of the data; or writing the report. CH and SL had full access to the raw data. The corresponding author had the final responsibility for the decision to submit for publication.

	Doxorubicin group (n=228)	Doxorubicin and ifosfamide group (n=227)
Age		
Median (IQR; years)	48 (41–55)	47 (39–54)
Range (years)	18–60	18–63
<40 years	52 (23%)	60 (26%)
40–49 years	78 (34%)	70 (31%)
≥50 years	98 (43%)	97 (43%)
Sex		
Men	103 (45%)	114 (50%)
Women	125 (55%)	113 (50%)
WHO performance status		
0	129 (57%)	123 (54%)
1	98 (43%)	103 (45%)
2	1 (<1%)	1 (<1%)
Histological type (local diagnosis)		
Liposarcoma	26 (11%)	31 (14%)
Leiomyosarcoma	54 (24%)	59 (26%)
Synovial sarcoma	38 (17%)	26 (11%)
Other	110 (48%)	111 (49%)
Histological grade (local diagnosis)		
Low (but clinically high)*	5 (2%)	7 (3%)
Intermediate	103 (45%)	103 (45%)
High	118 (52%)	109 (48%)
Unknown	2 (1%)	8 (4%)

Data are n (%) unless stated otherwise. *Primary tumour was graded as low but patient had rapidly progressive metastatic disease.

Table 1: **Baseline characteristics**

	Doxorubicin group (n=188)	Doxorubicin and ifosfamide group (n=184)
Progression	166 (88%)	162 (88%)
Toxic effects	3 (2%)	1 (1%)
Progression and toxic effects	3 (2%)	1 (1%)
Infection	3 (2%)	2 (1%)
Intercurrent death not a result of malignant disease	2 (1%)	2 (1%)
Pulmonary embolism	1 (1%)	2 (1%)
Other	4 (2%)	2 (1%)
Unknown	6 (3%)	12 (7%)

Data are n (% of total deaths).

Table 2: **Causes of death**

Results

We enrolled 455 patients between April 30, 2003, and May 25, 2010. 228 were randomly assigned to the doxorubicin group and 227 to the doxorubicin and ifosfamide group (figure 1). Table 1 shows patient characteristics at baseline. Although information about degree of differentiation and necrosis was available, missing data for mitotic count for ten patients precluded accurate distinction between intermediate and high grade; thus, they were stratified as high grade for randomisation. 363 (80%) of 455 patients had a central pathology review. Median age was 48 years (IQR 40–54), 195 (43%) of patients were aged 50–60 years. 15 patients were deemed ineligible by the study coordinator (IJ; figure 1), reasons were: inappropriate histological results on central review (n=9), treatment started before randomisation (n=1), previous treatment (n=1), too old (n=2), impaired renal function (n=1), only one kidney because of previous kidney cancer (n=1), and poor performance status (n=2). Eight patients did not start treatment and three did not receive the allocated treatment (figure 1). As a result, the safety population consisted of 447 patients and the per-protocol population of 432 patients (figure 1).

Median follow-up was 56 months (IQR 31–77) for the doxorubicin group versus 59 months (IQR 36–72) for the doxorubicin and ifosfamide group. 411 patients had disease progression (208 *vs* 203) and 372 patients died (188 *vs* 184). Most patients died as a result of progressive disease (table 2); 30 patients (13 *vs* 17) were still alive and progression-free at the cutoff date.

There was no significant difference between groups in terms of overall survival (figure 2A). Median overall survival was 12·8 months (95·5% CI 10·5–14·3) in the doxorubicin group versus 14·3 months (12·5–16·5) in the doxorubicin and ifosfamide group (HR 0·83, 95·5% CI 0·67–1·03; stratified log-rank test p=0·076). Overall survival at 1 year was 51% (95·5% CI 44–58) in the doxorubicin alone group versus 60% (53–66) in the doxorubicin and ifosfamide group, whereas at 2 years it was 28% (22–34) and 31% (25–38), respectively. No significant difference was noted between the groups in the per-protocol analysis (p=0·057).

