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ORIGINAL RESEARCH

Early phase trials in soft-tissue sarcomas: clinical benefit of inclusion in early lines of treatment, molecular screening, and histology-driven trials

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Background: The prognosis of patients with advanced soft-tissue sarcomas (STS) remains dismal, and systemic therapeutic options are limited. Early phase trials are becoming increasingly safe and effective. This study aimed to identify the prognostic factors for progression-free survival (PFS).

Patients and methods: This retrospective analysis included all STS patients participating in early phase trials at Gustave Roussy and Léon Bérard between 1 January 2012 and 31 December 2020.

Results: Overall, 199 patients accounted for 214 inclusions in advanced STS. The most frequent histotypes were well-differentiated/dedifferentiated liposarcomas (n = 55), leiomyosarcomas (n = 53), synovial sarcomas (n = 22), undifferentiated pleomorphic sarcomas (n = 15), angiosarcomas (n = 12), and myxoid liposarcomas (n = 10). The median PFS was 2.8 months (95% confidence interval 2.7-4.1 months). The median PFS in the first, second, and later lines was 8.3, 5.4, and 2.6 months, respectively ($P = 0.00015$). The median PFS was 2.8 months in case of molecular screening, 4.1 months in case of histology-driven screening, and 1.6 months ($P = 0.00014$) in the absence of either screening modalities. In univariate analysis, histotype ($P = 0.026$), complex genomics ($P = 0.008$), number of prior lines ($P < 0.001$), prior anthracyclines ($P < 0.001$), number of metastatic sites ($P = 0.003$), liver metastasis ($P < 0.001$), lung metastasis ($P < 0.001$), absence of molecular or histology-driven screening ($P < 0.001$), first-in-human trials ($P < 0.001$), dose-escalation cohorts ($P = 0.011$), and Royal Marsden Hospital (RMH) score >1 ($P < 0.001$) were significantly associated with shorter PFS. In multivariate analysis, independent prognostic factors for shorter PFS were myxoid liposarcoma ($P = 0.031$), ≥2 prior lines of treatment ($P = 0.033$), liver metastasis ($P = 0.007$), and RMH score >2 ($P = 0.006$). Factors associated with improved PFS were leiomyosarcomas ($P = 0.010$), molecular screening ($P = 0.025$), and histology-driven screening ($P = 0.010$). The median overall survival rates were 36.3, 12.6, and 9.2 months in the first, second, and later lines, respectively ($P = 0.0067$). The grade 3-4 toxicity rate was 36%.

Conclusions: Early phase trials provide an active therapeutic option for STS, even in first-line settings. Molecular screening and histology-driven trials further improve the clinical benefit.

Key words: soft-tissue sarcomas, early phase trials, drug development, screening, biomarker

INTRODUCTION

The standard-of-care first-line systemic treatment of soft-tissue sarcomas (STS) has been anthracycline-based chemotherapy for the past 40 years.[1] This treatment yields an objective response rate (ORR) of 20%-30%, a median progression-free survival (PFS) of 8 months, and a median overall survival (OS) of 18-20 months.[2-4] Later systemic lines are limited and more histotype tailored.[5] Thus, the prognosis of advanced STS remains dismal, and new drugs are needed.[6]

Drug development for STS patients is slower than that for other cancer types due to the rarity and heterogeneity of STS. Later phases of drug development are increasingly histotype specific,[7-9] as randomized controlled pan-histology trials have been consistently disappointing.[3,10,11] In sarcoma-expert centers,[12-14] selected histotypes are

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known for their particular sensitivity and resistance to certain classes of drugs—alveolar soft part sarcomas are chemoresistant, but sensitive to immunotherapy[15] and targeted therapies,[16] synovial sarcomas are more chemosensitive,[17] and solitary fibrous tumors[18] are responsive to tyrosine kinase inhibitors, among other examples.[19-21] As such, close collaboration between the sarcoma and early phase trial teams is needed to identify the signals of efficacy in these rare tumors.

The drug development field in oncology has been transformed over the past decade. Early phase trials have become increasingly safe, biomarker driven, and effective.[22] Thus, early phase trials may represent a valid therapeutic option,[23] specifically in STS, as some histotypes are notoriously resistant to all standard-of-care treatments. In the past decade, participation in early phase trials has been offered to patients at earlier stages of disease. This study aimed to investigate the clinical benefits of these new approaches.

Our main objective was to identify the prognostic factors for PFS in early phase trials for patients with STS. The secondary objectives were to describe other efficacy endpoints [OS, ORR, and disease-control rate (DCR)], their association with trials and patient clinical characteristics, and safety of early phase trials. Toward this goal, we analyzed the outcomes of STS patients treated in early phase trials between 2012 and 2020 in two expert sarcoma centers.

METHODS AND MATERIALS

Study design and population

All STS patients participating in early phase trials at the Drug Development Department of Gustave Roussy and the early phase trial unit of Centre Léon Bérard between 1 January 2012 and 31 December 2020 were included in this retrospective analysis. Patients with bone sarcomas, gastrointestinal stromal tumors (GISTs), and small round cell tumors were excluded.

