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Subgroup analysis of older patients treated within the randomized phase 3 doxorubicin versus doxorubicin plus evofosfamide (SARC021) trial

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Precis

In the SARC021 trail, efficacy outcomes for older patients with sarcoma did not significantly differ from those of younger patients with sarcoma treated with first-line chemotherapy. Older patients with sarcoma experienced more toxicity than younger patients treated with first-line chemotherapy.

Keywords:
Soft tissue sarcomas
Chemotherapy
Anthracycline
First-line
Older
Efficacy
Toxicity

ABSTRACT

Background: More than half of patients with soft tissue sarcoma (STS) are aged ≥65 years (older), however contemporary data on the efficacy/safety of anthracycline chemotherapy in older patients with STS are lacking.
Methods: SARC021 randomized patients to receive first-line doxorubicin or doxorubicin plus evofosfamide. The main aim of this study was to compare the outcome and safety of first-line anthracycline-based therapy in older patients compared with those <65 years. IRB approval was obtained at all participating sites and this research meets requirements for protection of human subjects.
Results: Of 640 patients, 209 (33%) were older, with a median age 70 (range 65–89) years. The median overall survival (OS) was 16.7 months (95%CI: 13.2–20.0) in older patients compared to 20.1 months (95%CI: 16.9–23.2) in those aged <65 years ($n = 431$), HR 1.21 (95%CI: 0.99–1.48), $p = .057$. The median progression-free survival (PFS) in older patients was 6.3 months (95%CI: 5.8–7.2) compared to 6.0 (95%CI: 5.1–6.4) in those <65 years, HR 0.86 (95%CI: 0.70–1.05), $p = .14$. Older patients had significantly more hematological (141 [67%] versus 208 [48%], $p < .0001$), non-hematological (131 [63%] versus 215 [50%], $p = .0097$) and ≥ Grade 3 adverse events (178 [85%] versus 299 [69%], $p = .0002$), compared to younger patients. More older patients (30, 14%) stopped treatment due to adverse events compared to younger patients (22, 5%), $p = .0001$.
Conclusions: The efficacy of first-line anthracycline-based chemotherapy did not differ significantly between older and younger advanced sarcoma patients. Significantly more older patients stopped chemotherapy due to adverse events. These results provide a benchmark for daily clinical practice and future trials in older patients.

1. Introduction

Soft tissue sarcomas (STS) are rare, heterogeneous tumors of mesenchymal origin, that account for approximately 1–2% of all adult cancers [1]. Almost half of STS are diagnosed in older patients aged ≥65 years, with the highest incidence in patients aged ≥75 years. There are 13.5 new cases per 100,000 per year in the United States [2,3]. Advancing age is a risk factor for the development of STS and an independent adverse prognostic factor for survival in the metastatic setting [1,4–8]. Older patients are often diagnosed with higher-grade, higher-stage tumors, and under-treatment is believed to contribute to worse survival [6–8]. Older patients with STS are under-represented in clinical trials; a recent analysis of 12 EORTC first-line chemotherapy trials found that only 12% ($n = 348$) of participants were aged ≥65 years [9]. In view of the ageing global population, contemporary, prospective data on the outcomes of older patients with STS are needed to inform clinical practice.

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Anthracycline-based schedules are the mainstay of treatment for advanced STS (either as single agent or in combination). Systemic therapies are used cautiously in older patients due to their toxicity; for example, advancing age is a risk factor for anthracycline-associated cardiotoxicity and pre-existing impaired renal function may preclude the use of ifosfamide [10,11].

SARC021 was a randomized phase III trial of single-agent doxorubicin versus doxorubicin plus the hypoxia-activated alkylating agent, evofosfamide, as first-line therapy for advanced STS [12].

The main aim of this study was to compare the outcome and toxicity of first-line anthracycline-based chemotherapy in older (≥65 years) and younger patients with advanced sarcomas. Secondary aims included a comparison of the efficacy and safety of doxorubicin and doxorubicin plus evofosfamide (DE) in older patients and an evaluation of patients ≥75 years of age treated within the trial.

2. Materials and Methods

In this study, older patients were defined as those aged 65 years or older. A retrospective analysis of the SARC021 clinical trial database was performed to identify older patients and those aged <65 years. Patient demographics, clinical details and prior treatments were collected for analysis. Response was defined according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Adverse events (AEs) were grouped into four categories (hematological, non-hematological, cardiac, and ≥ Grade 3 AEs) and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Cardiac function was assessed using either multi-gated radionuclide angiography (MUGA) or echocardiogram, and electrocardiogram (ECG), at baseline, after completion of four cycles and at termination of doxorubicin. A cardiac AE was defined as a drop in left ventricular ejection fraction (LVEF) of 10% from baseline resulting in a LVEF of <55%, an absolute LVEF of 45%, or a 20% decline in LVEF at any level.