Median progression-free survival was significantly higher in the doxorubicin and ifosfamide group (7·4 months, 95% CI 6·6–8·3) than in the doxorubicin group (4·6 months, 95% CI 2·9–5·6; HR 0·74, 95·5% CI 0·60–0·90, stratified log-rank test p=0·003; figure 2B). We confirmed this finding in the per-protocol analysis (p=0·0006). The effects of treatment differed between some subgroups (figure 3). Patients with high grade tumours and worse performance status benefited

more than did other patients. Figure 3 also shows a benefit of combination treatment for patients aged 40–49 years, which might have been a result of statistical imbalances for this age group—both for performance status and tumour grade—which favoured the combination treatment group (data not shown).

More patients went into remission and fewer progressed in the doxorubicin and ifosfamide group than in the doxorubicin group (table 3). 14 patients (seven in each group) died before the first response assessment and 27 were not evaluable. Best overall response to treatment differed significantly between the two groups in favour of doxorubicin and ifosfamide (31 [14%] of patients in the doxorubicin group and 60 [26%] in the doxorubicin and ifosfamide group had an overall response; χ^2 test, p=0·0006).

The occurrence of toxic effects differed between treatment groups. Roughly half of all patients completed six cycles of treatment, 102 (45%) of 228 patients with doxorubicin and 115 (51%) of 227 with doxorubicin and ifosfamide. Those taking doxorubicin and ifosfamide were more likely than those taking doxorubicin only to need a dose reduction (71 [32%] of 224 patients *vs* 20 [9%] of 223 had a reduction of doxorubicin; 84 [38%] of 224 had a reduction of ifosfamide). Likewise, treatment interruptions were more common in patients taking the combination compared with the single drug treatment (15 [7%] of 224 *vs* five [2%] of 223 needed interruption of doxorubicin, 17 [8%] of 224 required interruption of ifosfamide). More patients in the doxorubicin and ifosfamide group than in the doxorubicin group discontinued treatment because of toxic effects (table 4). However, treatment discontinuation because of disease progression occurred more often in those who received doxorubicin only than in those who received doxorubicin and ifosfamide (table 4).

Grade 3–4 adverse events were significantly more prevalent in patients treated with doxorubicin and ifosfamide than in those treated with doxorubicin only (table 5, appendix lists all grades). Although these data include all events, whatever the cause, doxorubicin and ifosfamide seems to have caused more grade 2 nausea (73 [33%] of 224 patients) and grade 3 nausea 14 [6%] of 224 patients) compared with doxorubicin (44 [20%] of 223 patients and four [2%] of 223 patients, respectively). Likewise, grade 2 and grade 3 vomiting was more common in the doxorubicin and ifosfamide group (53 [24%] and 13 [5%], respectively) compared with the doxorubicin group (32 [14%] and six [3%], respectively). Ifosfamide-related grade 2 encephalopathy occurred in four (2%) patients and ifosfamide-related grade 3 encephalopathy occurred in ten (4%). Only five cases of treatment-related renal disorder occurred, all in the doxorubicin and ifosfamide group. Despite the toxic effects associated with doxorubicin and ifosfamide, toxic deaths occurred in much the same proportion in each group (table 2).