In both centers, the trial selection decision is made after discussion between the sarcoma medical team and the drug development team. Patients with available standard-of-care therapeutic options are not usually offered inclusion in early phase trials in the first-line setting. The reasons for inclusion in the first-line setting in early phase trials are absence of standard-of-care therapeutic option due to histology, patient refusal of chemotherapy-based regimen, and medical contraindication to standard-of-care treatment (i.e. prior receipt of chemotherapy for a previous cancer with dose-limiting toxicity).

Two cohorts of patients were studied separately: one included patients with advanced STS (locally advanced non-resectable and/or metastatic) and the other included systemic treatment-naïve patients with localized resectable STS undergoing surgical resection after early phase trial treatment (neoadjuvant trial treatment).

The types of treatments tested in the trials were grouped into five categories based on the main molecule studied: chemotherapy, targeted therapy, immunotherapy, combination immunotherapy—targeted therapy, or other types of treatments. The other type of treatment group included two trials: one with nanoparticles and one with radiolabeled targeted treatment. The targeted therapy group included multikinase inhibitors, antibody—drug conjugates, and targeted antibodies. The immunotherapy group included immune checkpoint inhibitors, intratumoral immune-stimulating agents, bispecific T-cell engagers, and modified T-cell infusions.

Trials were classified based on screening by either molecular biology (e.g. biomarkers such as RB1 deletion, IDH mutation, PD-L1 expression, *TP53* wild-type), histology (either specific to all STS or to a certain histotype of STS), or neither of these two screening modalities (pan-tumor trials). Further, we recorded whether trials were first-in-human trials and/or escalation dose cohorts.

Data collection

This was a retrospective analysis, although efficacy and safety endpoints were prospectively collected within respective trials. The last follow-up status was checked for all patients in April 2021. Clinical data collected within trials included pathology [histotype, Federation Nationale des Centre de Lutte Contre le Cancer (FNCLCC) grade, STS with complex genomic profile or not], baseline characteristics at trial inclusion (age, performance status, number of metastatic sites, presence of liver and lung metastasis), and Royal Marsden Hospital (RMH) score.[24] The RMH score is a recognized prognostic score for inclusion of patients in early phase trials. It is based on lactate dehydrogenase (>normal) levels, albumin (<35 g/l) levels, and number of metastatic sites (>2). Patients with a favorable RMH score have a significantly longer survival in early phase trials[25] (scoring from 0 to 3, with 0 being favorable and 3 being unfavorable). All trial-related characteristics were recorded according to the specific protocol requirements. For instance, the Common Terminology Criteria for Adverse Events version 4 or 5 were used according to each trial specification.[26] Similarly, for the ORR and DCR, data were recorded either according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 or immune-related RECIST, as specified for each protocol.

All lines of treatment before and after inclusion in the trial were recorded retrospectively. Responses to these other lines of treatment were recorded as assessed by local radiology reports.

Statistical analysis

Categorical variables are reported as percentages and continuous variables as medians and ranges. Categorical variables were compared using the chi-square test or Fisher's exact test, as required. When exact *P* values could not be computed due to small numbers, Monte Carlo simulations of Fisher's test were used to simulate *P* values. The Wilcoxon rank sum test was used to compare continuous variables. PFS was defined as the time from the first day of treatment to progression as recorded in the protocol

or death. Time on treatment was defined as the time from the first dose of treatment to the end of treatment, as recorded in the protocol. OS was defined as the time from the first day of treatment to death. For the localized cohort, disease-free survival (DFS) was defined as the time from surgery to relapse or death.

Follow-up times were calculated using the reverse Kaplan–Meier method. Survival curves were generated using the Kaplan–Meier method and compared using log-rank tests. Associations between survival and variables of interest were assessed using univariate and multivariate Cox models. A hazard ratio (HR) of <1 indicated a favorable prognostic impact. All variables with $P < 0.1$ in univariate analysis were included in the multivariate analysis.

In the advanced-setting cohort, a subgroup analysis was carried out to examine anthracycline-naïve patients included in early phase trials.

All statistical tests were carried out using the R software v4.0.4 (script and data available upon request).

Ethical considerations

All patients signed informed consent at inclusion in specific trials. The use of the previously acquired data was declared to the French National Data Registry under the MR004 regulation and consent was waived for this specific retrospective study.

RESULTS

Patient characteristics

A total of 225 patients accounted for 240 inclusions: 214 inclusions in the advanced setting and 26 inclusions in the localized setting (Table 1). In the advanced setting, 13 patients were included in two early phase trials throughout the course of their disease and one patient was included in three early phase trials, therefore accounting for 29 inclusions for 14 patients. The other 211 patients were included only in one early phase trial.

In the advanced setting, the most frequent histotype was well-differentiated/dedifferentiated liposarcoma (WD/DDLPS; n = 55) followed by leiomyosarcoma (n = 53), synovial sarcoma (n = 22), undifferentiated pleomorphic sarcoma (UPS; n = 15), angiosarcoma (n = 12), myxoid liposarcoma (n = 10), myxofibrosarcoma (n = 7), and pleomorphic rhabdomyosarcoma ($N = 6$; Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.esmoop.2022.100425). The FNCLCC grades were 1, 2, and 3 in 25%, 31%, and 44% of the inclusions, respectively. There were 21 (10%), 50 (23%), and 143 (67%) inclusions in the first, second, and later lines, respectively. The median prior number of lines was significantly different across histotypes ($P < 0.001$): one in WD/DDLPS and UPS patients; two in angiosarcoma, synovial sarcoma, and other histotype patients; three in leiomyosarcoma and myxofibrosarcoma patients; and four in myxoid liposarcomas and pleomorphic rhabdomyosarcoma patients (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100425). Overall, 22 patients (10%) had locally advanced non-resectable disease. All these patients had been deemed unresectable in multidisciplinary tumor boards before inclusion.

