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Predictive and prognostic factors associated with soft tissue sarcoma response to chemotherapy: a subgroup analysis of the European Organisation for the Research and Treatment of Cancer 62012 study

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Abstract

Background: The European Organisation for Research and Treatment of Cancer (EORTC) 62012 study was a phase III trial of doxorubicin versus doxorubicin-ifosfamide chemotherapy in 455 patients with advanced soft tissue sarcoma (STS). Analysis of the main study showed that combination chemotherapy improved tumour response and progression free survival, but differences in overall survival (OS) were not statistically significant. We analysed factors prognostic for tumour response and OS, and assessed histological subgroup and tumour grade as predictive factors to identify patients more likely to benefit from combination chemotherapy.

Methods: Central pathology review was performed by six reference pathologists. Gender, age, performance status, time from first presentation with sarcoma to starting palliative chemotherapy, tumour grade, histological subgroup, and site of metastases were assessed as prognostic factors.

Results: 310 patients were included in this study. Discordance between local and central pathology opinion of tumour histology and tumour grade was observed in 98 (32%) and 122 (39%) cases respectively. In multivariate analysis, liposarcoma patients had improved tumour response compared to other histological subgroups, whilst patients with metastases other than lung, liver or bone had a poorer response (odds ratio (OR) 0.42, 95%CI 0.23 – 0.78; p=0.006). Patients with bone metastases had reduced OS (hazard ratio (HR) 1.56, 95%CI 1.16 – 2.09; p=0.003). By central pathology review, patients with undifferentiated pleomorphic sarcoma (UPS) had improved tumour response and OS with doxorubicin-ifosfamide compared to single-agent doxorubicin (OR 9.90, 95% CI 1.93 – 50.7 and HR 0.44, 95%CI 0.26 – 0.79 respectively). Grade III tumours had improved response with combination chemotherapy but there was no interaction between chemotherapy and grade on OS.

Conclusions: Prospective central pathology review of tumour histology should be integrated into future STS clinical trials. Doxorubicin-ifosfamide may be most appropriate for young, fit patients with advanced grade III UPS.

Keywords: Soft tissue sarcoma; chemotherapy; prognostic factors; predictive factors

Introduction

Soft tissue sarcomas (STS) are a group of rare aggressive tumours of mesenchymal origin, separated into over 50 different subtypes by histological and molecular classifications [1,2]. Chemotherapy is the mainstay of treatment for patients with unresectable metastatic disease, and is usually administered with palliative intent. Doxorubicin and ifosfamide have single-agent activity in STS [3,4], but the role of combination doxorubicin-ifosfamide has been less certain. The European Organisation for Research and Treatment of Cancer (EORTC) 62012 study was a multi-centre randomised phase III trial of first-line single-agent doxorubicin vs intensified doxorubicin-ifosfamide chemotherapy for young, fit patients with advanced intermediate or high grade STS [5]. Combination chemotherapy was associated with a significantly higher tumour response rate (complete + partial response, 26% vs 14%; $p<0.0006$) and improved progression free survival (PFS, hazard ratio (HR) 0.74, 95% confidence intervals (CI) 0.60 – 0.90; $p=0.003$), but overall survival (OS) was not significantly different (HR 0.83, 95% CI 0.67 – 1.03; $p=0.076$). Furthermore, combination chemotherapy was associated with significantly more toxicity (Grade 3-4 febrile neutropenia 46% vs 13%; $p<0.0001$). The study authors concluded that single-agent doxorubicin was appropriate for the majority of patients with advanced STS, however combination chemotherapy was justified for select patients in whom the primary aim of treatment was tumour shrinkage, to alleviate symptoms or to enable local disease control by subsequent surgery or radiotherapy.

A previous meta-analysis of seven heterogeneous EORTC-led clinical trials of first-line anthracycline-based chemotherapy for advanced STS reported younger age, good performance status (PS) and absence of liver metastases as prognostic of both improved tumour response to chemotherapy and OS [6]. Higher tumour grade and liposarcoma histology were other factors associated with improved tumour response to chemotherapy, whilst low

tumour grade and longer time elapsed from initial diagnosis of sarcoma to starting first-line chemotherapy were associated with improved OS.