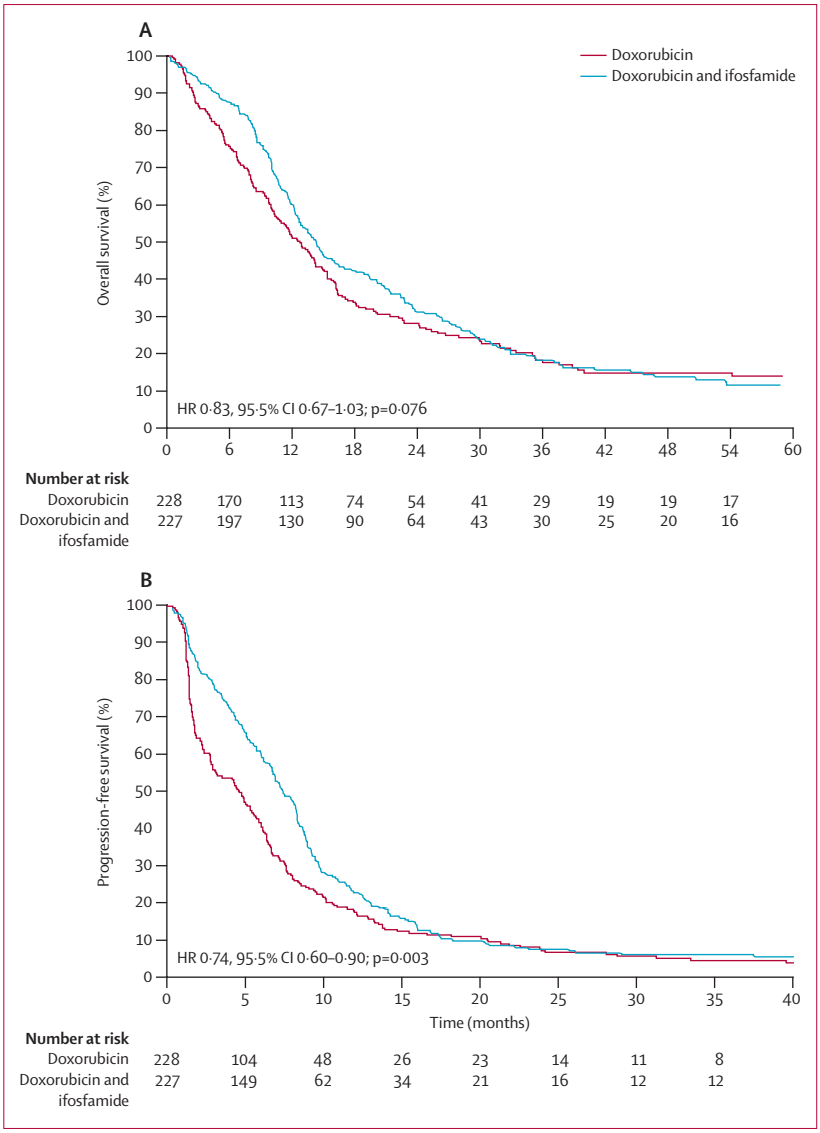

***Figure 2*: Kaplan-Meier curves for overall survival (A) and progression-free survival (B)**
HR=hazard ratio.

Post-protocol treatment did not differ substantially between groups other than that patients treated with doxorubicin were more likely to receive subsequent ifosfamide than were those who received doxorubicin and ifosfamide (table 6). We could not assess the effect of post-protocol treatment on patient survival because the data were incomplete. Once patients progressed while taking study treatment, investigators were required to collect only survival data.

Discussion

We found no improvement in overall survival from the administration of intensified combination chemotherapy with doxorubicin plus ifosfamide compared with doxorubicin alone. Although diseases driven by a specific

