Retrospective studies in mesenchymal tumours: clinical implications for the future

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Survival of soft tissue sarcoma patients after completing six cycles of first-line anthracycline containing treatment:

an EORTC-STBSG database study

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Abstract

Introduction

Doxorubicin based chemotherapy is standard first line treatment for patients with soft tissue sarcoma. Currently several options to improve survival after doxorubicin-based chemotherapy are being studied. This study reports on survival after completing 6 cycles of doxorubicin containing first line treatment, which is important when designing studies trying to improve outcomes of first line treatment.

Methods

A retrospective database analysis was performed on 2045 patients from 12 EORTC sarcoma trials receiving first line doxorubicin-based chemotherapy for advanced soft tissue sarcoma in order to establish progression free survival and overall survival after completing 6 cycles of first line doxorubicin-based chemotherapy. Endpoints were overall survival and progression free survival. Factors studied were histologic subtype and type of doxorubicin chemotherapy.

Results

748 of 2045 patients (36.6%) received at least 6 cycles and did not progress during or at the end of chemotherapy. 475 of 2045 (23.2%) patients received exactly 6 cycles and did not progress during or at the end of chemotherapy. Median progression free survival after 6 cycles of doxorubicin-based chemotherapy was 4.2 months (95% confidence interval 3.7-4.8) and median overall survival 15.7 months (14.0-17.8). Significant differences in progression free survival were found between chemotherapy regimens, but not for overall survival.

These data are also reported for patients receiving 7 or more cycles of chemotherapy and for patients with 3 or more cycles of chemotherapy.

Conclusion

This large retrospective study is the first to report progression free survival and overall survival after completion of 6 cycles of first line doxorubicin containing chemotherapy. These results are important when designing new studies exploring for example maintenance therapy after doxorubicin-based chemotherapy. Approximately one third of all patients may qualify for maintenance therapy.

Introduction

Soft tissue sarcomas (STS) are a rare group of tumours comprising approximately 1% of all cancers and containing approximately 70 different histological entities.[1] Clinical behaviour differs between the various histological entities.[1] Surgery is the primary treatment for localized disease when resection is possible with the option of adding neo-adjuvant or adjuvant radiotherapy.[2] For patients with locally advanced and/or distant metastatic disease the goal of treatment is to prolong survival and treatment mainly consists of systemic treatment, e.g. cytotoxic drugs and tyrosine kinase inhibitors.[2]

The current first line chemotherapy consists of anthracycline based chemotherapy either as monotherapy or combination therapy.[3] Survival remains poor for patients presenting with incurable disease. Overall survival (OS) with doxorubicin monotherapy is approximately 12.8 months and with doxorubicin/ifosfamide combination therapy approximately 14.3 months.[3] More recent trials report slightly better median OS for doxorubicin monotherapy with 17.6 months (GeDDiS), 16.9 months (PICASSO III) and 19.0 months (SARC021).[4-6] In 2016, Tap *et al.* reported the results of a phase Ib/II trial adding olaratumab, a PDGFRα blocking monoclonal antibody, to doxorubicin.[7] The results of this study were promising with an increase in progression free survival (PFS) of 2.5 months and an impressive increase in median OS from 14.7 months to 26.5 months with the addition of olaratumab.[7] This improvement in OS resulted in an accelerated approval by the U.S. Food and Drug Administration and a conditional approval by the European Medical Agency. However, recently the results of the phase III study with olaratumab, ANNOUNCE (NCT02451943), were presented during the annual meeting of the ASCO 2019 and did not show a difference between doxorubicin/placebo and doxorubicin/olaratumab. Based on these results olaratumab was withdrawn from the market.[8]

Now, other treatment strategies have to be studied to increase the PFS and OS of STS patients including the addition of maintenance therapy after completing six cycles of doxorubicin. In order to assist in the design of maintenance studies it is important to have survival data of patients after completing six cycles of doxorubicin containing treatment and to understand the extent of the attrition in the number of patients available for study, indeed the percentage who could possibly benefit from maintenance therapy by not having progressed before completing 6 cycles of treatment. This study reports the OS data of study patients completing six cycles of anthracycline or anthracycline combination therapy in the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group trial database.

Methods

Patients

The European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group study database contains data from 12 trials studying doxorubicin alone or in combination with ifosfamide.[3,9–19] All but one study, included patients with locally advanced or metastatic STS. The study by Steward *et al.* only included patients with metastatic STS.[12] Patients with at least 1 cycle of treatment were considered for this study. Reasons for exclusion were previous treatment with chemotherapy either as adjuvant or palliative treatment, patients without data on progression and death and patients diagnosed with Gastrointestinal Stromal Tumour (GIST). Among these patients, we focused on patients who did not progress before the end of treatment. End of treatment was considered to be 21 days after the date of administration of the last treatment. (Supplementary figure 1) Analysis was done in three different subgroups: patients who received exactly 6 cycles of doxorubicin containing chemotherapy, patients with 7 or more cycles and patients with less than 6 cycles who stopped treatment for reasons other than progression.

The EORTC studies 62012, 62061, 62091, 62962 and 62971 had treatment regimens including a maximum number of 6 cycles of doxorubicin, 62941 7 cycles and the other studies aimed for a cumulative dose of 550 mg/m^2 of doxorubicin allowing for more if the ejection fraction remained within certain limits.

Endpoints

Endpoints were PFS and OS after completing treatment, because the aim of the study was to determine PFS and OS after completion of 6 cycles of doxorubicin containing treatment in patients who did not have progressive disease at that time point. PFS was defined as the time between end of treatment and progression or death. OS was defined as the time between end of treatment and death. Also calculated were PFS from date of randomisation to date of progression or death and OS from date of randomisation to date of death. Patients progressing between start of treatment and 21 days after the last administration date were not considered for the PFS and OS after treatment analysis, because only those patients who do not have progression before the start of maintenance treatment will qualify for maintenance treatment. Time on treatment was calculated from date of randomisation or registration and the end of treatment.

Covariates

Patients were grouped according to treatment *i.e.* doxorubicin 75mg/m^2 monotherapy, doxorubicin 50mg/m^2 combined with ifosfamide 5g/m^2, doxorubicin 75mg/m^2 combined with ifosfamide 5g/m^2 and doxorubicin 75mg/m^2 combined with ifosfamide 10g/m^2. The other covariate considered in this study was histologic subtype. If central pathology review was available the central pathology diagnosis was used, if it was not present the

local pathology diagnosis was used. Only histologic subtypes comprising more than ten percent of patients were considered for separate analysis.

Statistics

PFS and OS were calculated using the Kaplan Meier method. PFS and OS were compared using a cox proportional hazard model. Significance was set at p=0.05.