We performed an analysis of the EORTC 62012 study to validate factors prognostic of tumour response to chemotherapy and OS in patients with advanced STS treated in a contemporary prospective randomised phase III clinical trial. We then explored histological subtype and tumour grade as predictive factors to identify patient subgroups more likely to benefit from treatment with combination chemotherapy.

Methods

Patients included in the subgroup analysis:

455 patients were recruited to the EORTC 62012 study (NCT00061984). The detailed eligibility criteria for the EORTC 62012 study have previously been published [5], including age ≤60 years, WHO performance status (PS) 0 or 1, and intermediate or high grade STS by local pathology opinion. Patients who received at least one cycle of chemotherapy were eligible for the subgroup analysis. A central pathology review of tumour histology and tumour grade was performed by six expert STS pathologists according to the World Health Organisation 2013 classification of tumours of soft tissue and bone [1] and the French Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) system [7] respectively. Cases without central pathology review, or without sarcoma histology, or where tumour grade was low or not assessable by central pathology review, or who did not meet other eligibility criteria for the main study were excluded (figure 1). The study population thereby consisted of 310 patients with characteristics similar to the main study population (table 1).

Histological subtypes were pooled for analysis into liposarcoma, leiomyosarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma (UPS) or 'other' subgroups. Gender, age, PS, time elapsed from initial presentation with sarcoma to starting palliative chemotherapy, tumour grade, histological subgroup, and site of metastases (liver, lung, bone and 'other') were assessed as factors prognostic for tumour response to chemotherapy and OS. Patients were included in the prognostic factor analysis based on central pathology review.

Histological subgroup and tumour grade were then assessed as factors predictive of improved tumour response and OS with combination chemotherapy. In this exploratory analysis,

histological subgroup and tumour grade were analysed according to both local and central pathology assignment.

Statistics:

Response to chemotherapy was reported based on local investigator assessment according to RECIST 1.0 [8]. Overall survival was computed from the date of randomization in the study to the date of death. Patients still alive at the time of the analysis were censored at their last follow-up date or the clinical trial cut-off date, whichever occurred first. Analyses for response rate (complete + partial response) were performed using logistic regression; analyses for overall survival were performed using Cox regression models. Factors included in the final multivariate models were identified using stepwise selection. A significance level of 0.15 was required to include a factor in the multivariate model, and a significance level of 0.05 was required for a factor to stay in the model.

Results

Central pathology review of tumour histology was available for 354/455 cases (78%). Discordance with local assessment was observed in 118 cases (33%), including six patients who did not have STS histology on central review. Central pathology review of tumour grade was available for 339/455 cases (75%). Discordance with local assessment was observed in 141 cases (42%). After excluding patients that failed other eligibility criteria, 310 patients were included in the subgroup analysis. Of these 310 patients, discordance between local and central pathology assessment of tumour histology and tumour grade was observed in 98 (32%) and 122 (39%) cases respectively. Consistent with the main study results, combination chemotherapy was associated with improved tumour response (odds ratio (OR) 2.44, 95% CI 1.38 – 4.31; p=0.002), but OS was not significantly different (HR 0.82, 0.64 – 1.04; p=0.105).

Prognostic factor analysis:

In multivariate analysis, gender, age, PS, time from first presentation with sarcoma to starting palliative chemotherapy, tumour grade, histological subgroup, and sites of metastases were assessed as potential factors prognostic for tumour response to chemotherapy and OS. Central pathology review of histology and tumour grade were used for this analysis.