Quality of life (QOL) assessments were performed at screening, on Day 1 of each cycle (pre-dose), at termination of treatment and every 3 months during follow-up. QOL assessments were completed by patients only. Two QOL instruments were administered, the EuroQOL-five dimension-five response level tool (EQ-5D-5 L) incorporating 5 items (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and scored 1 ("no problem") to 5 ("extreme problems"), and a 20-cm visual analog scale tool, the EuroQOL- visual acuity scale EQ-VAS) (scored 0 "the worse health you can imagine" to 100 "the best health you can imagine").

Descriptive statistics were used to compare baseline characteristics of older patients with those aged <65 years. Kaplan-Meier curves were used to summarize progression-free (PFS) and overall survival (OS) of older patients and those aged <65 years with *p*-value calculated from log-rank test. Response rates were compared between the two age groups using Fisher's exact test. Cox models were used to generate HRs and we also tested for interaction between treatment arm and age group. Comparison of AEs between older patients and those <65 years of age was similar to the analysis for older patients, but instead of treatment, age ≥65 was included as the covariable of interest in the analysis. We described the number of cycles administered for older patients and those <65 years of age and number of patients who stopped therapy due to AEs. Finally, 65 years is an arbitrary threshold for defining status. To determine how sensitive the results are to this value, we also did an analysis of patients over 75 years of age, defined as 'much older'.

Within the group of older patients, OS, PFS and response rate (RR) were compared between those treated with doxorubicin versus DE. Kaplan-Meier curves were used to summarize OS and PFS, with *p*-value calculated using the log-rank test. Univariable Cox-proportional hazards models were used to estimate hazard ratios, with corresponding 95% confidence intervals. Multivariable models included treatment arm, age, and all factors significant at the 0.05 level in univariable analyses. Response rates of older patients between the two treatment arms were compared using Fisher's exact test. Univariable logistic regression models were used to estimate hazard ratios, with corresponding 95% confidence intervals. Multivariable models included arm, age, and all factors significant at the 0.05 level in univariable analyses.

IRB approval was obtained at all participating sites and this research meets requirements for protection of human subjects.

3. Results

The primary analysis of the SARC021 trial showed no significant difference in OS (HR 1·06, 95%CI: 0·88–1·29), or PFS (HR 0·85, 95%CI: 0·70–1·03) between patients treated with doxorubicin and DE (as previously published) [12].

Of 640 participants in the SARC021 trial, there were 209 patients aged ≥65 years (33%) and 431 patients (67%) aged <65 years. Baseline characteristics are summarized in Table 1. The median age of older patients at baseline was 70 (range 65–89) years, and the median follow-up was 16.5 months. Patients aged <65 years commonly had a baseline ECOG performance status (PS) of 0, whereas older patients more frequently had PS of 1 ($p = .001$). Leiomyosarcoma was the most common histological subtype in both age groups and undifferentiated pleomorphic sarcoma was more frequent in older patients ($p = .006$). Older patients were more likely to have received prior radiation ($p = .04$).

There was no statistically significant difference in median OS between patients aged <65 years (20.1 months, 95%CI: 16.9–23.2) and older patients (16.7 months, 95%CI: 13.2–20.0), HR = 1.21 (95%CI:

Table 1
Characteristics of entire trial population.

	Patients <65 years ($n = 431$)	Patients ≥ 65 years old ($n = 209$)	p-value
Age: Median (years)	53	70	–
Sex			**0.021**
Female	246 (57%)	99 (47%)	
Male	185 (43%)	110 (53%)	
Ethnicity			0.77
Hispanic or Latino	23 (5%)	10 (5%)	
Not Hispanic or Latino	408 (95%)	199 (95%)	
Race			0.28
White	385 (89%)	197 (94%)	
Asian	13 (3%)	4 (2%)	
Black or African American	22 (5%)	5 (2%)	
Other	11 (3%)	3 (1%)	
ECOG performance status			**0.0011**
0	267 (62%)	98 (47%)	
1	160 (37%)	110 (53%)	
2	3 (1%)	1 (0%)	
Extent of disease			0.050
Locally advanced	57 (13%)	40 (19%)	
Metastatic disease	374 (87%)	169 (81%)	
Tumor grade			0.46
High grade	288 (67%)	130 (62%)	
Intermediate grade	130 (30%)	74 (35%)	
High/intermediate grade	12 (3%)	4 (2%)	
Low grade	1 (0%)	0 (0%)	
Histology			**0.0056**
Leiomyosarcoma	153 (35%)	77 (37%)	
Liposarcoma	75 (17%)	36 (17%)	
Undifferentiated pleomorphic sarcoma	41 (10%)	38 (18%)	
Other	162 (38%)	58 (28%)	
Prior radiotherapy			**0.043**
Yes	148 (34%)	120 (57%)	
No	283 (66%)	89 (43%)	
Prior neo(adjuvant) chemotherapy			0.66
Yes	27 (6%)	15 (7%)	
No	404 (94%)	194 (93%)	