Results

In total, 2045 patients were included in this study. Almost 50% of patients were treated with doxorubicin 75 mg/m^2 as monotherapy; the other patients were treated with one of the combination regimens. (Supplementary Table 1 shows the distribution of patients according to study and treatment regimen. Supplementary Table 2 shows the number of treatment cycles by study.) Median time on treatment was 15 weeks, corresponding to a median number of 5 cycles. Of all patients, 43.7% of patients (894) were treated with 6 or more cycles of chemotherapy, 70.2% of patients were treated with 3 or more cycles. Five hundred fifty-five patients (27.1%) received exactly 6 cycles of chemotherapy. Median follow-up for all patients was 4.1 years (Inter quartile range (IQR) 2.5-6.5 years). Most of the patients receiving more than 6 cycles, were included in studies studying the doxorubicin 50 mg/m^2/ifosfamide 5 gram/m^2 regimen. (Supplementary table 1)

Of these patients with at least 6 cycles of treatment 748 patients (83.7% of all patients treated with 6 or more cycles) did not progress before or at the end of treatment. For exactly 6 cycles, 475 patients (85.6% of patients treated with exactly 6 cycles) did not progress before the end of treatment. Table 1 shows the percentage of patients considered for this study per treatment strategy.

Baseline characteristics

Table 2a/b and 3a/b and supplementary table 1a-d show the characteristics of the included patients. No important differences exist between the different groups. The most common histologic subtype was leiomyosarcoma (31%), followed by the no longer existing histologic entity malignant fibrous histiocytoma (MFH) (13%) and synovial sarcoma (10%). (Supplementary Table 3) As none of the other subtypes did comprise ten percent of the patients as an entity, these were considered together when histologic subtype was studied (also MFH was added to the miscellaneous group as this entity no longer exists; smaller subgroups would reduce the statistical power).

Table 1 Distribution of patients per treatment strategy and number of cycles

	Treatment				
	DOX 75 (N= 948)	**DOX 50 - IFO 5 (N=614)**	**DOX 75 – IFO 5 (N=266)**	**DOX 75 - IFO 10 (N=217)**	**Total (N=2045)**
Number of patients with <u>at least</u> 6 cycles	403 (42.5)	270 (44.0)	103 (38.7)	118 (54.4)	895 (43.7)
Progression before / at end of treatment	67 (16.6)	55 (20.4)	15 (14.6)	9 (7.6	146 (16.3)
No progression before / at end of treatment	336 (83.4)	215 (79.6)	88 (85.4)	109 (92.4)	748 (83.6)
Number of patients with <u>less than</u> 6 cycles	545 (57.4)	344 (56.0)	163 (61.3)	99 (45.6)	1151 (56.3)
Progression before / at end of treatment	312 (57.2)	175 (50.9)	52 (31.9)	28 (28.3)	567 (49.3)
No progression before / at end of treatment	233 (42.8)	168 (49.1)	111 (68.1)	71 (71.7)	584 (50.7)

Table 2a Baseline characteristics

	Less than 6 cycles			**Exactly 6 cycles**			**More than 6 cycles**		
	PD before end of treatment (N=567)	**No PD before end of treatment (N=584)**	**Total (N=1151)**	**PD before end of treatment (N=80)**	**No PD before end of treatment (N=475)**	**Total (N=555)**	**PD before end of treatment (N=66)**	**No PD before end of treatment (N=273)**	**Total (N=339)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Gender									
Male	273 (48.1)	284 (48.6)	557 (48.4)	45 (56.3)	226 (47.6)	271 (48.8)	26 (39.4)	139 (50.9)	165 (48.7)
Female	294 (51.9)	299 (51.2)	593 (51.5)	35 (43.8)	248 (52.2)	283 (51.0)	40 (60.6)	134 (49.1)	174 (51.3)

Table 2a Continued.

	Less than 6 cycles			Exactly 6 cycles			More than 6 cycles		
	PD before end of treatment (N=567)	No PD before end of treatment (N=584)	Total (N=1151)	PD before end of treatment (N=80)	No PD before end of treatment (N=475)	Total (N=555)	PD before end of treatment (N=66)	No PD before end of treatment (N=273)	Total (N=339)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Missing	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Age									
< 40 rs	122 (21.5)	124 (21.2)	246 (21.4)	26 (32.5)	125 (26.3)	151 (27.2)	18 (27.3)	80 (29.3)	98 (28.9)
40-50 yrs	137 (24.2)	122 (20.9)	259 (22.5)	20 (25.0)	115 (24.2)	135 (24.3)	11 (16.7)	64 (23.4)	75 (22.1)
50-60 yrs	164 (28.9)	170 (29.1)	334 (29.0)	19 (23.8)	148 (31.2)	167 (30.1)	13 (19.7)	73 (26.7)	86 (25.4)
>=60 yrs	134 (23.6)	156 (26.7)	290 (25.2)	13 (16.3)	85 (17.9)	98 (17.7)	16 (24.2)	49 (17.9)	65 (19.2)
Missing	10 (1.8)	12 (2.1)	22 (1.9)	2 (2.5)	2 (0.4)	4 (0.7)	8 (12.1)	7 (2.6)	15 (4.4)
Performance status									
PS 0	223 (39.3)	265 (45.4)	488 (42.4)	38 (47.5)	274 (57.7)	312 (56.2)	25 (37.9)	127 (46.5)	152 (44.8)
PS 1	275 (48.5)	265 (45.4)	540 (46.9)	34 (42.5)	189 (39.8)	223 (40.2)	32 (48.5)	120 (44.0)	152 (44.8)
PS 2+	67 (11.8)	51 (8.7)	118 (10.3)	8 (10.0)	11 (2.3)	19 (3.4)	9 (13.6)	24 (8.8)	33 (9.7)
Missing	2 (0.4)	3 (0.5)	5 (0.4)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.7)	2 (0.6)

Table 2b Baseline characteristics

	Exactly 6 cycles - no PD				
	Treatment				
	DOX 75 (N=223)	DOX 50-IFO 5 (N=80)	DOX 75-IFO 5 (N=63)	DOX 75-IFO 10 (N=109)	Total (N=475)
	N (%)	N (%)	N (%)	N (%)	N (%)
Gender					
Male	102 (45.7)	34 (42.5)	30 (47.6)	60 (55.0)	226 (47.6)
Female	121 (54.3)	45 (56.3)	33 (52.4)	49 (45.0)	248 (52.2)
Missing	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.2)
Age					
< 40 yrs	45 (20.2)	23 (28.8)	26 (41.3)	31 (28.4)	125 (26.3)
40-50 yrs	54 (24.2)	15 (18.8)	9 (14.3)	37 (33.9)	115 (24.2)
50-60 yrs	77 (34.5)	19 (23.8)	14 (22.2)	38 (34.9)	148 (31.2)
>=60 yrs	47 (21.1)	21 (26.3)	14 (22.2)	3 (2.8)	85 (17.9)
Missing	0 (0.0)	2 (2.5)	0 (0.0)	0 (0.0)	2 (0.4)
Performance status					
PS 0	132 (59.2)	39 (48.8)	38 (60.3)	65 (59.6)	274 (57.7)
PS 1	84 (37.7)	37 (46.3)	24 (38.1)	44 (40.4)	189 (39.8)
PS 2+	7 (3.1)	3 (3.8)	1 (1.6)	0 (0.0)	11 (2.3)
Missing	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.2)