In the localized resectable cohort, the most common histology was myxoid liposarcomas (n = 15), followed by well-differentiated liposarcomas (n = 3). The median age was 52 years, and all but one patient had a performance status of 0 or 1. Only four patients (18%) had FNCLCC grade 3 STS.

Efficacy in advanced soft-tissue sarcomas

Trial characteristics. The patients were included in 46 different trials: 8 required molecular screening (53 inclusions, 25%) and 24 were histology-driven (132 inclusions, 62%). There were 9, 117, 58, 18, and 12 inclusions in chemotherapy-based, targeted therapy-based, immunotherapy-based, immunotherapy–targeted therapy combination, or other therapy regimens, respectively (Table 1; Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100425). Radiation therapy was administered during the trial in 49 patients (23%). Patients included in immunotherapy trials were more likely to receive radiation therapy as part of the trial ($P < 0.001$; Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100425). Overall, 49% of the patients were included in trials of combination treatment (n = 104). Inclusions were made in first-in-human trials for 84 patients (39%) and in dose-escalation cohorts in 127 patients (59%).

Distribution of population in trials. Owing to the small numbers, we could not test for association between histotype and type of treatment tested in the trial (Supplementary Tables S2 and S3, available at https://doi.org/10.1016/j.esmoop.2022.100425). However, Monte Carlo simulation suggested that this allocation was not random ($P < 0.001$). We noted that WD/DDLPSs were more likely to receive targeted therapy (n = 43; 78% versus 55% in the entire cohort). Histological grade was significantly different according to the type of treatment ($P = 0.046$): grade 1 STS were more frequently included in targeted therapy regimens (n = 31/117; 34% versus 25% of grade 1 STS in the entire cohort).

The association between the type of STS and molecular or histology-driven screening could not be tested, but simulations suggested that this was not random ($P < 0.001$). Leiomyosarcomas and pleomorphic rhabdomyosarcomas were included in trials with molecular screening in most cases (45% and 67%, respectively), whereas all other histotypes were included in histology-driven trials in most cases (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100425). Furthermore, molecular screening was seen only in targeted therapy (n = 51/117; 44%) and immunotherapy trials (n = 2/58; 3.4%; Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100425). Targeted therapy trials were the only class of drugs for which inclusions were more likely to be restricted by molecular screening. Most inclusions

Table 1. Characteristics of patients with advanced and localized soft-tissue sarcomas in early phase trials

	Advanced, $N = 214$	Localized, $N = 26$
Center		
CLB	89 (42%)	12 (46%)
GR	125 (58%)	14 (54%)
Sex		
Female	116 (54%)	9 (35%)
Male	98 (46%)	17 (65%)
Age at inclusion, years (median, IQR)	56 (47, 64)	52 (44, 58)
Histotype		
WD/DDLPS	55 (26%)	3 (12%)
Leiomyosarcoma	53 (25%)	1 (4%)
UPS	15 (7%)	1 (4%)
Angiosarcoma	12 (5%)	—
Synovial sarcoma	22 (10%)	1 (4%)
Myxoid liposarcoma	10 (5%)	15 (58%)
Myxofibrosarcoma	7 (3%)	1 (4%)
Pleomorphic rhabdomyosarcoma	6 (3%)	1 (4%)
Other	34 (16%)	3 (12%)
FNCLCC grade		
1	42 (25%)	10 (45%)
2	51 (31%)	8 (36%)
3	72 (44%)	4 (18%)
Unknown	49	4
Genomic profile		
Simple	110 (52%)	20 (77%)
Complex	103 (48%)	6 (23%)
Unknown	1	—
Number of prior lines	2 (1, 4)	—
Systemic treatment line of trial		
First line	21 (10%)	26 (100%)
Second line	50 (23%)	—
Third line or more	143 (67%)	—
Prior anthracycline treatment	173 (81%)	—
Stage		
Localized	—	26 (100%)
Locally advanced inoperable	22 (10%)	—
Metastatic	192 (90%)	—
Number of metastatic sites		
0-1	94 (44%)	26 (100%)
2+	120 (56%)	—
Presence of liver metastasis	46 (21%)	—
Presence of lung metastasis	125 (58%)	—
Main molecule in trial		
Chemotherapy	9 (4%)	11 (42%)
Targeted therapy	117 (55%)	—
Immunotherapy	58 (27%)	1 (4%)
Immunotherapy—targeted therapy	18 (8%)	—
Others	12 (6%)	14 (54%)
Screening		
Molecular	53 (25%)	—
Histology-driven	132 (62%)	26 (100%)
None	29 (14%)	—
Adriamycin combination	5 (2.3%)	—
Radiation therapy during trial	49 (23%)	25 (96%)
Combination treatment during trial	104 (49%)	25 (96%)
First-in-human	84 (39%)	14 (54%)
Dose escalation	127 (59%)	15 (58%)
Performance status		
0	82 (38%)	20 (77%)
1	122 (57%)	5 (19%)
2	7 (3%)	1 (4%)
3	2 (1%)	—
Unknown	1	0
RMH score		
0	42 (22%)	22 (85%)
1	90 (46%)	4 (15%)
2	50 (26%)	—
3	12 (6%)	—
Unknown	20	—