In both univariate and multivariate analysis, liposarcoma histology and 'other' metastatic disease sites were prognostic for tumour response to chemotherapy (table 2). Patients with liposarcoma had improved tumour response to chemotherapy compared to other histological subgroups (overall p=0.014), whilst patients with metastases at sites other than lung, liver or bone had poorer tumour response to chemotherapy (OR 0.42, 95% CI 0.23 – 0.78; p=0.006). 'Other' metastatic disease sites included lymph node metastases (92 cases), skin metastases (9 cases) and other soft tissue metastases (77 cases). Grade III tumours were associated with

improved tumour response to chemotherapy, but this was not statistically significant (OR 1.43, 95% CI 0.76 – 2.67).

In univariate analysis, PS 1 (HR 1.37, 95% CI 1.06 – 1.77; p=0.017), shorter time from initial presentation with sarcoma to starting palliative chemotherapy (HR 1.49, 95% CI 1.08 – 2.07; p=0.014), and presence of bone metastases (HR 1.44, 95% CI 1.00 – 2.07; p=0.052) were associated with reduced OS. However, only bone metastases remained statistically significant (HR 1.56, 95% CI 1.16 – 2.09; p=0.003) in the final multivariate model (table 3).

Predictive factor analysis:

Tumour grade (grade II or III) and histological subtype, grouped into liposarcoma, leiomyosarcoma, synovial sarcoma, UPS, or 'other', were assessed as predictive factors. Outcomes differed depending on local or central pathology assignment of histological subtype (table 4). By local pathology assessment of histology, synovial sarcomas and 'other' subgroups had a higher response rate with combination chemotherapy compared to single-agent doxorubicin (43.5% vs 11.1% (OR 6.15, 95% CI 1.43 – 26.39) and 29.0% vs 10.5% (OR 3.48, 95% CI 1.27 – 9.53) for synovial sarcoma and 'other' respectively), whilst tumour response rates for liposarcoma, leiomyosarcoma and UPS subgroups did not differ significantly by treatment arm. In contrast, by central pathology assessment, the UPS subgroup had a higher response rate with combination chemotherapy than with single-agent doxorubicin (42.3% vs 6.9% (OR 9.90, 95% CI 1.93 – 50.7)), but response did not differ significantly between treatment arms for liposarcoma, leiomyosarcoma, synovial sarcoma or 'other' subgroups. Analysis of OS by local pathology assessment showed no interaction between histological subgroup and treatment arm, whilst patients with UPS by central pathology review had improved OS with combination chemotherapy compared with single-agent doxorubicin (HR 0.44, 95% CI 0.26 – 0.79) (figure 2).

Irrespective of local or central pathology assessment, grade III tumours had an improved response rate with combination chemotherapy compared with single-agent doxorubicin (OR 2.93, 95% CI 1.30 – 6.61 and 3.64, 95% CI 1.72 – 7.70 by local and central pathology assessment respectively). Response rate in grade II tumours by either local or central pathology assessment did not differ significantly by treatment arm. No interaction between treatment arm and tumour grade was identified in OS analysis, irrespective of local or central pathology assessment of grade.

Discussion

We observed a substantial discordance between local pathology assessment and central pathology expert review of histological subtype and tumour grade. This degree of discordance is consistent with levels reported by other STS studies [9-13]. STS pathology is highly complex, and the classifications of STS subtypes are constantly evolving. Despite the growing role of molecular pathology to facilitate diagnosis, the identification of STS subtypes still largely relies on interpretation of tumour morphology and immunohistochemistry. Central pathology review therefore fulfils an important role in verifying the diagnosis. In contrast to local pathology opinion, which may be refined by access to additional tumour samples and clinical and radiological correlates, central pathology assessment was wholly dependent on the specimen submitted for review. As STS tumours contain areas of heterogeneity, this explains some of the discordance observed between local and central pathology opinions.