Table 3a Tumour and treatment characteristics

	Less than 6 cycles			Exactly 6 cycles			More than 6 cycles		
	PD before end of treatment (N=567)	No PD before end of treatment (N=584)	Total (N=1151)	PD before end of treatment (N=80)	No PD before end of treatment (N=475)	Total (N=555)	PD before end of treatment (N=66)	No PD before end of treatment (N=273)	Total (N=339)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Histopathological grading									
Grade I and II	38 (6.7)	30 (5.1)	68 (5.9)	6 (7.5)	52 (10.9)	58 (10.5)	8 (12.1)	24 (8.8)	32 (9.4)
Grade III	331 (58.4)	366 (62.7)	697 (60.6)	46 (57.5)	331 (69.7)	377 (67.9)	33 (50.0)	152 (55.7)	185 (54.6)
Missing	198 (34.9)	188 (32.2)	386 (33.5)	28 (35.0)	92 (19.4)	120 (21.6)	25 (37.9)	97 (35.5)	122 (36.0)
Site of primary tumour									
Other	284 (50.1)	257 (44.0)	541 (47.0)	32 (40.0)	245 (51.6)	277 (49.9)	26 (39.4)	106 (38.8)	132 (38.9)
Extremities	129 (22.8)	143 (24.5)	272 (23.6)	27 (33.8)	152 (32.0)	179 (32.3)	17 (25.8)	73 (26.7)	90 (26.5)
Missing	154 (27.2)	184 (31.5)	338 (29.4)	21 (26.3)	78 (16.4)	99 (17.8)	23 (34.8)	94 (34.4)	117 (34.5)
Histology									
Leiomyosarcoma	192 (33.9)	180 (30.8)	372 (32.3)	23 (28.8)	128 (26.9)	151 (27.2)	25 (37.9)	79 (28.9)	104 (30.7)
Synovial sarcoma	32 (5.6)	59 (10.1)	91 (7.9)	10 (12.5)	71 (14.9)	81 (14.6)	6 (9.1)	29 (10.6)	35 (10.3)
Other	315 (55.6)	317 (54.3)	632 (54.9)	44 (55.0)	266 (56.0)	310 (55.9)	35 (53.0)	151 (55.3)	186 (54.9)

Table 3a Continued.

	Less than 6 cycles			Exactly 6 cycles			More than 6 cycles		
	PD before end of treatment (N=567)	No PD before end of treatment (N=584)	Total (N=1151)	PD before end of treatment (N=80)	No PD before end of treatment (N=475)	Total (N=555)	PD before end of treatment (N=66)	No PD before end of treatment (N=273)	Total (N=339)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Missing	28 (4.9)	28 (4.8)	56 (4.9)	3 (3.8)	10 (2.1)	13 (2.3)	0 (0.0)	14 (5.1)	14 (4.1)
Prior Surgery									
No surgery	60 (10.6)	57 (9.8)	117 (10.2)	10 (12.5)	19 (4.0)	29 (5.2)	3 (4.5)	25 (9.2)	28 (8.3)
Non optimal surgery	104 (18.3)	77 (13.2)	181 (15.7)	18 (22.5)	23 (4.8)	41 (7.4)	10 (15.2)	64 (23.4)	74 (21.8)
Complete surgery	155 (27.3)	128 (21.9)	283 (24.6)	13 (16.3)	66 (13.9)	79 (14.2)	35 (53.0)	106 (38.8)	141 (41.6)
Unknown	248 (43.7)	322 (55.1)	570 (49.5)	39 (48.8)	367 (77.3)	406 (73.2)	18 (27.3)	78 (28.6)	96 (28.3)
Prior radiotherapy									
No	435 (76.7)	390 (66.8)	825 (71.7)	58 (72.5)	279 (58.7)	337 (60.7)	43 (65.2)	191 (70.0)	234 (69.0)
Yes	119 (21.0)	171 (29.3)	290 (25.2)	19 (23.8)	153 (32.2)	172 (31.0)	23 (34.8)	82 (30.0)	105 (31.0)
Missing	13 (2.3)	23 (3.9)	36 (3.1)	3 (3.8)	43 (9.1)	46 (8.3)	0 (0)	0 (0)	0 (0)

Table 3a Continued.

	Less than 6 cycles			Exactly 6 cycles			More than 6 cycles		
	PD before end of treatment (N=567)	No PD before end of treatment (N=584)	Total (N=1151)	PD before end of treatment (N=80)	No PD before end of treatment (N=475)	Total (N=555)	PD before end of treatment (N=66)	No PD before end of treatment (N=273)	Total (N=339)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Primary site involved									
No	195 (34.4)	219 (37.5)	414 (36.0)	35 (43.8)	244 (51.4)	279 (50.3)	36 (54.5)	112 (41.0)	148 (43.7)
Yes	310 (54.7)	288 (49.3)	598 (52.0)	37 (46.3)	192 (40.4)	229 (41.3)	25 (37.9)	133 (48.7)	158 (46.6)
Missing	62 (10.9)	77 (13.2)	139 (12.1)	8 (10.0)	39 (8.2)	47 (8.5)	5 (7.6)	28 (10.3)	33 (9.7)
Metastatic Site involved									
No	79 (13.9)	99 (17.0)	178 (15.5)	10 (12.5)	49 (10.3)	59 (10.6)	10 (15.2)	45 (16.5)	55 (16.2)
Yes	426 (75.1)	408 (69.9)	834 (72.5)	62 (77.5)	387 (81.5)	449 (80.9)	51 (77.3)	200 (73.3)	251 (74.0)
Missing	62 (10.9)	77 (13.2)	139 (12.1)	8 (10.0)	39 (8.2)	47 (8.5)	5 (7.6)	28 (10.3)	33 (9.7)