Bold values indicate a significant p-value <0.05

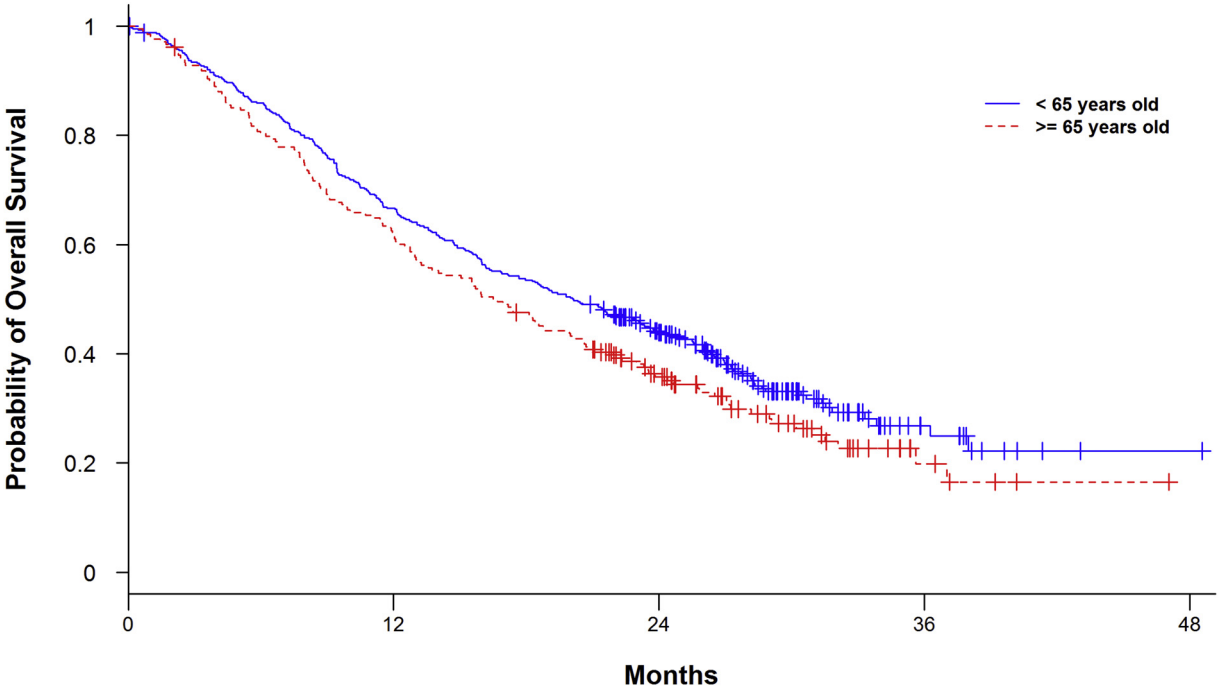

Fig. 1. OS older patients aged ≥65 years vs. patients aged <65 years.

0.99–1.48), $p = .057$ (Fig. 1). No significant difference in median PFS was observed between patients aged <65 years (6.0 months, 95%CI: 5.1–6.4) compared to older patients (6.3 months, 95%CI: 5.8–7.2), HR = 0.86 (95%CI: 0.70–1.05), $p = .14$ (Fig. 2). No significant difference in response rate was observed between those <65 years (103, 24%) compared to older patients (46, 22%), $p = .60$. On multivariable analysis (Tables 2 and 3), PS of 1 or 2 was associated with significantly worse OS than PS 0 (HR 1.92 [1.57, 2.32], $p < .001$) and significantly worse PFS (HR 1.47, [1.20, 1.79], $p < .001$). Patients with pleomorphic sarcoma had significantly worse OS compared to those with leiomyosarcoma (HR 1.61 [1.18–2.20], $p = .002$), as did 'other' subtypes compared to leiomyosarcoma (HR 1.65 [1.31–2.08], $p < .001$).