The eligibility criteria of previous clinical trials in STS frequently included patients with a variety of different histological subtypes. However, as treatments of individual subtypes are progressively refined, clinical trials increasingly recruit STS patients with specific histological subtypes. The EORTC 62043 study, a single-arm phase II trial of pazopanib in patients with advanced STS for example, assessed treatment response in four histological cohorts of STS (leiomyosarcoma, liposarcoma, synovial sarcoma and 'others') [14]. On the basis of this study, patients with liposarcoma were excluded from the subsequent phase III PALETTE trial [15]. Different conclusions could be drawn from our subgroup analysis of histological subtype as a predictive factor of response to combination chemotherapy, dependent on whether local pathology or central pathology assessment of tumour histology was used. This analysis was exploratory, and was limited by small numbers of patients in each histological subgroup, but it highlights the importance of accurate pathology

classification in STS studies, and suggests a role for incorporating mandatory prospective central pathology review into future trial protocols. This should become possible in practice as shared digital platforms become increasingly common.

Our analysis suggested that UPS, synovial sarcoma, and 'other' histological subtypes were most likely to respond to treatment with combination chemotherapy. The histological subgroup labelled 'other' encompassed a pooled collection of rarer STS subtypes with diverse pathologies. Together, this subgroup represented a third (104/310) of all patients included in this analysis, which individually were too infrequent to be analysed separately. Only UPS by central review classification had improved OS with combination chemotherapy. Interestingly, a contemporary study of peri-operative epirubicin + ifosfamide chemotherapy in localised high-risk soft tissue sarcomas of the trunk and extremities also reported improved OS outcomes in UPS compared to other histological subtypes [16]. The lack of OS advantage with combination chemotherapy in synovial sarcoma and 'other' subtypes despite improved tumour response rates is consistent with a separate analysis of the EORTC 62012 study, which demonstrated that the absence of tumour progression and not the extent of disease remission defines prognosis in STS [17]. Synovial sarcomas are considered to be chemosensitive tumours. Previous studies have suggested that synovial sarcomas have higher responses rates to chemotherapy than other STS subtypes, including improved response rates to regimens containing ifosfamide [18]. UPS are aggressive high grade tumours with no discernable histological differentiation [19]. They are diagnosed by exclusion of other pleomorphic subtypes, including leiomyosarcoma and liposarcoma. Samples identified as UPS on central pathology review therefore include poorly differentiated STS subtypes, which have been re-classified on the basis of the submitted specimen. Such poorly differentiated tumours may have aggressive tumour biology that benefit more from combination chemotherapy. This would support the parallel observation that high grade tumours were

more likely to respond to combination chemotherapy than intermediate grade lesions, although tumour grade did not influence OS.

We used central pathology assessment of tumour histology and tumour grade for the prognostic factor analysis, as this had been undertaken by a small panel of expert sarcoma pathologists. The prognostic factor analysis identified that liposarcoma histology was associated with improved tumour response rate compared to other histological subgroups. Previous studies have also suggested that liposarcomas are associated with a higher response rate [6]. The liposarcoma subgroup consisted of disparate subtypes including dedifferentiated liposarcoma, pleomorphic liposarcoma and myxoid liposarcoma. Myxoid liposarcomas are considered chemosensitive, whilst dedifferentiated liposarcomas are considered less sensitive to chemotherapy. Unfortunately, the specific liposarcoma subtype present was not recorded centrally, and analysis to refine tumour response rate by liposarcoma subtype was not possible, although the small number of liposarcoma patients included in the study (25 cases by central pathology review) would have limited more detailed analysis.

PS is a well-established prognostic factor [20]. The EORTC 62012 study recruited patients aged ≤60 with WHO PS 0 or 1. It is therefore striking that PS was prognostic of OS despite eligibility criteria restricting the study population to young fit patients. Time between initial diagnosis of sarcoma and commencing palliative chemotherapy has previously been identified as prognostic [6]. Patients with a shorter time to starting palliative chemotherapy from initial diagnosis (3 – 12 months) had worse OS. This cohort consisted of patients with poor tumour biology and rapidly progressive disease. A longer interval between initial diagnosis and starting chemotherapy (>12 months) implied less aggressive disease and was associated with improved OS, whilst patients presenting with metastatic disease (interval from initial diagnosis <3 months) represented a mix of these two patient populations. The presence of bone metastases was the only factor prognostic for OS in the final multivariate

model. Bone metastases were reported in 44/310 (14.1%) patients included in the subgroup analysis. A previous multi-centre retrospective analysis identified bone metastases as a poor prognostic feature, and suggested routine use of bisphosphonate therapy for patients with metastatic bone disease to delay the onset of skeletal related events (e.g. pathological fracture, spinal cord compression, or hypercalcaemia) [21].