Table 3b Tumour and treatment characteristics

Exactly 6 cycles - no PD					
	Treatment				
	DOX 75 (N=223)	DOX 50-IFO 5 (N=80)	DOX 75-IFO 5 (N=63)	DOX 75-IFO 10 (N=109)	Total (N=475)
	N (%)	N (%)	N (%)	N (%)	N (%)
Histopathological grading					
Grade I and II	26 (11.7)	12 (15.0)	8 (12.7)	6 (5.5)	52 (10.9)
Grade III	158 (70.9)	38 (47.5)	33 (52.4)	102 (93.6)	331 (69.7)
Unknown	39 (17.5)	30 (37.5)	22 (34.9)	1 (0.9)	92 (19.4)
Site of primary tumour					
Other	130 (58.3)	40 (50.0)	17 (27.0)	58 (53.2)	245 (51.6)
Extremities	76 (34.1)	15 (18.8)	12 (19.0)	49 (45.0)	152 (32.0)
Missing	17 (7.6)	25 (31.3)	34 (54.0)	2 (1.8)	78 (16.4)
Histology					
Leiomyosarcoma	66 (29.6)	25 (31.3)	13 (20.6)	24 (22.0)	128 (26.9)
Synovial sarcoma	37 (16.6)	8 (10.0)	7 (11.1)	19 (17.4)	71 (14.9)
Other	119 (53.4)	42 (52.5)	40 (63.5)	65 (59.6)	266 (56.0)
Missing	1 (0.4)	5 (6.3)	3 (4.8)	1 (0.9)	10 (2.1)
Prior Surgery					
No surgery	8 (3.6)	11 (13.8)	0 (0.0)	0 (0.0)	19 (4.0)
Non optimal surgery	11 (4.9)	12 (15.0)	0 (0.0)	0 (0.0)	23 (4.8)
Complete surgery	42 (18.8)	24 (30.0)	0 (0.0)	0 (0.0)	66 (13.9)
Unknown	162 (72.6)	33 (41.3)	63 (100.0)	109 (100.0)	367 (77.3)
Prior radiotherapy					
No	115 (51.6)	57 (71.3)	41 (65.1)	66 (60.6)	279 (58.7)
Yes	66 (29.6)	22 (27.5)	22 (34.9)	43 (39.4)	153 (32.2)
Missing	42 (18.8)	1 (1.3)	0 (0.0)	0 (0.0)	43 (9.1)
Primary site involved					
No	122 (54.7)	42 (52.5)	22 (34.9)	58 (53.2)	244 (51.4)
Yes	86 (38.6)	38 (47.5)	17 (27.0)	51 (46.8)	192 (40.4)
Missing	15 (6.7)	0 (0.0)	24 (38.1)	0 (0.0)	39 (8.2)

Table 3b Continued.

	Exactly 6 cycles - no PD				
	Treatment				
	DOX 75 (N=223)	DOX 50-IFO 5 (N=80)	DOX 75-IFO 5 (N=63)	DOX 75-IFO 10 (N=109)	Total (N=475)
	N (%)	N (%)	N (%)	N (%)	N (%)
Metastatic Site involved					
No	22 (9.9)	14 (17.5)	5 (7.9)	8 (7.3)	49 (10.3)
Yes	186 (83.4)	66 (82.5)	34 (54.0)	101 (92.7)	387 (81.5)
Missing	15 (6.7)	0 (0.0)	24 (38.1)	0 (0.0)	39 (8.2)

Patients treated with at least 6 cycles of treatment

Considering the 748 patients with at least 6 cycles of treatment and without progression before or at the end of treatment, the median PFS from randomisation was 9.4 months (95% confidence interval: 8.9-9.9) and median PFS from end of treatment was 4.3 months (95% confidence interval: 3.8-4.7). (Supplementary table S4 shows the PFS per treatment regimen) PFS for the different histologies was comparable and is provided in supplementary table 5.

Median OS from randomisation was 19.5 months (95% confidence interval: 18.2-21.3) and median OS from end of treatment was 14.5 months (95% confidence interval: 12.8-16.1). (Supplementary table 6) The median OS according to histology were approximately the same and are provided in supplementary table 7.

Patients treated with exactly 6 cycles of treatment

Because longer treatment duration could lead to bias, we also did the analysis for patients treated with exactly 6 cycles. For this analysis, 475 patients were included (85.6% of the total receiving 6 cycles). The median PFS from randomisation was 8.7 months (95% confidence interval: 8.2-9.1) and the median PFS from end of treatment was 4.2 months (95% confidence interval: 3.7-4.8). (Supplementary table 8) A significant effect of treatment on PFS was found, patients receiving doxorubicin monotherapy had a worse PFS compared to patients receiving doxorubicin 75mg/m^2 combined with ifosfamide 10 g/m^2 combination therapy (p=0.021 and p=0.036 respectively, as already reported by Judson *et al.* [3]). In this analysis, no significant effect of histology on PFS was found. (Supplementary table 9)

Median OS from randomisation for these patients was 20.1 months (95% confidence interval: 18.3-22.3 months) and median OS from end of treatment was 15.7 months (95% confidence interval: 14.0-17.8). There was no statistically significant effect of treatment regimen or histology on OS. (Supplementary table 10 and 11)

Patients treated with less than 6 cycles and no progressive disease

The progression-free survival for patients treated with less than 6 cycles of doxorubicin-containing treatment regimens was 3.8 months (95% confidence interval 3.5-4.3 months) from randomisation. (Supplementary table 12) OS was 10.0 months (95% confidence interval 9.1-10.8 months). (Supplementary table 14) As there can be a bias due to the number of cycles given, no formal statistical comparisons were done. The median progression-free survival and OS for the different treatment regimens are shown in supplementary tables 13 and 15 respectively, but did not differ.

Discussion

In this study, we report the progression-free and OS of patients completing 6 cycles of doxorubicin-based chemotherapy who did not progress before completion of this treatment. Knowledge of the PFS and OS of patients completing 6 cycles of doxorubicin without progressive disease is essential for planning maintenance studies with cytotoxic chemotherapy or tyrosine kinase inhibitors. It is also important to know what percentage of the total number of patients receiving systemic therapy is likely to be available for such trials.

The prognosis of patients with metastatic STS remains poor, with a median OS of 12.8 to 14.3 months respectively in a recently reported study of first-line doxorubicin versus doxorubicin/ifosfamide.[3] More recent studies show a median OS around 18 months.[4-6] As already mentioned in the introduction, since 2016 olaratumab has been introduced in some countries in addition to doxorubicin following the demonstration of a major increase in OS in a phase II trial.[7] However, the results of the phase III ANNOUNCE study did not show an improved OS of the addition of olaratumab to doxorubicin, as was recently presented during the annual meeting of ASCO 2019, leading to the withdrawal from the market.[8] Now, one of the other strategies that could be explored to improve the OS of STS patients is the addition of maintenance therapy after first-line chemotherapy. This is a well-established concept in colorectal cancer, non-small cell lung cancer and ovarian cancer.[20-22] Progression after first-line treatment can result in a deterioration in performance status making it difficult or impossible to administer second-line treatment. Maintenance treatment is intended to improve OS by prolonging the progression-free survival after first-line treatment by direct continuation of chemotherapy. In STS, this is even more a problem, because doxorubicin is first-line treatment and has a maximum safe cumulative dose of 450mg/m^2 (6 cycles), although even at this dose there is evidence of cardiac damage in a significant percentage of patients. Administration of

higher cumulative doses, e.g. 600mg/m^2 (8 cycles) as in the olaratumab study, is only possible with the co-administration of the cardioprotective agent cardioxane since the risk of cardiotoxicity at this dose without cardioprotection is in the region of 50%. An alternative to doxorubicin would be the use of liposomal doxorubicin, which does not have the cardiotoxic potential of doxorubicin.[16] When considering maintenance treatment, one needs to take into account the risks of this therapy and the loss in quality of life caused by the maintenance treatment. Drugs that have some proven utility against sarcomas and could be used in maintenance treatment include pazopanib and trabectedin, which are both well-tolerated.[23-25] Although the concept of maintenance treatment after doxorubicin is attractive, maintenance studies had trouble recruiting due to the temporary registration and availability of olaratumab in most of the western world. Probably, these trials will now recruit more easily, because olaratumab failed in the phase III trial. For designing future studies of maintenance therapy in STS, data on PFS and OS in this setting are essential.