As shown in Table 4, hematological (anemia, neutropenia, thrombocytopenia) and non-hematological (fatigue, reduced appetite, diarrhea) AEs were significantly more common in older patients. There were 494 patients with at least one follow-up echocardiogram. There was no significant difference in cardiotoxicity between those <65 years (35, 8%) and older patients (20, 20%), $p = .60$. Dexrazoxane was administered

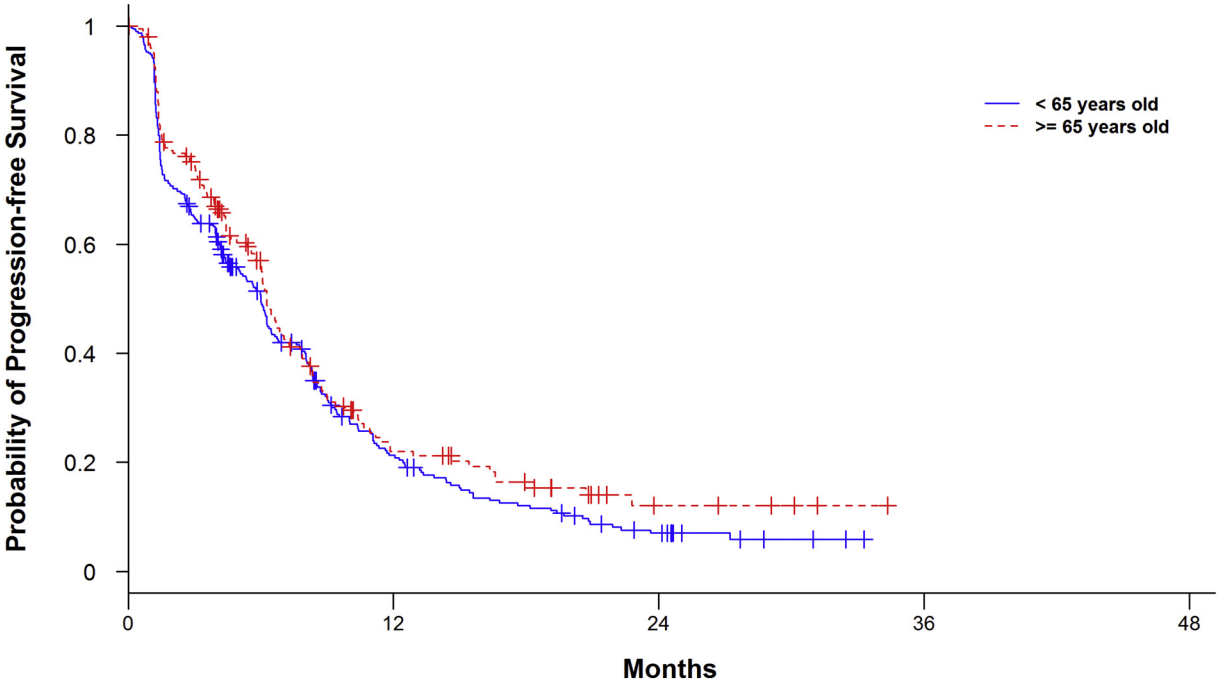

Fig. 2. PFS older patients aged ≥65 years vs. patients aged <65 years.

Table 2
Overall survival: cox proportional hazard regression.

	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	P value
Age ≥ 65	1.21 (0.99–1.48)	0.057	1.08 (0.87–1.31)	0.515
Doxorubicin plus Evofosfamide (vs Dox alone)	1.08 (0.89–1.3)	0.451	1.11 (0.92–1.34)	0.293
ECOG 1 or 2 (vs ECOG 0)	2.02 (1.66–2.44)	<0.001	1.92 (1.57–2.33)	<0.001
Continuous (vs bolus)	0.85 (0.64–1.14)	0.291		
Locally advanced (vs distant metastatic)	0.92 (0.7–1.21)	0.539		
Prior radiation (vs No)	0.92 (0.75–1.12)	0.380		
Histology (vs Leiomyosarcoma)*				
Liposarcoma	1.15 (0.86–1.55)	0.345	1.12 (0.83–1.50)	0.457
Pleomorphic sarcoma/malignant fibrous histocytoma	1.68 (1.23–2.29)	0.001	1.61 (1.18–2.20)	0.002
Other	1.76 (1.4–2.22)	<0.001	1.65 (1.31–2.08)	<0.001
Gender male (vs female)	1.12 (0.93–1.36)	0.235		

* Likelihood ratio test p value ≤.001, therefore included in multivariable analysis.