CLB, Centre Léon Bérard; FNCLCC, Fédération Nationale des Centre de Lutte Contre le Cancer; GR, Gustave Roussy; IQR, interquartile range; RMH, Royal Marsden Hospital; UPS, Undifferentiated Pleomorphic Sarcoma; WD/DDLPS, Well-differentiated and dedifferentiated liposarcoma.

were made in histology-driven trials for all other treatment cohorts. Histology of patients included in pan-tumor trials were as follows (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100425): 12 WD/DDLPS, 6 leiomyosarcomas, 3 UPS, 1 synovial sarcoma, 3 myxoid liposarcoma, 1 pleomorphic rhabdomyosarcoma, and 3 other histotypes (1 clear cell sarcoma, 1 histiocytoid tumor, and 1 extraskeletal myxoid chondrosarcoma).

Patients included in immunotherapy trials were more heavily pre-treated and had a greater disease burden (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100425). The median number of prior lines of treatment was significantly higher in the immunotherapy cohort compared to all other treatment cohorts (4 versus 2, $P < 0.001$). Among patients included in immunotherapy trials, 78% had two or more metastatic sites (chemotherapy, 56%; targeted therapy, 45%; combination immunotherapy—targeted therapy, 67%; others, 42%; $P < 0.001$).

The median time on treatment was not significantly different according to treatment type ($P = 0.22$; Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100425) but was significantly different according to treatment line: 3.4 [95% confidence interval (CI) = 1.9-8.4] versus 3.4 (95% CI = 2.3-6.2) versus 2.3 (95% CI = 1.9-2.8) months for the first, second, and later lines, respectively ($P = 0.017$; Figure 1).

Survival. The median PFS for the entire cohort was 2.8 months (95% CI 2.7-4.1 months). WD/DDLPS and myxofibrosarcoma had the longest median PFS (5.3 and 5.4 months, respectively), followed by UPS (4.3 months), other histotypes (4.2 months), and leiomyosarcomas (3.3 months).

The median PFS for patients included in the first, second, or later lines was 8.3 [95% CI 5.3-not reached (NR)], 5.4 (95% CI 2.8-8.1), and 2.6 months (95% CI 2.1-3.1 months), respectively ($P = 0.00015$; Figure 2). The 6-month PFS rates were 64%, 44%, and 18% in the first, second, and later lines, respectively ($P < 0.001$). The 3-month PFS rates were 79%, 58%, and 42% in the first, second, and later lines, respectively ($P = 0.007$). The median PFS was 2.8 months (95% CI 1.9-3.7) in molecular screening trials, 4.1 months (95% CI 3.0-5.5 months) in histology-driven trials, and 1.6 months (95% CI 1.3-2.2 months; $P = 0.00014$) in pan-tumor trials (Figure 3).

Figure 1. Swimmer's plot by histotype and line of treatment of advanced soft-tissue sarcoma patients included in early phase trials.
For each histotype, patients are grouped by treatment line of early phase trial, starting (top) with patients included in the first-line setting (L1) then in the second line (L2) or later lines (L3). The figure is colored by type of treatment in the trial and shows that treatment type allocation is dependent on histotype and line of treatment. EOT, end of treatment; UPS, undifferentiated pleomorphic sarcoma; WD/DDLPS, well-differentiated and dedifferentiated liposarcoma.

In univariate analysis, factors significantly associated with shorter PFS were particular histotypes ($P = 0.026$), complex genomics ($P = 0.008$), number of prior lines ($P = 0.00037$), prior anthracycline treatment ($P = 0.00046$), number of metastatic sites ($P = 0.0033$), liver metastasis ($P = 0.00071$), lung metastasis ($P = 0.00087$), absence of molecular or histology-driven screening ($P = 0.0002$), first-in-human trials ($P = 0.00047$), dose-escalation cohorts ($P = 0.011$), and RMH score >1 ($P < 0.0001$; Table 2).

In multivariate analysis, factors that were significantly associated with shorter PFS were myxoid liposarcoma histology (HR = 3.14; $P = 0.031$), inclusion after two previous lines of treatment (HR = 3.59; $P = 0.033$), presence of liver metastasis (HR = 2.32; $P = 0.007$), and RMH score >1 (HR = 2.20; $P = 0.006$). The factors that were significantly associated with improved PFS were leiomyosarcoma histology (HR = 0.17; $P = 0.010$), molecular screening (HR = 0.44; $P = 0.025$), and histology-driven trials (HR = 0.40; $P = 0.010$). Leiomyosarcoma histology was associated with unfavorable prognosis in univariate analysis (HR = 1.59; 95% CI 1.02-2.49) and with favorable prognosis in multivariate analysis, as the latter accounts for number of