In summary, we performed an analysis of the EORTC 62012 study, a large phase III trial of single-agent doxorubicin versus a doxorubicin-ifosfamide combination for advanced STS. This subgroup analysis highlights the importance of the sarcoma pathologist to the assessment of clinical trial outcomes. Single-agent doxorubicin remains standard of care first-line chemotherapy for patients with advanced soft tissue sarcoma. However, combination doxorubicin-ifosfamide is indicated for selected patients, and this analysis suggests combination treatment may be most appropriate to consider in patients ≤60 yrs old, PS 0 or 1, with poorly differentiated, grade III tumours including UPS.

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Conflict of interest statement

None declared.

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Figure 1: Subgroup analysis flow chart

Figure 2: Interaction of histological subtype with treatment on overall survival (A: central pathology review; B: local pathology review)

Figure 1:

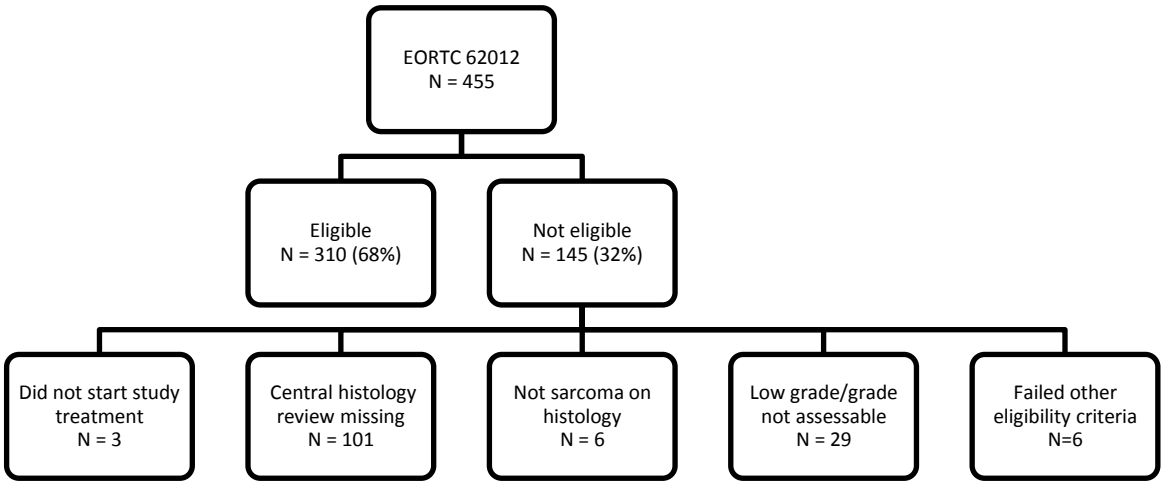
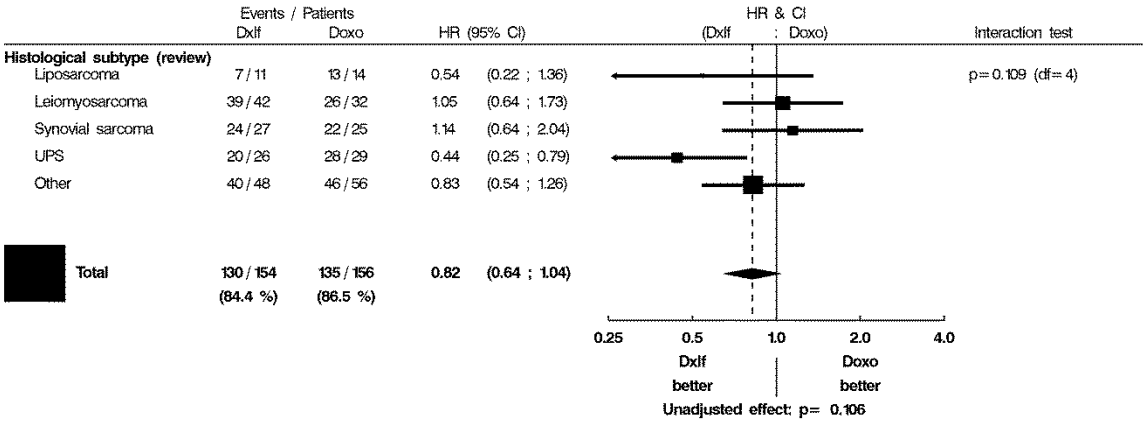