Table 3
Progression Free Survival: Cox Proportional Hazard Regression.

	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Age ≥ 65	0.86 (0.70–1.05)	0.140	0.78 (0.63–0.96)	0.020
Doxorubicin plus Evofosfamide (vs Dox alone)	0.86 (0.71–1.04)	0.128	0.84 (0.70–1.02)	0.086
ECOG 1 or 2 (vs ECOG 0)	1.38 (1.14–1.67)	0.001	1.47 (1.2–1.79)	<0.001
Continuous (vs bolus)	0.89 (0.67–1.18)	0.433		
Locally advanced (vs distant metastatic)	0.92 (0.7–1.22)	0.562		
Prior radiation (vs No)	0.9 (0.74–1.1)	0.296		
Histology (vs Leiomyosarcoma)*				
Liposarcoma	0.81 (0.61–1.07)	0.139		
Pleomorphic sarcoma/malignant fibrous histocytoma	1.12 (0.89–1.41)	0.322		
Other	1.14 (0.84–1.57)	0.398		
Gender male (vs female)	1.18 (0.97–1.42)	0.094		

* Likelihood ratio test p value = .98, therefore not included in multivariable analysis.

to 22 patients <65 years and 12 in the older age group. Two of these patients experienced cardiotoxicity (both <65 years). AEs of Grade ≥ 3 were significantly more common in older patients ($p = .0002$). The most common Grade 3 AE was anemia (<65 years: $n = 125$ [30%], older: $n = 83$ [40%]) and most frequent Grade 4 AE was neutropenia (<65 years: $n = 55$ [13%], older: $n = 47$ [23%]).

Both age groups received a median of 6 cycles (range 0–6). In those <65 years, 154 (36%) underwent dose reductions compared to 93 (44%) in the older age group, $p = .7$. Significantly more older patients (30, 14%) stopped therapy due to AEs compared to those <65 years (22, 5%), $p = .0001$. Baseline ECOG performance status (PS) of 1 or 2 was associated with significantly greater hematologic AEs compared to PS 0 (OR 1.68 [1.22, 2.33], $p = .002$) and remained significant in multivariable analysis after accounting for age and treatment arm (OR 1.55 [1.11–2.17], $p = .010$). Patient age ≥ 65 years was also associated with significantly more hematologic AEs compared with age < 65 years (OR 2.07 1.47–2.95, $p < .001$), and remained significant in multivariable analysis after accounting for ECOG performance status and treatment arm (OR 1.95 1.38–2.80, $p < .001$).

On univariable analysis, factors associated with higher non-hematological AE were age ≥ 65 years (OR 1.57 1.12–2.21, $p = .01$), DE combination treatment (OR 1.67 1.22–2.31, $p = .02$), baseline PS 1 or 2 (OR 2.00 [1.44, 2.78], $p < .001$) and prior radiation (OR 1.48 [1.06, 2.07], 0.021). On multivariable analysis, DE combination treatment arm, ECOG performance status of 1 or 2 and prior radiation remained independently associated with non- hematological AEs ($p = .001$, $p < .001$ and $p = .015$ respectively), however older age was no longer associated with non-hematological AEs when controlling for these variables ($p = .072$).

Baseline PS of 1 or 2 was associated with significantly more Grade ≥ 3 AEs than PS 0, HR 1.93 (1.30, 2.89), $p = .001$.

In patients aged <65 years, QOL data were available for 127 patients (29%) at baseline and 131 patients (30%) at study termination. For older patients, QOL data were available at baseline in 61 (29%) and 57 (27%) at study termination. Patients aged <65 years had a significantly higher (worse) mean anxiety/depression score (2.04, SD 0.98) at baseline compared with older patients (1.62, SD 0.78), $p = .004$. Older patients had numerically higher (worse) mean mobility score (1.82, SD 1.14) at termination of the study compared to <65 years (1.5, SD 0.78), $p = .063$. There were no differences in EQ-VAS scores between patients aged <65 years and older patients.

The comparison of 103 older patients treated with doxorubicin and 106 treated with DE, demonstrated that the baseline characteristics were well-balanced between the arms (Table 5). There was no significant difference in median OS between the doxorubicin (17.0 months, 95%CI: 12.9–20.6) and the DE arm (16.2 months, 95%CI: 11.5–23.0),

Table 4
Adverse events (all grades): patients <65 years versus older patients.