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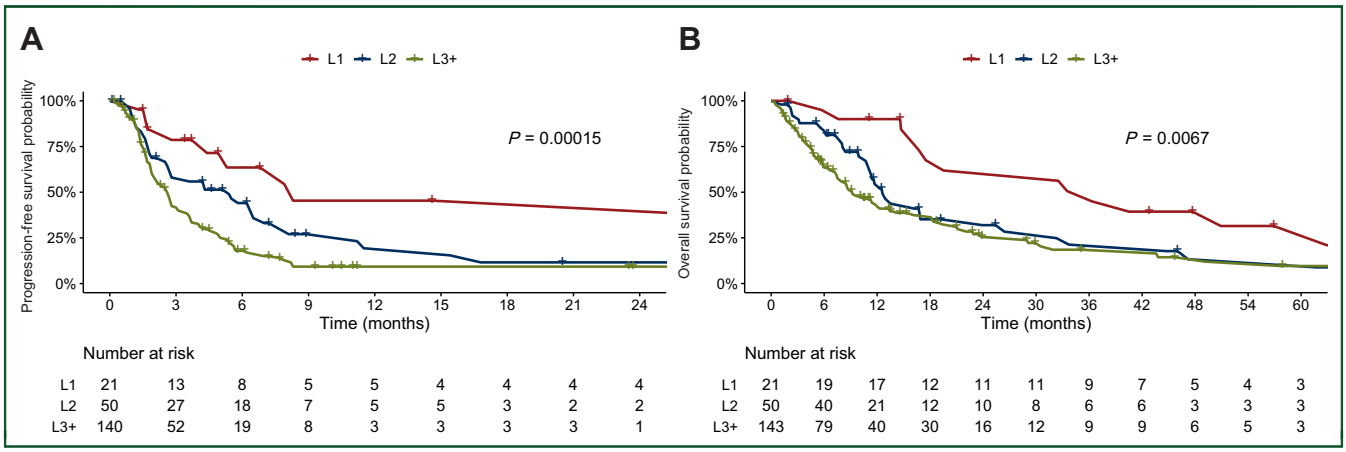

Figure 2. Kaplan–Meier survival curves according to line of treatment at inclusion in early phase trials for advanced soft-tissue sarcoma patients.
(A) Progression-free survival. (B) Overall survival.
L1, first-line setting; L2, second-line setting; L3+, third line or later. *P* values are log-rank for comparison of survival curves.

previous lines and leiomyosarcoma patients were more heavily pre-treated.

Within a median follow-up of 35 months, the median OS in the entire population was 12.3 months (95% CI 10.5-16.7). In the first, second, and later lines, the median OS was 36.3 (95% CI 17.5-NR), 12.6 (95% CI 11.3-26.4), and 9.2 (95% CI 7.5-13.4) months, respectively ($P = 0.0067$).

As reported in patients' characteristics and displayed by the long median OS in first-line setting, inclusions in the first-line setting were histotype driven. Thus, histotypes of STS patients included in the first line were as follows: 11 WD/DDLPS, 3 UPS, 1 myxoid liposarcoma, 1 myxofibrosarcoma, 2 inflammatory myofibroblastic tumors, 1 pigmented villonodular synovitis, and 1 malignant peripheral nerve sheath tumor (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2022.100425). The subgroup analysis of histotype-specific survival curves and median PFS in the WD/DDLPS, UPS, and other histotype groups displayed consistent trends of improved survival in the first-line setting, followed by the second-line setting (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100425; Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100425). Only one patient was included in the first-line setting in the myxofibrosarcoma cohort and had dismal prognosis. In multivariate analysis accounting for histology, inclusion in the second-line compared to the first-line setting was not associated with shorter PFS, but inclusion in later lines remained an independent prognostic factor for dismal PFS.

Response rate. The ORR was 9.5% (n = 19/214), and the DCR was 61.5% (n = 123) in the entire advanced STS cohort. No responses were noted in angiosarcoma, myxofibrosarcoma, or pleomorphic rhabdomyosarcoma patients (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2022.100425). Both ORR ($P = 0.038$) and DCR ($P = 0.013$) were significantly higher in earlier lines of treatment: 25% and 85% in the first line, 11% and 70% in the second line, and 6.8% and 55% after the second line, respectively. Neither ORR nor DCR differed by drug class. The ORRs were 8.3%, 12%, and 0% in the trials with molecular screening, histology-driven screening, and pan-tumor trials, respectively ($P = 0.12$). Meanwhile, the DCRs