It is important to realise that of all patients included in the database, only 43.7% received 6 cycles or more and only 83.7% of these did not progress before the end of treatment (36.6% of all patients). Patients treated with more than 6 cycles have a similar OS as patients receiving exactly 6 cycles of doxorubicin, but patients receiving less than 6 cycles without progressive disease at the end of treatment have a worse survival. Based on this database study we roughly estimate that only one third of all patients (all patients receiving 6 or more cycles and no progressive disease at end of treatment) will qualify for maintenance treatment.

The PFS of 8.7 months and the OS of 20.1 months from randomisation is much longer than the mean OS of patients included in first line studies. Of course, this is an expected difference because responding patients will have a better prognosis compared to patients not responding to chemotherapy. On the other hand, this improved survival should be accounted for when planning maintenance studies and single arm phase II studies.

One of the major limitations of this study is the long interval between the first included patient and the last included patient. Ifosfamide was already available in the early years of this study, but trabectedin, pazopanib and gemcitabine/docetaxel are new second or later line treatments prolonging PFS and/or OS.[19,23,26] These new second line treatments will cause bias when comparing older regimens like doxorubicin 50mg/m^2 combined with ifosfamide 5g/m^2 to newer regimens like doxorubicin 75mg/m^2 combined with ifosfamide 10g/m^2. The improved supportive care over the years will increase this bias somewhat further.

In this study, treatment regimen had only a significant effect on PFS, with doxorubicin 75mg/m^2 combined with ifosfamide 10g/m^2 having the best PFS. No significant effect

on OS was found, but a trend towards an increase in OS was found for patients with doxorubicin/ifosfamide combination therapy, which is more or less comparable with our study on this regimen, showing only a very little improvement in OS compared with doxorubicin 75mg/m^2 monotherapy.[3] The increase in PFS without an increase in OS in this study could be the effect of sequentially using these agents compared to using them concurrently. For other tumours like colorectal cancer it has been shown that sequential treatment is comparable to concurrent treatment.[27] Second, as the study design selects for responding patients, the difference in OS between this study and the EORTC 62012 study could be caused by the increased response rate with doxorubicin/ifosfamide.

Importantly, this study shows no effect of histology on the outcome of patients, although the number of separately studied subtypes was small. This is in contrast to earlier studies, showing a better survival in for example synovial sarcoma.[28] These differences could be caused by the low number of included patients in this study, or by the exclusion of patients with progression during treatment, thereby selecting for responding patients.

Conclusions

This is the first study reporting the progression-free survival and OS of patients completing 6 cycles of doxorubicin containing treatment without progressive disease before completion of treatment. These data are important for future study design and daily patient care as one of the ways forwards to improve survival in advanced STS could be maintenance treatment for the minority of patients whose disease is sensitive to chemotherapy. Future trials on maintenance treatment after first-line doxorubicin should only include patients receiving at least 6 (or more) cycles of doxorubicin or, when also including patients with less than 6 cycles of doxorubicin, should stratify for the number of cycles doxorubicin given.

Declarations

Ethics approval and consent to participate

All patients consented to participate in the different trials. For all studies, ethical approval was provided by the medical ethical committees of the different participating hospitals. Information about the ethics approval is provided in the manuscripts of the individual studies.

Consent for publication

Not applicable

Data availability

The data used in this manuscript is available on request. The data is stored at EORTC. For conditions and procedures to assess the data: https://www.eortc.org/data-sharing/

Conflicts of interest

AJV, SL, SM, IJ, MT and HG have nothing to disclose. ALC reports personal fees from Pharmamar, Lilly, Novartis and Amgen, all outside the submitted work. EW reports personal fees from Novartis, Lilly, Nanobiotix, Bayer, PharmaMar, Milestone, Menarini and New Oncology, all outside the submitted work.

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Author contributions

Study design: A.J.V., S.L., H.G.; Data acquisition: S.M., M.T., I.J., E.W., H.G., A.L.C.; Statistical analysis and interpretation: A.J.V., S.L., H.G.; Manuscript preparation: A.J.V., H.G.; Manuscript editing and review: All authors.; All authors read and approved the final manuscript.

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Supplementary data

It contains additional tables (also referred to in the manuscript) providing additional data about: the included number of patients per study and regimen and number of cycles and the distribution of histological subtype and grade in the different subgroups.

Also, additional data on overall and progression free survival according to number of cycles is presented.

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Supplementary data

Supplementary table 1 Included patients per study and regimen

	Protocol												
	62012 (N=433)	**62061 (N=38)**	**62091 (N=41)**	**62801 (N=94)**	**62842 (N=194)**	**62851 (N=538)**	**62883 (N=111)**	**62901 (N=107)**	**62903 (N=309)**	**62941 (N=39)**	**62962 (N=41)**	**62971 (N=100)**	**Total (N=2045)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Treatment													
DOX 75	216 (49.9)	38 (100.0)	41 (100.0)	94 (100.0)	0 (0.0)	272 (50.6)	0 (0.0)	107 (100.0)	0 (0.0)	39 (100.0)	41 (100.0)	100 (100.0)	948 (46.4)
DOX 50-IFO 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	194 (100.0)	266 (49.4)	0 (0.0)	0 (0.0)	154 (49.8)	0 (0.0)	0 (0.0)	0 (0.0)	614 (30.0)
DOX 75-IFO 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	111 (100.0)	0 (0.0)	155 (50.2)	0 (0.0)	0 (0.0)	0 (0.0)	266 (13.0)
DOX 75-IFO 10	217 (50.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	217 (10.6)