	Patients <65 years old ($n = 431$)	Patients ≥ 65 years old ($n = 209$)	*p*-value
Hematological AE			**<0.0001**
No	205 (48%)	67 (32%)	
Yes	208 (48%)	141 (67%)	
Non-Hematological AE			**0.0097**
No	198 (46%)	77 (37%)	
Yes	215 (50%)	131 (63%)	
Cardiac AE			0.60
No	295 (68%)	144 (69%)	
Yes	35 (8%)	20 (10%)	
≥ Grade 3 AE			**0.0002**
No	114 (26%)	30 (14%)	
Yes	299 (69%)	178 (85%)	

Table 5
Baseline characteristics of older patients.

	Doxorubicin alone ($n = 103$)	Doxorubicin plus evofosfamide ($n = 106$)	p-value
Age: Median (years)	70 (65–84)	69 (65–89)	0.29
Sex			0.96
Female	49 (48%)	50 (47%)	
Male	54 (52%)	56 (53%)	
Ethnicity			0.55
Hispanic or Latino	4 (4%)	6 (6%)	
Not Hispanic or Latino	99 (96%)	100 (94%)	
Race			0.51
White	95 (92%)	102 (96%)	
Asian	2 (2%)	2 (2%)	
Black or African American	4 (4%)	1 (1%)	
Other	2 (2%)	1 (1%)	
ECOG performance status			0.39
0	52 (50%)	46 (43%)	
1	51 (50%)	59 (56%)	
2	0 (0%)	1 (1%)	
Extent of disease			0.65
Locally advanced	82 (80%)	87 (82%)	
Metastatic disease	21 (20%)	19 (18%)	
Tumor grade			1.00
High grade	64 (62%)	66 (62%)	
Intermediate grade	36 (35%)	38 (36%)	
High/intermediate grade	2 (2%)	2 (2%)	
Histology			0.58
Leiomyosarcoma	35 (34%)	42 (40%)	
Liposarcoma	15 (15%)	21 (20%)	
Undifferentiated pleomorphic sarcoma	19 (18%)	19 (18%)	
Other	34 (33%)	23 (22%)	
Prior radiotherapy			0.75
Yes	45 (44%)	44 (42%)	
No	58 (56%)	62 (58%)	
Prior neo(adjuvant) chemotherapy			0.39
Yes	9 (9%)	6 (6%)	
No	94 (91%)	100 (94%)	

HR 1.08 (0.89–1.3), $p = .45$. There was no significant difference in median PFS between the doxorubicin (6.1 months, 95%CI: 4.7–7.2) and the DE arm (6.5 months, 95% CI 4.9–8.2), HR 1.08 (0.89–1.3) and $p = .45$ (Fig. 3). There was no significant difference in response rate between the doxorubicin (19, 18%) and the DE arm (27, 25%), $p = .22$. As shown in Table 6, hematological AEs occurred with similar frequency in both treatment arms. Non-hematological AEs were more common in the DE arm ($p = .0014$). The most frequent non-hematological AEs were fatigue, nausea, stomatitis and constipation. There was no significant difference in cardiac AEs between the doxorubicin (8, 8%) and DE arm (12, 11%), $p = .40$. Grade 3 and 4 AEs occurred in 85 patients (83%) in the doxorubicin arm and 93 patients (88%) in the DE arm, $p = .37$. Significantly more patients treated with DE (58, 55%) had a dose reduction compared to doxorubicin (35, 34%), $p = .003$.

Thirty-nine patients aged ≥75 years participated in the SARC021 trial (Dox $n = 19$, DE $n = 20$), and 30 of these patients were deceased at the time of analysis. The median OS of 'much older' patients was 16.7 months (95%CI: 7.5–23.0) and the median PFS was 4.4 months (95%CI: 2.8–6.5). There was no significant difference in median OS and PFS between 'much older' patients treated with doxorubicin and DE. Nine of these 39 patients had a radiological response (doxorubicin $n = 5$, DE $n = 4$, $p = .72$). Five patients discontinued treatment due to toxicity (doxorubicin n = 1, DE n = 4).