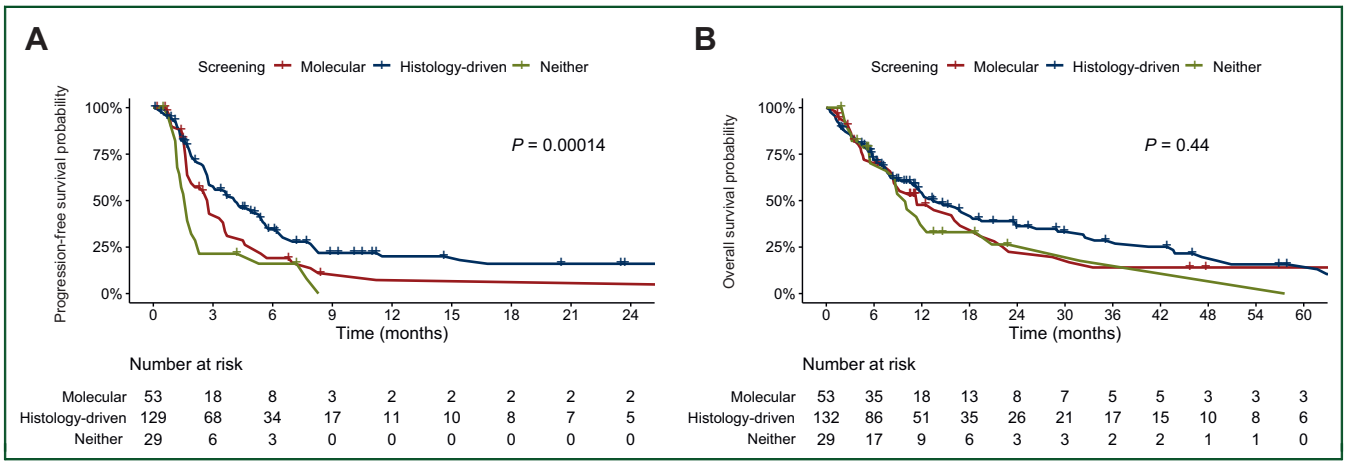

Figure 3. Kaplan–Meier survival curves according to molecular or histology-driven screening at inclusion in early phase trials for advanced soft-tissue sarcoma patients.
(A) Progression-free survival. (B) Overall survival. *P* values are log-rank for comparison of survival curves.

Table 2. Survival according to clinical characteristics for advanced soft-tissue sarcoma patients included in early phase trials

	n	Median PFS (months)	3-month PFS rate (%)	6-month PFS rate (%)	Univariate Cox HR (95% CI)	Univariate Cox *P* value	Multivariate Cox HR (95% CI; *P* value)
Sex						0.82	
Female	116	3.5	53	32	—		—
Male	98	2.8	45	31	0.96 (0.70-1.32)		—
Age at inclusion					1.00 (0.99-1.01)	0.67	—
Histotype						**0.026**	
WD/DDLPS	55	5.3	54	45	—		—
Leiomyosarcoma	53	3.3	52	19	1.59 (1.02-2.49)		**0.17 (0.04-0.65, *P* = 0.010)**
UPS	15	4.3	52	22	1.39 (0.71-2.74)		0.47 (0.11-2.01, *P* = 0.311)
Angiosarcoma	12	1.8	18	9.1	2.75 (1.39-5.44)		0.45 (0.08-2.52, *P* = 0.361)
Synovial sarcoma	22	2.7	35	17	1.98 (1.11-3.53)		1.12 (0.54-2.31, *P* = 0.755)
Myxoid liposarcoma	10	1.6	33	22	1.38 (0.61-3.10)		**3.14 (1.11-8.88, *P* = 0.031)**
Myxofibrosarcoma	7	5.4	51	34	1.32 (0.52-3.36)		0.24 (0.04-1.42, *P* = 0.115)
Pleomorphic rhabdomyosarcoma	6	2.5	—	—	2.56 (0.99-6.62)		0.27 (0.05-1.54, *P* = 0.140)
Other	34	4.2	66	38	0.88 (0.52-1.51)		0.92 (0.35-2.46, *P* = 0.875)
FNCLCC Grade						0.082	
1	42	5.4	62	43	—		—
2	51	2.8	49	29	1.65 (0.99-2.75)		2.02 (0.99-4.10, *P* = 0.052)
3	72	2.8	45	27	1.69 (1.04-2.73)		1.99 (1.00-3.99, *P* = 0.051)
Genomic Profile						**0.008**	
Simple	110	3.7	54	37	—		—
Complex	103	2.7	43	19	1.54 (1.12-2.12)		3.10 (0.89-10.84, *P* = 0.076)
Number of prior lines					1.16 (1.07-1.25)	**0.00037**	—
Systemic treatment line of trial						**0.00028**	
First line	21	8.3	79	64	—		—
Second line	50	5.4	58	44	2.06 (0.98-4.33)		2.97 (0.89-9.95, *P* = 0.077)
Third line or more	143	2.6	42	18	3.40 (1.70-6.81)		**3.59 (1.11-11.59, *P* = 0.033)**
Prior anthracycline treatment						**0.00046**	
No	41	6.5	74	57	—		—
Yes	173	2.7	43	22	2.27 (1.43-3.58)		1.20 (0.55-2.59, *P* = 0.648)
Number of metastatic sites						**0.0033**	
0-1	94	5.3	61	42	—		—
2+	120	2.7	39	17	1.62 (1.18-2.24)		0.75 (0.40-1.42, *P* = 0.378)
Presence of liver metastasis						**0.00071**	
No	168	3.5	52	34	—		—
Yes	46	2.1	35	5.90	1.93 (1.32-2.82)		**2.32 (1.26-4.30, *P* = 0.007)**
Presence of lung metastasis						**0.00087**	
No	89	5.4	59	45	—		—
Yes	125	2.7	42	17	1.76 (1.26-2.46)		1.51 (0.77-2.95, *P* = 0.228)
Main molecule in trial						0.7	
Chemotherapy	9	3.5	50	38	—		—
Targeted therapy	117	3.5	53	32	1.03 (0.45-2.36)		—
Immunotherapy	58	2.8	44	23	1.17 (0.50-2.74)		—
Immunotherapy—targeted therapy	18	3.7	56	31	1.00 (0.37-2.68)		—
Other	12	1.9	28	18	1.61 (0.58-4.45)		—
Screening						**0.0002**	
Molecular	53	2.8	43	19	0.61 (0.37-1.00)		**0.44 (0.21-0.90, *P* = 0.025)**
Histology-driven	132	4.1	58	35	0.40 (0.26-0.63)		**0.40 (0.20-0.80, *P* = 0.010)**
Neither	29	1.6	21	16	—		—
Adriamycin combination						0.4	
No	209	2.8	49	28	—		—
Yes	5	—	80	—	0.43 (0.06-3.1)		—
Radiation therapy during trial						0.17	
No	165	2.8	45	27	—		—
Yes	49	5.0	64	34	0.77 (0.53-1.12)		—
Combination treatment during trial						0.1	
No	110	2.6	43	25	—		—
Yes	104	4.0	56	32	0.77 (0.56-1.05)		—
First-in-human						**0.00047**	
Yes	84	2.5	39	18	1.77 (1.28-2.43)		1.64 (0.92-2.92, *P* = 0.094)
No	130	3.7	55	34	—		—
Dose escalation						**0.011**	
Yes	127	2.8	45	23	1.53 (1.10-2.12)		0.85 (0.46-1.57, *P* = 0.595)
No	87	4.3	55	36	—		—
Performance status						0.066	
0-1	204	2.8	49	29	—		—
2+	9	2.5	33	—	2.17 (0.95-4.95)		2.02 (0.64-6.31, *P* = 0.229)