Supplementary table 2 Distribution of number of cycles by study

	Study												
Number of cycles	**62012**	**62061**	**62091**	**62801**	**62842**	**62851**	**62883**	**62901**	**62903**	**62941**	**62962**	**62971**	**Total**
1	34	6	5	6	10	59	10	12	26	3	4	4	179
2	94	7	9	20	33	107	18	22	62	6	10	28	416
3	30	0	1	15	20	56	15	13	36	5	4	13	208
4	32	2	3	7	23	63	18	12	28	4	6	15	213
5	17	1	0	14	17	40	13	5	21	2	0	5	135
6	225	22	23	8	25	70	31	16	81	6	14	34	555
7	1	0	0	10	12	48	5	21	26	13	2	1	139
8	0	0	0	7	29	46	1	6	14	0	1	0	104
9	0	0	0	2	4	23	0	0	5	0	0	0	34
10	0	0	0	3	13	14	0	0	8	0	0	0	38
11	0	0	0	1	0	5	0	0	2	0	0	0	8
12	0	0	0	0	4	1	0	0	0	0	0	0	5
13	0	0	0	1	1	1	0	0	0	0	0	0	3
14	0	0	0	0	0	3	0	0	0	0	0	0	3
15	0	0	0	0	2	1	0	0	0	0	0	0	3
16	0	0	0	0	0	1	0	0	0	0	0	0	1
17	0	0	0	0	1	0	0	0	0	0	0	0	1

Supplementary table 3a distribution of histological subtype and grade in patients treated with more than 6 cycles

	More than 6 cycles		
	Pts who progress before or at the end of treatment (N=66)	**Pts who did not progress before or at the end of treatment (N=273)**	**Total (N=339)**
	N (%)	**N (%)**	**N (%)**
Histological cell type			
MFH	5 (7.6)	39 (14.3)	44 (13.0)
Fibrosarcoma	5 (7.6)	13 (4.8)	18 (5.3)
Liposarcoma	6 (9.1)	25 (9.2)	31 (9.1)
Leiomyosarcoma	25 (37.9)	79 (28.9)	104 (30.7)
Rhabdomyosarcoma	2 (3.0)	4 (1.5)	6 (1.8)
Angiosarcoma	2 (3.0)	10 (3.7)	12 (3.5)
Synovial sarcoma	6 (9.1)	29 (10.6)	35 (10.3)
Neurogenic sarcoma	5 (7.6)	19 (7.0)	24 (7.1)
Miscellaneous	6 (9.1)	27 (9.9)	33 (9.7)
Unclassified	4 (6.1)	14 (5.1)	18 (5.3)
Missing	0 (0.0)	14 (5.1)	14 (4.1)
Histopathological grade			
I	8 (12.1)	24 (8.8)	32 (9.4)
II	15 (22.7)	59 (21.6)	74 (21.8)
III	18 (27.3)	93 (34.1)	111 (32.7)
Missing	25 (37.9)	97 (35.5)	122 (36.0)

Supplementary table 3b distribution of histological subtype and grade in patients treated with exactly 6 cycles

	Exactly 6 cycles		
	Pts who progress before or at the end of treatment (N=80)	**Pts who did not progress before or at the end of treatment (N=475)**	**Total (N=555)**
	N (%)	**N (%)**	**N (%)**
Histological cell type			
MFH	5 (6.3)	35 (7.4)	40 (7.2)
Fibrosarcoma	4 (5.0)	8 (1.7)	12 (2.2)
Liposarcoma	4 (5.0)	65 (13.7)	69 (12.4)
Leiomyosarcoma	23 (28.8)	128 (26.9)	151 (27.2)
Rhabdomyosarcoma	0 (0.0)	10 (2.1)	10 (1.8)
Angiosarcoma	3 (3.8)	22 (4.6)	25 (4.5)
Synovial sarcoma	10 (12.5)	71 (14.9)	81 (14.6)
Neurogenic sarcoma	10 (12.5)	13 (2.7)	23 (4.1)
Miscellaneous	13 (16.3)	92 (19.4)	105 (18.9)
Unclassified	5 (6.3)	21 (4.4)	26 (4.7)
Missing	3 (3.8)	10 (2.1)	13 (2.3)
Histopathological grade			
I	6 (7.5)	52 (10.9)	58 (10.5)
II	16 (20.0)	162 (34.1)	178 (32.1)
III	30 (37.5)	169 (35.6)	199 (35.9)
Missing	28 (35.0)	92 (19.4)	120 (21.6)

Supplementary table 3c distribution of histological subtype and grade in patients treated with less than 6 cycles and stopped for other reasons then progression

	Less than 6 cycles		
	Pts who progress before or at the end of treatment (N=567)	**Pts who did not progress before or at the end of treatment (N=584)**	**Total (N=1151)**
	N (%)	**N (%)**	**N (%)**
Histological cell type			
MFH	58 (10.2)	79 (13.5)	137 (11.9)
Fibrosarcoma	11 (1.9)	22 (3.8)	33 (2.9)
Liposarcoma	47 (8.3)	47 (8.0)	94 (8.2)
Leiomyosarcoma	192 (33.9)	180 (30.8)	372 (32.3)
Rhabdomyosarcoma	16 (2.8)	16 (2.7)	32 (2.8)
Angiosarcoma	23 (4.1)	14 (2.4)	37 (3.2)
Synovial sarcoma	32 (5.6)	59 (10.1)	91 (7.9)
Neurogenic sarcoma	18 (3.2)	29 (5.0)	47 (4.1)
Miscellaneous	93 (16.4)	80 (13.7)	173 (15.0)
Unclassified	49 (8.6)	30 (5.1)	79 (6.9)
Missing	28 (4.9)	28 (4.8)	56 (4.9)
Histopathological grade			
I	38 (6.7)	30 (5.1)	68 (5.9)
II	140 (24.7)	162 (27.7)	302 (26.2)
III	191 (33.7)	204 (34.9)	395 (34.3)
Missing	198 (34.9)	188 (32.2)	386 (33.5)

Supplementary table 3d distribution of histological subtype and grade in patients treated with exactly 6 cycles according to treatment protocol

	Exactly 6 cycles - no PD				
	DOX 75 (N=223)	**DOX 50-IFO 5 (N=80)**	**DOX 75-IFO 5 (N=63)**	**DOX 75-IFO 10 (N=109)**	**Total (N=475)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Histological cell type					
MFH	9 (4.0)	12 (15.0)	7 (11.1)	7 (6.4)	35 (7.4)
Fibrosarcoma	2 (0.9)	1 (1.3)	3 (4.8)	2 (1.8)	8 (1.7)
Liposarcoma	36 (16.1)	7 (8.8)	6 (9.5)	16 (14.7)	65 (13.7)
Leiomyosarcoma	66 (29.6)	25 (31.3)	13 (20.6)	24 (22.0)	128 (26.9)
Rhabdomyosarcoma	6 (2.7)	1 (1.3)	2 (3.2)	1 (0.9)	10 (2.1)
Angiosarcoma	12 (5.4)	2 (2.5)	2 (3.2)	6 (5.5)	22 (4.6)
Synovial sarcoma	37 (16.6)	8 (10.0)	7 (11.1)	19 (17.4)	71 (14.9)
Neurogenic sarcoma	4 (1.8)	4 (5.0)	5 (7.9)	0 (0.0)	13 (2.7)
Miscellaneous	40 (17.9)	11 (13.8)	8 (12.7)	33 (30.3)	92 (19.4)
Unclassified	10 (4.5)	4 (5.0)	7 (11.1)	0 (0.0)	21 (4.4)
Missing	1 (0.4)	5 (6.3)	3 (4.8)	1 (0.9)	10 (2.1)
Histopathological grade					
I	26 (11.7)	12 (15.0)	8 (12.7)	6 (5.5)	52 (10.9)
II	78 (35.0)	12 (15.0)	19 (30.2)	53 (48.6)	162 (34.1)
III	80 (35.9)	26 (32.5)	14 (22.2)	49 (45.0)	169 (35.6)
Missing	39 (17.5)	30 (37.5)	22 (34.9)	1 (0.9)	92 (19.4)