EORTC 62012
N = 455
Eligible
N = 310 (68%)
Not eligible
N = 145 (32%)
Did not start study treatment
N = 3
Central histology review missing
N = 101
Not sarcoma on histology
N = 6
Low grade/grade not assessable
N = 29
Failed other eligibility criteria
N=6

Figure 2:

A.


Events / Patients
Dxlf
Doxo
HR (95% CI)
HR & CI
(Dxlf : Doxo)
Interaction test
Histological subtype (review)
Liposarcoma 7 / 11 13 / 14 0.54 (0.22 ; 1.36)
Leiomyosarcoma 39 / 42 26 / 32 1.05 (0.64 ; 1.73)
Synovial sarcoma 24 / 27 22 / 25 1.14 (0.64 ; 2.04)
UPS 20 / 26 28 / 29 0.44 (0.25 ; 0.79)
Other 40 / 48 46 / 56 0.83 (0.54 ; 1.26)
p = 0.109 (df = 4)
Total 130 / 154 (84.4 %) 135 / 156 (86.5 %) 0.82 (0.64 ; 1.04)
0.25
0.5
1.0
2.0
4.0
Dxlf better
Doxo better
Unadjusted effect: p = 0.106

B.

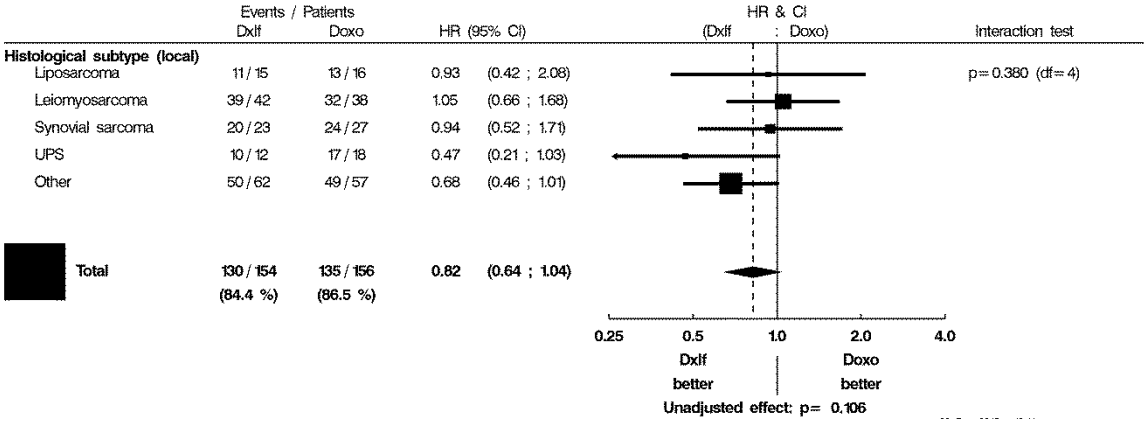

Events / Patients
Dxlf
Doxo
HR (95% CI)
HR & CI
(Dxlf : Doxo)
Interaction test
Histological subtype (local)
Liposarcoma 11 / 15 13 / 16 0.93 (0.42 ; 2.08)
Leiomyosarcoma 39 / 42 32 / 38 1.05 (0.66 ; 1.68)
Synovial sarcoma 20 / 23 24 / 27 0.94 (0.52 ; 1.71)
UPS 10 / 12 17 / 18 0.47 (0.21 ; 1.03)
Other 50 / 62 49 / 57 0.68 (0.46 ; 1.01)
p = 0.380 (df = 4)
Total 130 / 154 (84.4 %) 135 / 156 (86.5 %) 0.82 (0.64 ; 1.04)
0.25
0.5
1.0
2.0
4.0
Dxlf better
Doxo better
Unadjusted effect: p = 0.106