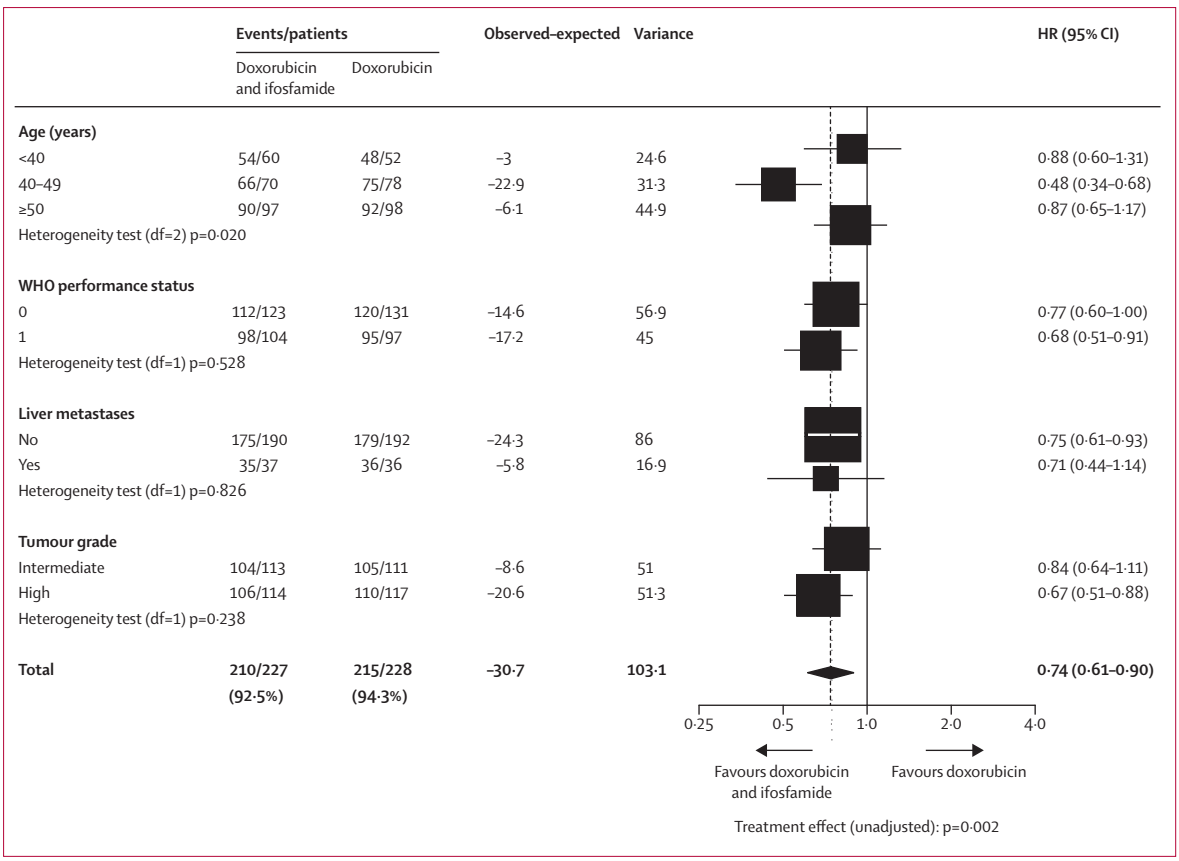

Figure 3: **Progression-free survival by subgroup**

	Doxorubicin group (n=228)	Doxorubicin and ifosfamide group (n=227)
Complete response	1 (<1%)	4 (2%)
Partial response	30 (13%)	56 (25%)
Stable disease	105 (46%)	114 (50%)
Progressive disease	74 (32%)	30 (13%)
Early death (progression)	4 (2%)	5 (2%)
Early death (other cause)	3 (1%)	2 (1%)
Not evaluable	11 (5%)	16 (7%)

Data are n (%).

Table 3: **Responses to treatment**

molecular abnormality—eg, gastrointestinal stromal tumours—might be amenable to targeted treatment, cytotoxic chemotherapy with doxorubicin or doxorubicin plus ifosfamide is still used to treat most advanced soft-tissue sarcoma. The introduction of haemopoietic growth factor support has enabled higher doses of ifosfamide to be routinely used. Most data for high-dose combinations come from single-centre phase 2 studies of highly selected groups of patients.[12–14] Few randomised studies have been done, mostly with a dose of dose of 5 g/m², none of which have shown a survival advantage (panel). For example, a randomised trial[20] done by the EORTC Soft Tissue and Bone Sarcoma Group compared doxorubicin alone with a combination of doxorubicin and ifosfamide 5 g/m² or a four-drug regimen of cyclophosphamide, vincristine, doxorubicin, and dacarbazine. The combination treatments did not significantly increase the proportion of patients who responsed, progression-free survival, or overall survival and were significantly more toxic than the single drug treatment.[20] A phase 3 study comparing single-agent doxorubicin with a combination of doxorubicin with either ifosfamide 7·5 g/m², or mitomycin and cisplatin showed a greater proportion of responses with combination treatment but no difference in survival.[21] Similarly, a trial[22] comparing doxorubicin plus dacarbazine with or without ifosfamide, for treatment of soft-tissue sarcoma and bone sarcoma also showed a significantly greater proportion of responses and longer progression-free survival, but no survival advantage, for the ifosfamide-containing regimen than for the regimen without ifosfamide.