Supplementary table 4 Progression free survival of patients treated with ≥6 cycles

Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
PFS from Randomisation			
DOX 75	336	308	8.48 (7.92, 9.10)
DOX 50-IFO 5	215	188	10.61 (9.82, 11.70)
DOX 75-IFO 5	88	81	9.31 (8.25, 11.60)
DOX 75-IFO 10	109	98	9.66 (8.77, 11.37)
Total	748	675	9.40 (8.94, 9.89)
PFS from End of treatment			
DOX 75	336	308	3.42 (3.12, 4.07)
DOX 50-IFO 5	215	188	4.70 (3.68, 5.68)
DOX 75-IFO 5	88	81	4.93 (3.61, 6.97)
DOX 75-IFO 10	109	98	4.99 (4.37, 6.67)
Total	748	675	4.27 (3.84, 4.73)

Supplementary table 5 Progression free survival from End of treatment by histology for patients treated with ≥6 cycles

Histology	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
		DOX 75	
Leiomyosarcoma	103	97	3.42 (2.92, 4.44)
Synovial sarcoma	44	41	3.42 (2.07, 4.34)
Other	183	166	3.42 (2.76, 4.44)
		DOX 50-IFO 5	
Leiomyosarcoma	58	52	3.25 (2.10, 4.53)
Synovial sarcoma	26	25	3.81 (2.14, 5.62)
Other	120	101	6.93 (5.03, 8.44)
		DOX 75-IFO 5	
Leiomyosarcoma	22	21	3.99 (2.60, 7.36)
Synovial sarcoma	11	10	3.19 (0.92, 11.93)
Other	50	45	6.34 (3.15, 10.09)
		DOX 75-IFO 10	
Leiomyosarcoma	24	22	4.90 (2.92, 8.51)
Synovial sarcoma	19	19	4.24 (2.96, 8.28)
Other	65	56	5.13 (4.37, 7.43)

Supplementary table 6 Overall survival of patients treated with ≥6 cycles

Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
OS from Randomisation			
DOX 75	336	237	18.73 (16.99, 21.88)
DOX 50-IFO 5	215	162	18.92 (16.66, 21.49)
DOX 75-IFO 5	88	77	19.19 (15.01, 23.75)
DOX 75-IFO 10	109	83	23.59 (19.32, 28.19)
Total	748	559	19.48 (18.20, 21.29)
OS from End of treatment			
DOX 75	336	237	13.96 (11.99, 16.76)
DOX 50-IFO 5	215	162	12.81 (10.94, 16.10)
DOX 75-IFO 5	88	77	15.05 (10.58, 18.89)
DOX 75-IFO 10	109	83	18.89 (14.95, 23.79)
Total	748	559	14.52 (12.78, 16.10)

Supplementary table 7 Overall survival from End of treatment by histology for patients treated with ≥6 cycles

Histology	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	Hazard Ratio (95% CI)
DOX 75				
Leiomyosarcoma	103	70	16.59 (11.17, 22.11)	1.00
Synovial sarcoma	44	36	14.23 (9.30, 18.43)	1.18 (0.79, 1.76)
Other	183	127	12.94 (11.27, 16.76)	1.08 (0.80, 1.44)
DOX 50-IFO 5				
Leiomyosarcoma	58	49	10.68 (8.08, 13.08)	1.00
Synovial sarcoma	26	22	12.29 (7.56, 16.10)	1.10 (0.66, 1.83)
Other	119	80	18.63 (13.96, 22.34)	0.56 (0.39, 0.80)

Supplementary table 7 Continued.

Histology	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	Hazard Ratio (95% CI)
DOX 75-IFO 5				
Leiomyosarcoma	22	21	15.97 (9.20, 22.37)	1.00
Synovial sarcoma	11	10	14.78 (4.73, 26.71)	1.27 (0.60, 2.71)
Other	50	42	11.53 (7.75, 20.47)	0.93 (0.55, 1.58)
DOX 75-IFO 10				
Leiomyosarcoma	24	20	17.35 (9.99, 26.71)	1.00
Synovial sarcoma	19	17	18.89 (8.15, 25.10)	1.37 (0.71, 2.63)
Other	65	46	18.04 (11.37, 27.17)	0.85 (0.50, 1.44)

Supplementary table 8 Progression free survival of patients treated with exactly 6 cycles

Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	Hazard Ratio (95% CI)	P-Value (Score test)
PFS from Randomisation					
DOX 75	223	209	7.59 (7.23, 8.38)	1.00	0.021 (df=3)
DOX 50-IFO 5	80	74	8.85 (7.33, 10.81)	0.84 (0.65, 1.10)	
DOX 75-IFO 5	63	59	9.10 (7.36, 11.40)	0.74 (0.55, 0.99)	
DOX 75-IFO 10	109	98	9.66 (8.77, 11.37)	0.71 (0.56, 0.90)	
Total	475	440	8.67 (8.18, 9.13)		
PFS from End of treatment					
DOX 75	223	209	3.38 (2.73, 4.07)	1.00	0.036 (df=3)
DOX 50-IFO 5	80	74	4.47 (3.06, 5.88)	0.86 (0.66, 1.12)	
DOX 75-IFO 5	63	59	4.73 (3.12, 6.97)	0.75 (0.56, 1.00)	
DOX 75-IFO 10	109	98	4.99 (4.37, 6.67)	0.73 (0.57, 0.92)	
Total	475	440	4.24 (3.71, 4.80)		

Supplementary table 9 PFS from End of treatment by histology for patients treated with exactly 6 cycles

Histology	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
		DOX 75	
Leiomyosarcoma	66	64	3.19 (2.60, 4.73)
Synovial sarcoma	37	35	2.89 (1.94, 4.07)
Other	119	110	3.71 (2.27, 5.09)
		DOX 50-IFO 5	
Leiomyosarcoma	25	23	3.29 (2.04, 5.88)
Synovial sarcoma	8	8	4.09 (0.03, 14.23)
Other	42	38	7.43 (3.48, 9.63)
		DOX 75-IFO 5	
Leiomyosarcoma	13	12	3.68 (2.37, 6.51)
Synovial sarcoma	7	6	3.19 (0.92, 14.78)
Other	40	38	5.80 (3.09, 10.09)
		DOX 75-IFO 10	
Leiomyosarcoma	24	22	4.90 (2.92, 8.51)
Synovial sarcoma	19	19	4.24 (2.96, 8.28)
Other	65	56	5.13 (4.37, 7.43)

Supplementary table 10 Overall survival of patients treated with exactly 6 cycles

Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	Hazard Ratio (95% CI)	P-Value (Score test)
			OS from Randomisation		
DOX 75	223	148	18.96 (17.08, 22.34)	1.00	0.340 (df=3)
DOX 50-IFO 5	80	63	20.11 (15.67, 24.61)	1.08 (0.81, 1.46)	
DOX 75-IFO 5	63	56	19.19 (15.01, 24.87)	1.15 (0.84, 1.56)	
DOX 75-IFO 10	109	83	23.59 (19.32, 28.19)	0.86 (0.66, 1.12)	
Total	475	350	20.14 (18.30, 22.34)		

Supplementary table 10 Continued.

Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Months)	Hazard Ratio (95% CI)	P-Value (Score test)
OS from End of treatment					
DOX 75	223	148	14.59 (12.55, 17.81)	1.00	0.356 (df=3)
DOX 50-IFO 5	80	63	14.52 (11.53, 20.30)	1.09 (0.81, 1.47)	
DOX 75-IFO 5	63	56	15.05 (10.58, 20.47)	1.15 (0.85, 1.57)	
DOX 75-IFO 10	109	83	18.89 (14.95, 23.79)	0.87 (0.66, 1.14)	
Total	475	350	15.74 (14.00, 17.81)		

Supplementary table 11 Overall survival from End of treatment by histology for patients treated with exactly 6 cycles

Histology	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
DOX 75			
Leiomyosarcoma	66	38	17.31 (12.55, 28.88)
Synovial sarcoma	37	30	14.23 (9.30, 18.43)
Other	119	80	14.00 (11.63, 18.27)
DOX 50-IFO 5			
Leiomyosarcoma	25	22	13.08 (8.64, 23.59)
Synovial sarcoma	8	7	12.52 (7.56, 16.95)
Other	42	29	20.76 (13.70, 30.62)
DOX 75-IFO 5			
Leiomyosarcoma	13	12	15.05 (11.33, 27.10)
Synovial sarcoma	7	6	13.37 (2.50, 26.71)
Other	40	35	15.31 (7.06, 21.85)
DOX 75-IFO 10			
Leiomyosarcoma	24	20	17.35 (9.99, 26.71)
Liposarcoma	19	17	18.89 (8.15, 25.10)
Other	65	46	18.04 (11.37, 27.17)

Supplementary table 12 Progression free survival of patients treated with less than 6 cycles *AND* no progressive disease before end of treatment

Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
PFS from Randomisation			
DOX 75	233	222	2.76 (2.27, 3.09)
DOX 50-IFO 5	169	155	3.88 (3.32, 4.90)
DOX 75-IFO 5	111	107	6.93 (5.85, 8.11)
DOX 75-IFO 10	71	65	5.09 (3.84, 7.29)
Total	584	549	3.81 (3.45, 4.30)

Supplementary table 13 PFS from End of treatment by histology for patients treated with less than 6 cycles *AND* no progressive disease before end of treatment

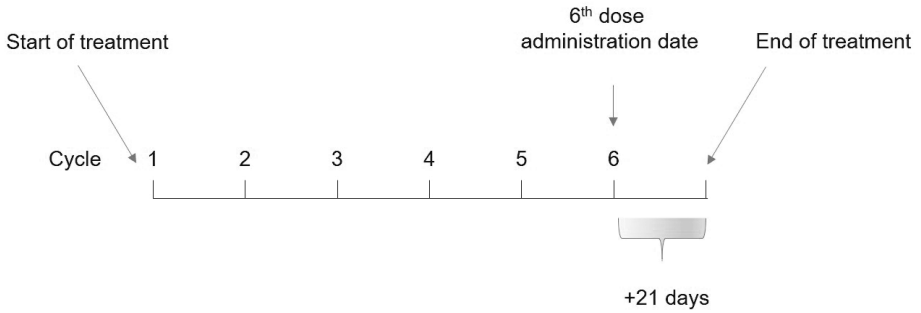
Histology	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
DOX 75			
Leiomyosarcoma	53	52	3.12 (1.71, 3.88)
Synovial sarcoma	23	21	2.79 (1.68, 14.92)
Other	147	140	2.56 (2.23, 2.96)
DOX 50-IFO 5			
Leiomyosarcoma	58	55	3.48 (2.79, 4.90)
Synovial sarcoma	23	23	4.57 (3.09, 9.07)
Other	78	70	3.75 (2.76, 5.19)
DOX 75-IFO 5			
Leiomyosarcoma	43	43	7.13 (3.84, 8.51)
Synovial sarcoma	7	7	8.57 (6.14, 12.75)
Other	54	50	6.21 (5.16, 9.07)
DOX 75-IFO 10			
Leiomyosarcoma	26	26	5.06 (2.66, 7.23)
Synovial sarcoma	6	6	9.53 (2.79, 37.49)
Other	38	32	4.63 (3.22, 8.18)

Supplementary table 14 Overall survival of patients treated with less than 6 cycles *AND* no progressive disease before end of treatment

Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
OS from Randomisation			
DOX 75	233	194	8.15 (7.29, 9.76)
DOX 50-IFO 5	169	136	10.02 (8.21, 12.06)
DOX 75-IFO 5	111	103	12.12 (9.92, 13.93)
DOX 75-IFO 10	71	55	11.70 (9.95, 14.78)
Total	584	488	10.02 (9.07, 10.81)

Supplementary table 15 Overall survival from End of treatment by histology for patients treated with less than 6 cycles *AND* no progressive disease before end of treatment

Histology	Patients (N)	Observed Events (O)	Median (95% CI) (Months)
DOX 75			
Leiomyosarcoma	53	47	5.85 (3.38, 9.43)
Synovial sarcoma	23	13	17.05 (10.55, 32.10)
Other	147	125	5.26 (4.04, 6.80)
DOX 50-IFO 5			
Leiomyosarcoma	58	50	6.31 (4.47, 8.77)
Synovial sarcoma	23	19	9.00 (4.73, 21.65)
Other	78	61	6.60 (4.76, 10.28)
DOX 75-IFO 5			
Leiomyosarcoma	43	41	8.31 (5.98, 11.70)
Synovial sarcoma	7	7	11.89 (7.92, 19.12)
Other	54	48	9.99 (5.03, 13.90)
DOX 75-IFO 10			
Leiomyosarcoma	26	24	9.48 (7.56, 12.98)
Liposarcoma	6	4	15.28 (6.31, N)
Other	38	26	8.61 (5.68, 17.02)



Supplementary figure 1 Definition of end of treatment