Table 1: Patient characteristics

	Analysis population	
	All patients (N=455)	**All eligible patients (N=310)**
	N (%)	**N (%)**
Treatment		
Doxorubicin	228 (50.1)	156 (50.3)
Doxorubicin + ifosfamide	227 (49.9)	154 (49.7)
Gender		
Male	217 (47.7)	148 (47.7)
Female	238 (52.3)	162 (52.3)
Age		
< 40 yrs	112 (24.6)	73 (23.5)
40-49 yrs	148 (32.5)	94 (30.3)
>= 50 yrs	195 (42.9)	143 (46.1)
Performance status		
0	252 (55.4)	176 (56.8)
1	201 (44.2)	134 (43.2)
2	2 (0.4)	0 (0.0)
Time since initial diagnosis		
< 3 m	156 (34.3)	95 (30.6)
3-12 m	128 (28.1)	96 (31.0)
> 12 m	171 (37.6)	119 (38.4)
Tumor grade (*central review*)		
I	18 (4.0)	0 (0.0)
II	131 (28.8)	128 (41.3)
III	190 (41.8)	182 (58.7)
Not assessed/Unknown	116 (25.5)	0 (0.0)
Histological subtype (*central review*)		
Liposarcoma	34 (7.5)	25 (8.1)
Leiomyosarcoma	85 (18.7)	74 (23.9)
Synovial sarcoma	54 (11.9)	52 (16.8)
UPS	58 (12.7)	55 (17.7)
Other	117 (25.7)	104 (33.5)
Not a sarcoma	6 (1.3)	0 (0.0)
Missing	101 (22.2)	0 (0.0)
Liver metastases	80 (17.6)	53 (17.1)
Lung metastases	310 (68.1)	227 (73.2)
Bone metastases	65 (14.3)	44 (14.2)
Other metastases	360 (79.1)	239 (77.1)

Table 2: Prognostic factors for best overall response (CR + PR) – multivariate analysis stratified by treatment

		Full Multivariate Model		Reduced Model stepwise selection	
Parameter	**Levels**	**Odds Ratio (95% CI)**	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Gender	Male	1.00	0.223		
	Female	1.47 (0.79, 2.74)			
Age	< 40 yrs	1.00	0.752		
	40-49 yrs	1.14 (0.49, 2.67)			
	>= 50 yrs	0.87 (0.37, 2.05)			
Performance status	0	1.00	0.907		
	1	0.96 (0.53, 1.76)			
Time since initial diagnosis	< 3 months	1.00	0.728		
	3-12 months	0.76 (0.34, 1.66)			
	> 12 months	0.98 (0.46, 2.07)			
Histological grade	II	1.00	0.267		
(*central review*)	III	1.43 (0.76, 2.67)			
Histological subtype	Liposarcoma	1.00	**0.004**	1.00	**0.014**
(*central review*)	Leiomyosarcoma	0.14 (0.04, 0.45)		0.21 (0.08, 0.59)	
	Synovial sarcoma	0.19 (0.06, 0.63)		0.30 (0.11, 0.84)	
	UPS	0.20 (0.06, 0.62)		0.29 (0.10, 0.81)	
	Other	0.12 (0.04, 0.36)		0.19 (0.07, 0.50)	
Liver metastases	No	1.00	0.180		
	Yes	0.53 (0.21, 1.35)			
Lung metastases	No	1.00	0.140		
	Yes	1.85 (0.82, 4.19)			
Bone metastases	No	1.00	0.317		
	Yes	1.56 (0.65, 3.72)			
Other metastases	No	1.00	**0.020**	1.00	**0.006**
	Yes	0.44 (0.22, 0.88)		0.42 (0.23, 0.78)	