Other studies have investigated the role of dose intensification. For example, a randomised phase 2 trial of ifosfamide 6 g/m² versus 12 g/m² with doxorubicin showed no advantage for disease-free survival or overall survival for the higher dose.[23] Dose intensification of the

doxorubicin, ifosfamide, and dacarbazine regimen—originally developed in the late 1980s—produced no improvement in responses, progression-free survival, or overall survival compared with the standard dose regimen.[24] A phase 3 trial of dose intensification of doxorubicin (75 mg/m² *vs* 50 mg/m²) with ifosfamide 5 g/m² showed no improvement in responses or overall survival, but did show a longer progression-free survival for patients taking the higher dose of doxorubicin.[25] Other studies of dose intensification showed no advantage compared with doxorubicin alone.[26,27] Two meta-analyses of dose-intensive chemotherapy and ifosfamide-based combination chemotherapy have provided the same conclusion.[28,29]

In this context, our study was uniquely powered for overall survival as the primary endpoint. Nonetheless, it failed to show a significant improvement in overall survival. However, we did note a significant 2·8 month improvement in median progression-free survival with the dose-intensified regimen, and a greater proportion of patients responded to the combination therapy than to doxorubicin alone.

The study was not masked, which might have biased the assessment of response and disease progression. However, we deemed the cost and practical implications of having an intravenous ifosfamide plus mesna matching placebo to be too great. Additionally, because overall survival was the primary endpoint, any possible bias in assessment of response or progression-free survival was thought to be of lesser importance. As in most previous studies, combination treatment was significantly more toxic than the single-drug regimen, but there was no excess of toxic deaths.

The proportion of patients who had a response in both groups was lower than reported in some—but not all—previous EORTC studies,[10,11] and lower for the combination than that reported in single-centre studies.[12–14] Eligible patients had to have high grade disease and progression within 6 weeks of study entry; thus, the prognosis for participants was poor. Several other factors—eg, competing trials and institutional bias—probably also affected patient selection, but both groups were probably affected equally. In some centres young patients with chemosensitive disease—eg, those with synovial sarcoma—might have electively been given combination treatment rather than being entered into the trial. However, the high proportion of patients with synovial sarcoma suggests that such a bias did not have a major role.

How can these data be used to guide clinical practice? If palliative chemotherapy is being given to control metastatic—typically pulmonary—disease, rather than to relieve acute symptoms, then sequential single-drug chemotherapy will probably be less toxic without significantly impairing survival. Conversely, if acute symptoms are best relieved by tumour shrinkage, the use of combination treatment would be justified; likewise, if chemotherapy is being given before surgery or radiotherapy, then combination treatment could be used to debulk the tumour. Clinical situations might also exist for which delaying disease progression for as long as possible is the priority; for example, if adjacent critical structures such as nerves are involved. Although more toxic than single drug, the combination did seem safe, at least for this age group. This study only recruited patients up to age 60 years. Although some older patients can

	Doxorubicin group (n=228)	Doxorubicin and ifosfamide group (n=227)
Progression of disease or death caused by progressive disease	95 (42%)	47 (21%)
Toxic effect (including toxic death)	6 (3%)	40 (18%)
Toxic death	5 (2%)	2 (1%)
Patient's refusal (not related to toxic effects)	4 (2%)	10 (4%)
Intercurrent death (not related to malignant disease or toxic effects)	4 (2%)	1 (<1%)
Other	12 (5%)	11 (5%)

Data are n (%).

Table 4: **Reasons for discontinuation of treatment**

	Doxorubicin group (n=223)	Doxorubicin and ifosfamide group (n=224)
Neutropenia	83 (37%)	93 (42%)
Leucopenia	40 (18%)	97 (43%)
Febrile neutropenia	30 (13%)	103 (46%)
Anaemia	10 (4%)	78 (35%)
Thrombocytopenia	1 (<1%)	75 (33%)

Data are n (%).

Table 5: **Grade 3–4 adverse events**

	Doxorubicin group (n=215)	Doxorubicin and ifosfamide group (n=210)
Surgery	44 (20%)	43 (20%)
Chemotherapy	136 (63%)	134 (64%)
Doxorubicin	12 (6%)	27 (13%)
Epirubicin	3 (1%)	1 (<1%)
Ifosfamide	99 (46%)	32 (15%)
Trofosfamide	6 (3%)	13 (6%)
Trabectedin	33 (15%)	37 (18%)
Docetaxel	25 (12%)	34 (16%)
Paclitaxel	5 (2%)	6 (3%)
Gemcitabine	32 (15%)	40 (19%)
Dacarbazine	7 (3%)	18 (9%)
Temozolomide	0 (0%)	1 (<1%)
Pazopanib	14 (7%)	14 (7%)
Eribulin	7 (3%)	11 (5%)
Etoposide	8 (4%)	11 (5%)

Data are n (%).