Continued

Table 2. Continued

	n	Median PFS (months)	3-month PFS rate (%)	6-month PFS rate (%)	Univariate Cox HR (95% CI)	Univariate Cox *P* value	Multivariate Cox HR (95% CI; *P* value)
RMH score						**<0.0001**	
0-1	132	4.1	58	36	—		—
2-3	62	2.1	28	2.9	2.60 (1.81-3.72)		**2.20 (1.26-3.84, *P* = 0.006)**

95% CI, 95% confidence interval; FNCLCC, Fédération Nationale des Centre de Lutte Contre le Cancer; HR, hazard ratio; PFS, progression-free survival; RMH, Royal Marsden Hospital; UPS, undifferentiated pleomorphic sarcoma; WD/DDLPS, well-differentiated and dedifferentiated liposarcoma.
Bold values indicate significant statistical tests.

were 62.5%, 67%, and 35.7%, respectively ($P = 0.01$). For first-in-human trials and escalation cohorts, the ORRs were significantly lower (4% versus 13%; $P = 0.032$, and 5% versus 16%; $P = 0.012$, respectively; Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2022.100425).

Anthracycline-naïve patients. A subgroup of 41 patients were included without prior anthracycline treatment (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2022.100425). Of them, 18 patients had WD/DDLPS. These patients had lower-grade STS (grade 1: 47% versus 20% in patients who received prior anthracyclines; $P = 0.005$), were less pre-treated (median prior lines: 0 versus 3; $P < 0.001$), and had lower disease burden (29% versus 62% patients with more than one metastatic site; $P < 0.001$). Most patients in this cohort were included in the first-line setting (51%; n = 21).

Compared to patients who had received prior anthracycline treatment, anthracycline-naïve patients had significantly higher ORRs (21% versus 6.8%; $P = 0.015$) and DCRs (82% versus 57%; $P = 0.003$; Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2022.100425). The median PFS in this subgroup was 6.5 months (95% CI 5.3-NR months), whereas it was 2.7 months in patients who received a prior anthracycline-based chemotherapy regimen (95% CI 2.2-3.5 months; $P = 0.00031$; Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2022.100425).

The median OS was 32.5 months (95% CI 16.7-62.9 months) in anthracycline-naïve patients and 10.5 months (95% CI 8.4-13.5 months) in non-anthracycline-naïve patients, respectively ($P = 0.00026$). As with patients included in the first-line setting, this long OS displays an important histotype-specific trend.

After the end of the trial, 12 patients received anthracyclines (31%). No response was recorded to anthracyclines given after the trial. The median PFS with anthracyclines administered after the trial was 1.9 months. This lack of response to anthracyclines also points toward histotype selection: patients included in early phase trials without prior receipt of anthracyclines had STS histotypes known for their poor sensitivity to anthracyclines.

Efficacy in localized resectable soft-tissue sarcomas

Patients were included in three trials, two of which were combinations with radiation therapy. Thus, 25 of 26 patients in this cohort received radiation therapy preoperatively. The ORR and DCR were 69% and 100%, respectively. The end of the treatment was due to planned surgery in all cases. Median DFS was not reached. With a median follow-up of 49.4 months (4.1 years), only four patients relapsed (15%) at 9.1, 10.6, 21.4, and 60.8 months (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2022.100425).