4. Discussion

This SARC021 sub-analysis demonstrated no significant difference in median OS, PFS and response rate between older patients and patients aged <65 years. However, older participants experienced significantly more hematological and grade ≥ 3 AEs, and were more likely to stop treatment early. Our study also showed no significant difference in median OS, PFS and response rate between older patients treated with doxorubicin compared with doxorubicin plus evofosfamide, however, non-hematological AEs were significantly more common in the combination arm. There are few contemporary data regarding the safety and efficacy of first-line anthracycline-based therapy in advanced soft tissue sarcomas. The available studies are of historic cohorts and do not represent current diagnostic classification and salvage systemic therapy schedules [9,13]. Furthermore, compared to previous studies, our study is strengthened by central pathology review and consistent treatment within a prospective clinical trial.

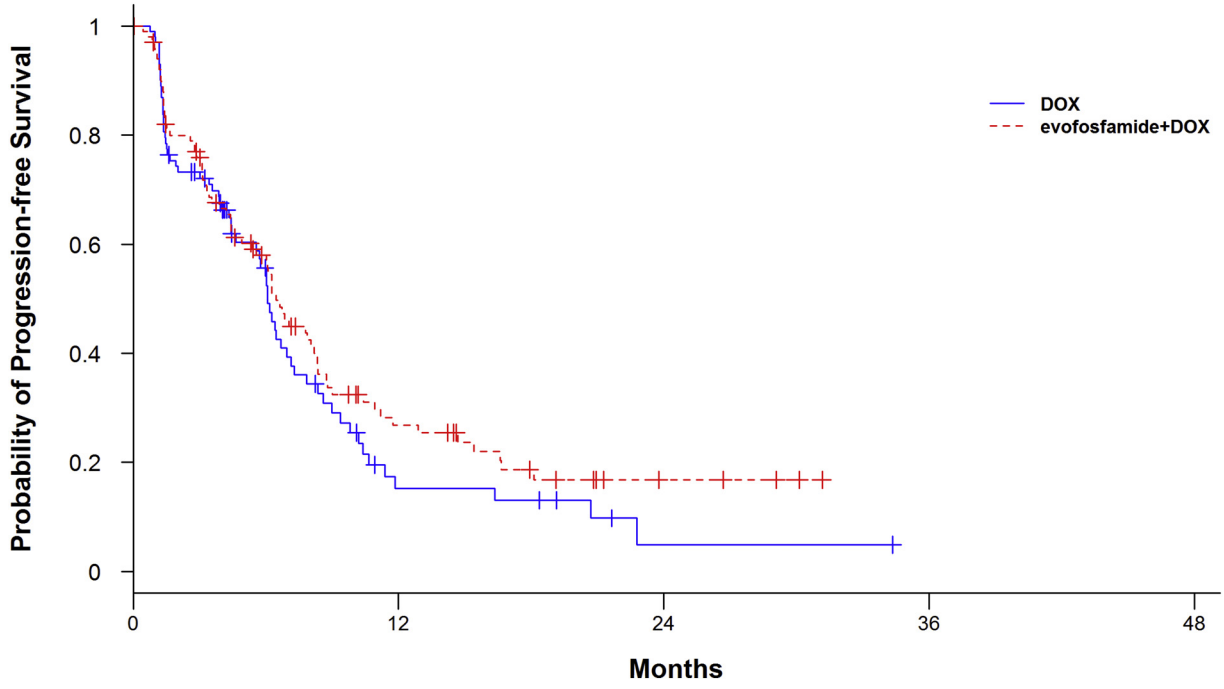

Fig. 3. PFS by treatment arm among older patients aged ≥65 years.

Table 6
Older patients: adverse events (all grades).

	Doxorubicin alone (n = 103)	Doxorubicin plus evofosfamide (n = 106)	p-value
Hematological AE			
No	35 (34)	32 (30)	0.53
Yes	67 (65)	74 (70)	
Non-Hematological AE			
No	49 (48)	28 (26)	**0.0012**
Yes	53 (51)	78 (74)	
Cardiac AE			
No	72 (70)	72 (68)	0.40
Yes	8 (8)	12 (11)	
≥ Grade 3 AE			
No	17 (17)	13 (12)	0.37
Yes	85 (83)	93 (88)	

Bold values indicate a significant p-value <0.05

Physiological changes associated with ageing can impact pharmacokinetic and pharmacodynamic properties leading to an increased risk of toxicity [14-16]. Many physicians are cautious to use combination chemotherapy in older patients despite several solid tumor trials showing that doublet chemotherapy can be used safely in carefully selected patients [17-19]. Predicting which patients are at greater risk of toxicity is challenging due to significant inter-individual variability [13-16]. The G8 (Geriatric 8) assessment screening tool is currently recommended by the Society of Geriatric Oncology (SIOG) to identify patients who require comprehensive geriatric assessment (CGA) [20]. Management of high-risk patients by a geriatrician-led multidisciplinary team can improve tolerance to chemotherapy, although provision may be limited by costs and resources [21]. Anemia and neutropenia were the most commonly reported grade 3 and 4 AEs respectively. High rates of hematological AEs in older patients are likely to reflect depleted bone marrow reserves [16].