Table 6: **Post-protocol treatment**

Panel: Research in context

Systematic review

We searched PubMed for reports published in English from Jan 1, 1983, to Jan 1, 2014, for all randomised trials assessing dose intensification for treatment of soft-tissue sarcoma with the terms: "randomis(z)ed", "trial(s)", "advanced", "soft tissue", "sarcoma(s)", "ifosfamide", and "doxorubicin". We found eight randomised trials[20–27] and two meta-analyses.[28,29] Our search also returned single group and randomised phase 2 trials of higher dose treatment. Combination treatment has been shown to improve the proportion of patients who responded and progression-free survival but not overall survival in some, but not all trials.[22,25,26]

Interpretation

In our study both doxorubicin and ifosfamide doses were higher than those used in previous randomised trials. However, we did not show an improvement in overall survival. If the goal of treatment is disease control, doxorubicin alone remains an appropriate treatment but combination treatment can be justified if tumour shrinkage is desired, either to relieve symptoms or before another intervention. The lack of improvement in overall survival shows the need for better treatments for advanced soft tissue sarcoma.

tolerate intensive combination treatment, the regimen we used is very myelosuppressive, therefore our data cannot be extrapolated to patients older than 60 years.

These data should also be considered in the context of the diversification of chemotherapy and other systemic treatment that is taking place in the management of soft-tissue sarcoma. Individual sarcoma subtypes are being treated increasingly differently; for instance, paclitaxel for angiosarcoma,[6] gemcitabine plus docetaxel for leiomyosarcoma and undifferentiated pleomorphic sarcoma,[8,9] and ifosfamide being more favoured for synovial sarcoma and less so for leiomyosarcoma.[30] This trend might explain why fewer than half the patients in the doxorubicin only group later received ifosfamide as second-line treatment.

The results of our study are important in relation to other studies comparing doxorubicin with a combination of doxorubicin and an alkylating drug, for example, a phase 3 trial of palifosfamide, the results of which were presented at the European Cancer Congress 2013 (ClinicalTrials.gov NCT00718484).[31] The combination treatment did not improve progression-free survival. An ongoing study is comparing doxorubicin with doxorubicin plus the hypoxia-activated alkylating drug TH-302 (ClinicalTrials.gov NCT01440088) with a primary endpoint of overall survival. Pazopanib has recently been approved for the treatment of soft-tissue sarcoma on the basis of its effect on progression-free survival.[32] Nevertheless, an urgent need still exists for treatment that improves survival in patients with advanced disease.

Contributors

IJ wrote the protocol, reviewed all the case record forms for eligibility and protocol violations, recruited patients, and wrote and edited the report with SL. JV, HG, JTH, PS, J-YB, JMK, JS, JW, PH, AK-H, TA, and WTAvdG recruited patients, and reviewed and revised the report. CH, SL, and SM work at EORTC on project management and statistical support. CF, PCWH, APdT reviewed cases and reviewed the report. All authors reviewed the final version of the report.

Declaration of interests

We have no competing interests.