Toxicity

No toxic deaths were reported in either the localized or advanced setting. Eleven deaths were reported during the trial, all in the advanced cohort. The end of treatment was due to toxicity in 18 patients (7%). Grade 3-4 toxicity was reported in 87 patients (36%) and was significantly different according to RMH score and class of drug in the trial ($P = 0.001$ and $P = 0.003$, respectively; Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2022.100425). Targeted therapy treatments yielded higher grade 3-4 toxicity rates ($N = 55/117$; 47%; $P = 0.003$). The rate of grade 3-4 toxicity was significantly higher in patients with RMH score >1 than in those with a lower RMH score [53% (n = 33/62) versus 30% (n = 47/158); $P = 0.001$]. First-in-human trials and dose-escalation cohorts did not yield higher toxicity rates ($P = 0.7$ and $P = 0.5$, respectively).

DISCUSSION

This study found a 6-month PFS rate of 64% in the first-line therapy, a 3-month PFS rate of 58% in the second-line therapy, and a 3-month PFS rate of 42% in later lines with early phase trials in STS. This is superior to the classical 40% at 3 months recognized as active drugs.[27] A promising efficacy in phase II trials is suggested in STS when the 6-month PFS rate is 30%-56% in the first-line setting and the 3-month PFS rate is >40% in the second-line setting.[27] Although these thresholds have yet to be updated with newer trials, our data compare favorably to these recognized endpoints. Importantly, participation in early phase trials in the first-line treatment did not seem to impair OS in our cohort.[28,29]

As previously mentioned, patients included in the first-line setting in early phase trials had no safe standard-of-care therapeutic option or refused standard-of-care chemotherapy. However, participation in early phase trials in the first-line setting did not seem to impair OS in our cohort.[28,29] Further, multivariate analysis, accounting for histotype

differences, showed that inclusion after second line was an independent adverse prognostic factor for PFS, but not inclusion in the second line. Further, patients may be less fit for inclusion in early phase trials after multiple lines of treatment. As most STS histotypes have limited therapeutic systemic options after failure of anthracycline in the first-line setting, early phase trials provide a valid therapeutic option in the second-line setting, after careful selection of the trial between the sarcoma team and the drug development team. Further, inclusion in the second line rather than the first line allows to compare disease trajectory between standard-of-care and trial treatments within the same patient population, using the PFS2/PFS1 ratio.

We describe two unusual subgroups of patients for early phase trials in STS: anthracycline-naïve patients and localized resectable patients with a combination of radiation therapy. In the anthracycline-naïve cohort, patients included in this setting were overall anthracycline resistant. In the localized cohort, the trials tested concurrent radiation with a systemic drug which was known to be safe. In both cohorts, patients were highly selected, and caution is advised before including STS patients in early phase trials in these settings. While inclusion in early phase trials in these settings should not be routinely recommended, our study suggests that after careful multidisciplinary discussions in specific situations, some early phase trials have a clinical benefit for STS patients in anthracycline-naïve and localized sarcomas.

Compared to other previous reports of STS patients included in early phase trials,[30,31] our survival data showed a mild improvement in PFS and OS. Jones et al. reported a median PFS of 2.1 months in 2011, whereas ours is 2.8 months.[30] In 2014, Cassier et al. reported a median OS of 9.1 months, whereas ours is 12.3 months.[31] Some of these discrepancies may be explained by the progress made since these reports.

The landscape of drugs tested is more diverse and effective, with the notable introduction of immunotherapy[32] and an increase in number of combination trials.[33] Dose-escalation protocols allow a faster dose increase. Thus, more patients are on efficient doses.[34] Early phase trial designs have shifted to more adaptive (and sometimes Bayesian) designs and frequently include expansion cohorts, allowing the selection of specific histotypes in case of early signals of efficacy.[35] Furthermore, our data showed that allocation to treatments was not random: clinicians chose to include patients in certain trials based on improved knowledge of sarcoma biology and sensitivity to class of drugs.

Importantly, screening on molecular biology or histology yielded better survival and response rates than did pan-tumor trials. Histology-driven trials displayed the greatest clinical benefit. In the later phases of drug development, the field of sarcoma is moving toward histotype-specific trials due to recent failures of pan-histology phase III trials.[3,10,36] Our data support a clinical benefit of histology-driven trials in the early phase of drug development.

The survival benefit from molecular screening in early phase trials seemed inferior to that from histology-driven trials. Molecular screening in early phase trials is based on pre-clinical molecular rationale, whereas histology-driven trials are more commonly based on clinical experience of sensitivity to certain classes of drugs. However, multivariate analysis showed an improved PFS for both histology-driven and molecular screening with similar HRs in multivariate analysis, highlighting that the discrepancy in PFS improvement observed between these two screening methods might be driven by other confounding factors, such as histotypes or class of drugs tested.

This study has some limitations. First, it is a retrospective study with inherent bias, although our main endpoints of survival, response, and toxicity were prospectively recorded within trials. Second, there was a bias toward inclusion of particular histotypes and FNCLCC grade STS in trials according to the class of drugs tested. However, this is representative of clinical practice. Third, patients who are offered enrollment in early phase trials are always highly selected and particularly fit patients. Thus, inclusion of STS patients in early phase trials in the first-line, anthracycline-naïve, or neoadjuvant settings should only be considered in highly selected cases, after discussion in multidisciplinary tumor boards and in-depth discussion with the patients.

In conclusion, our data suggest that early phase trials can be a valid therapeutic option for early-stage STS patients, after careful selection by sarcoma and early phase trial teams. Molecular and histology-driven screening improve the clinical benefit for patients.

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