Table 3: Prognostic factor analysis for OS – multivariate stratified by treatment

		Full Multivariate Model		Reduced Model stepwise selection	
Parameter	**Levels**	**Hazard Ratio (95% CI)**	**P-value**	**Hazard Ratio (95% CI)**	**P-value**
Gender	Male	1.00	0.064		
	Female	0.78 (0.60, 1.01)			
Age	< 40 yrs	1.00	0.502		
	40-49 yrs	1.17 (0.80, 1.71)			
	>= 50 yrs	1.25 (0.86, 1.82)			
Performance status	0	1.00	**0.017**		
	1	1.37 (1.06, 1.77)			
Time since initial diagnosis	< 3 months	1.00	**0.014**		
	3-12 months	1.49 (1.08, 2.07)			
	> 12 months	0.99 (0.72, 1.35)			
Histological grade	II	1.00	0.240		
(*central review*)	III	1.17 (0.90, 1.50)			
Histological subtype	Liposarcoma	1.00	0.257		
(*central review*)	Leiomyosarcoma	1.78 (1.04, 3.02)			
	Synovial sarcoma	1.60 (0.90, 2.86)			
	UPS	1.77 (1.02, 3.07)			
	Other	1.74 (1.05, 2.90)			
Liver metastases	No	1.00	0.230		
	Yes	1.23 (0.88, 1.73)			
Lung metastases	No	1.00	0.712		
	Yes	1.06 (0.79, 1.42)			
Bone metastases	No	1.00	0.052	1.00	**0.003**
	Yes	1.44 (1.00, 2.07)		1.56 (1.16, 2.09)	
Other metastases	No	1.00	0.198		
	Yes	1.23 (0.90, 1.69)			

Table 4: Interaction of histological subtype on response to treatment (A: local pathology assessment;

B: central pathology assessment)

A.

Histological subtype (local)	Total (N=310) N (%)	Doxo Responders (N = 22) N (row %)	Total (N = 156) N (column %)	DxIf Responders (N = 44) N (row %)	Total (N = 154) N (column %)	OR (95% CI)
Liposarcoma	31 (10)	6 (37.5)	16 (10.3)	5 (33.3)	15 (9.7)	0.83 (0.19, 3.64)
Leiomyosarcoma	80 (26)	4 (10.5)	38 (24.4)	9 (21.4)	42 (27.3)	2.32 (0.65, 8.27)
Synovial sarcoma	50 (16)	3 (11.1)	27 (17.3)	10 (43.5)	23 (14.9)	6.15 (1.43, 26.39)
UPS	30 (10)	3 (16.7)	18 (11.5)	2 (16.7)	12 (7.8)	1.00 (0.14, 7.10)
Other	119 (38)	6 (10.5)	57 (36.5)	18 (29.0)	62 (40.3)	3.48 (1.27, 9.53)

B.

Histological subtype (central)	Total (N=310) N (%)	Doxo Responders (N = 22) N (row %)	Total (N = 156) N (column %)	DxIf Responders (N = 44) N (row %)	Total (N = 154) N (column %)	OR (95% CI)
Liposarcoma	25 (8)	7 (50.0)	14 (9.0)	5 (45.5)	11 (7.1)	0.83 (0.17, 4.06)
Leiomyosarcoma	74 (24)	4 (12.5)	32 (20.5)	8 (19.0)	42 (27.3)	1.65 (0.45, 6.05)
Synovial sarcoma	52 (17)	4 (16.0)	25 (16.0)	9 (33.3)	27 (17.5)	2.63 (0.69, 9.98)
UPS	55 (18)	2 (6.9)	29 (18.6)	11 (42.3)	26 (16.9)	9.90 (1.93, 50.7)
Other	104 (33)	5 (8.9)	56 (35.9)	11 (22.9)	48 (31.2)	3.03 (0.97, 9.47)