Acknowledgments

We thank Anne Kirkpatrick and the other staff at EORTC headquarters who contributed to the success of the trial. We are grateful to all the patients who took part, and their relatives, and thank the participating centres who worked on the study, including P Woll (Weston Park Hospital, Sheffield, UK), D Stark and M Marples (St James's Hospital, Leeds, UK), M Leahy (Christie Hospital, Manchester, UK), R D Issels and L Lindner (Klinikum der Universität München, Munich, Germany), M Verrill (Newcastle General Hospital, Newcastle-upon-Tyne, UK), C M Wendtner (University of Cologne, Cologne, Germany), V Gruenwald (Med Hochsch Hannover, Hannover, Germany), G Folprecht (Universitätsklinikum Carl Gustav Carus, Dresden, Germany), A K L Reynders (University Medical Center Groningen, Groningen, Netherlands), T Gil (Hôpital Universitaire, Bordet-Erasme, Brussels, Belgium), I Hennig (Nottingham General Hospital, Nottingham, UK), F Cowie and J D White (Gartnavel General Hospital, Glasgow, UK), O S Nielsen (Aarhus University Hospital, Aarhus, Denmark), J Vermorken and J Van Den Brande (The Antwerp University Hospital, Antwerp, Belgium), S Leyvraz (CHU Vaudois, Lausanne, Switzerland), J Baselga (Hospital de Vall d'Hebron, Barcelona, Spain), A Casado Herraez (San Carlos University Hospital, Madrid, Spain), D Cameron (Western General Hospital, Edinburgh, UK), D Spooner (Queen Elisabeth Hospital, Birmingham, UK), S Bauer (University of Duisburg-Essen, Essen, Germany), S Rorke (Dr Bliss Murphy Centre, St John's, NL, Canada), R Tozer (Juravinski Cancer Centre, Hamilton, ON, Canada), J-W Henning (South Medical Clinic, Calgary, AB, Canada), G Mechtersheimer (Universitätsklinik Heidelberg, Heidelberg, Germany), S Daugaard (University of Copenhagen, Copenhagen, Denmark), R Sciot (UZ Leuven, Leuven, Belgium), and F Collin (CGFL Dijon, Dijon, France). We acknowledge NHS funding to the Royal Marsden/ICR National Institute for Health Research Biomedical Research Centre and researchers at the NIHR University College London Hospital's Biomedical Research Centre. This study was supported by a donation from Cancer Research UK through the EORTC Charitable Trust. The EORTC received financial support from Amgen for the cost of pegfilgrastim. The contribution of NCIC Clinical Trials Group was supported by the Canadian Cancer Society Research Institute (grant 021039).

References

1 Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet* 2004; **364:** 1127–34.

2 Blay JY, El Sayadi H, Thiesse P, Garret J, Ray-Coquard I. Complete response to imatinib in relapsing pigmented villonodular synovitis/tenosynovial giant cell tumor (PVNS/TGCT). *Ann Oncol* 2008; **19:** 821–22.

3 Rutkowski P, Van Glabbeke M, Rankin CJ, et al, and the European Organisation for Research and Treatment of Cancer Soft Tissue/Bone Sarcoma Group, and the Southwest Oncology Group. Imatinib mesylate in advanced dermatofibrosarcoma protuberans: pooled analysis of two phase II clinical trials. *J Clin Oncol* 2010; **28:** 1772–91.

4 Wagner AJ, Malinowska-Kolodziej I, Morgan JA, et al. Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. *J Clin Oncol* 2010; **28:** 835–40.

5 Karavasilis V, Seddon BM, Ashley S, Al-Muderis O, Fisher C, Judson I. Significant clinical benefit of first-line palliative chemotherapy in advanced soft-tissue sarcoma: retrospective analysis and identification of prognostic factors in 488 patients. *Cancer* 2008; **112:** 1585–91.

6 Penel N, Bui BN, Bay JO, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. *J Clin Oncol* 2008; **26:** 5269–74.

7 Skubitz KM, Haddad PA. Paclitaxel and pegylated-liposomal doxorubicin are both active in angiosarcoma. *Cancer* 2005; **104:** 361–66.

8 Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. *Gynecol Oncol* 2008; **109:** 329–34.

9 Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002. *J Clin Oncol* 2007; **25:** 2755–63.

10 van Oosterom AT, Mouridsen HT, Nielsen OS, et al, and the EORTC Soft Tissue and Bone Sarcoma Group. Results of randomised studies of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) with two different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients. *Eur J Cancer* 2002; **38:** 2397–406.

11 Patel SR, Vadhan-Raj S, Burgess MA, et al. Results of two consecutive trials of dose-intensive chemotherapy with doxorubicin and ifosfamide in patients with sarcomas. *Am J Clin Oncol* 1998; **21:** 317–21.

12 Reichardt P, Tilgner J, Hohenberger P, Dörken B. Dose-intensive chemotherapy with ifosfamide, epirubicin, and filgrastim for adult patients with metastatic or locally advanced soft tissue sarcoma: a phase II study. *J Clin Oncol* 1998; **16:** 1438–43.