Older patients have been under-represented in clinical trials. One third of patients in SARC021 were older, which provided an opportunity to better understand outcomes and toxicity in comparison with patients aged <65 years. More clinical trials specifically for older patients are needed, such as the EPAZ phase II randomized trial of pazopanib versus doxorubicin as first-line treatment for older patients (≥60 years) with advanced STS [22,23]. The median age of patients in the EPAZ trial was 71 (range 60–88) years [24]. Pazopanib was non-inferior to doxorubicin in terms of median PFS (4.4 versus 5.3 months) and OS (12.3 versus 14.3 months respectively) [24]. AEs were typical for known side effects. The EPAZ doxorubicin arm ($n = 39$) had slightly lower median PFS and OS compared to older patients in our study. A recent study of older patients treated within the randomized phase III trial of trabectedin versus dacarbazine in pre-treated liposarcoma and leiomyosarcoma, demonstrated the safety and efficacy of trabectedin in patients over the age of 65 years [25]. Consequently, there is evidence to support the use of palliative systemic therapies in older patients with metastatic sarcomas.

Comprehensive QOL assessments should be incorporated as endpoints in trials, as patient reported outcomes are a vital component of evaluation of the net clinical benefit of a treatment. Older patients may consider QOL as more important than survival, compared with younger patients [26]. Although QOL analysis in SARC021 did not identify significant differences between younger and older patients, EQ-5D-5 L contains five questions and EQ-VAS only one measurement, which may not adequately assess the complex interplay of STS and its treatment on all aspects of daily functioning. Only patients with a good PS were enrolled into SARC021, which may not represent the older population in clinical practice. Very few patients completed QOL assessments and interpretation of these data are limited.

This study provides a contemporary benchmark of first-line anthracycline-based therapy in older patients with advanced soft tissue sarcoma. Our data show that anthracycline-based chemotherapy appears to be effective in older patients. However, the increased rates of AEs in older patients highlight the need for less toxic treatments and optimization of supportive care. Future studies should incorporate geriatric assessment tools and evaluate whether alternative drugs or schedules can be safely and effectively used in this population. Greater attention should be given to QOL, in order to guide interpretation of treatment efficacy and optimize patient care.

Conflict of Interest Disclosures

Eugenie Younger, Yao Lu, Zsuzsanna Pápai, and Patrick Schöffski have no conflict of interest disclosures. Brian A. Van Tine reports personal fees from Threshold and EMD Serono. Steven Attia reports grants from Threshold Pharmaceuticals, during the conduct of the study; grants from Bayer, AB Science, CytRx, Novartis, Diaachi Sankyo, Lilly, Karyopharm Pharmaceuticals, Epizyme, Blueprint Medicines, Genmab, CBA Pharmaceuticals, Desmoid Tumor Research Foundation, Merck, Deciphera, Takeda Oncology, Philogen, Gradilis, Incyte, Morphotek, grants and non-financial support from TRACON Pharmaceuticals and from Immune Design, outside the submitted work. William D. Tap reports personal fees from Eli Lilly, EMD Serono, Novartis, Eisai, Janssen, Immune Design, Adaptimmune, Daiichi Sankyo, Blueprint, Loxo, GlaxoSmithKline, outside the submitted work. In addition, Dr. Tap has a patent Companion Diagnostic for CDK4 inhibitors - 14/854,329 pending to MSKCC/SKI. Denise Reinke reports grants from Threshold Pharmaceuticals, during the conduct of the study. Karla Ballman reports grants from SARC Foundation, during the conduct of the study. Robin L. Jones reports consultant work for Threshold, Adaptimmune, Blueprint, Clinigen, Eisai, Epizyme, Daiichi Sankyo, Deciphera, Immunedesign, Eli Lilly, Merck and PharmaMar.

Author Contributions

Robin L. Jones and Eugenie Younger: conceptualization, methodology, formal analysis, writing – original draft. Karla Ballman and Yao Lu: methodology, formal analysis, writing – review & editing. Zsuzsanna Pápai, Brian A. Van Tine, Steven Attia, Patrick Schöffski, Denise Reinke and William D. Tap: formal analysis, resources, writing – review & editing.

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