13 Leyvraz S, Zweifel M, Jundt G, et al, and the Swiss Group for Clinical Cancer Research. Long-term results of a multicenter SAKK trial on high-dose ifosfamide and doxorubicin in advanced or metastatic gynecologic sarcomas. *Ann Oncol* 2006; **17:** 646–51.

14 Van Glabbeke M, Verweij J, Judson I, Nielsen OS, and the EORTC Soft Tissue and Bone Sarcoma Group. Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas. *Eur J Cancer* 2002; **38:** 543–49.

15 Guillou L, Coindre JM, Bonichon F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. *J Clin Oncol* 1997; **15:** 350–62.

16 Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000; **92:** 205–16.

17 WHO. Handbook for reporting results for cancer treatment. Geneva: World Health Organization, 1979.

18 Cancer Therapy Evaluation Program. Common Toxicity Criteria, version 2.0. DCTD, NCI, NIH, DHHS, 1998.

19 Van Glabbeke M, Van Oosterom AT, Oosterhuis JW, et al. Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2,185 patients treated with anthracycline-containing first-line regimens—A European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. *J Clin Oncol* 2002; **7:** 821–28.

20 Santoro A, Tursz T, Mouridsen H, et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *J Clin Oncol* 1995; **13:** 1537–45.

21 Edmonson JH, Ryan LM, Blum RH, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. *J Clin Oncol* 1993; **11:** 1269–75.

22 Antman K, Crowley J, Balcerzak SP, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. *J Clin Oncol* 1993; **11:** 1276–85.

23 Worden FP, Taylor JM, Biermann JS, et al. Randomized phase II evaluation of 6 g/m² of ifosfamide plus doxorubicin and granulocyte colony-stimulating factor (G-CSF) compared with 12 g/m² of ifosfamide plus doxorubicin and G-CSF in the treatment of poor-prognosis soft tissue sarcoma. *J Clin Oncol* 2005; **23:** 105–12.

24 Fayette J, Penel N, Chevreau C, et al. Phase III trial of standard versus dose-intensified doxorubicin, ifosfamide and dacarbazine (MAID) in the first-line treatment of metastatic and locally advanced soft tissue sarcoma. *Invest New Drugs* 2009; **27:** 482–89.

25 Le Cesne A, Judson I, Crowther D, et al. Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: A trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. *J Clin Oncol* 2000; **18:** 2676–84.

26 Maurel J, López-Pousa A, de Las Peñas R, et al. Efficacy of sequential high-dose doxorubicin and ifosfamide compared with standard-dose doxorubicin in patients with advanced soft tissue sarcoma: an open-label randomized phase II study of the Spanish group for research on sarcomas. *J Clin Oncol* 2009; **27:** 1893–98.

27 Bui-Nguyen B, Ray-Coquard I, Chevreau C, et al, and the GSF-GETO French Sarcoma Group. High-dose chemotherapy consolidation for chemosensitive advanced soft tissue sarcoma patients: an open-label, randomized controlled trial. *Ann Oncol* 2012; **23:** 777–84.

28 Verma S, Younus J, Stys-Norman D, Haynes AE, Blackstein M, and the Sarcoma Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Dose-intensive chemotherapy with growth factor or autologous bone marrow/stem cell transplant support in first-line treatment of advanced or metastatic adult soft tissue sarcoma: a systematic review. *Cancer* 2008; **112:** 1197–205.

29 Verma S, Younus J, Stys-Norman D, Haynes AE, Blackstein M, and the Members of the Sarcoma Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. Meta-analysis of ifosfamide-based combination chemotherapy in advanced soft tissue sarcoma. *Cancer Treat Rev* 2008; **34:** 339–47.

30 Sleijfer S, Ouali M, van Glabbeke M, et al. Prognostic and predictive factors for outcome to first-line ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas: an exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG). *Eur J Cancer* 2010; **46:** 72–83.

31 Ryan CW, Schoffski P, Merimsky O, et al. PICASSO 3: a phase 3 international randomized double blind placebo-controlled study of doxorubicin plus palifosfamide vs. doxorubicin plus placebo for patients in first-line for metastatic soft tissue sarcoma. *Eur J Cancer* 2013; **49** (suppl 2): abstr 3802,S876.

32 van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012; **379:** 1879–86.