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Systemic Treatment for Advanced Soft Tissue Sarcoma beyond Doxorubicin and Ifosfamide

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ABSTRACT

Systemic therapy is the backbone in the management of advanced soft-tissue sarcoma.At present, anthracycline-based regimes represents the standard first-line treatment, but there are other active drugs widely used, providing additional therapeutic options and increasing overall survival among patients with advanced disease. Histologic subtype, patient characteristics, and expected toxicity profile are factors to take into account in the election of second and subsequent lines, giving the absence of direct comparative studies or predictive biomarkers.

Keywords: Advanced soft-tissue sarcoma; Chemotherapy; Targeted therapies; Systemic therapy

INTRODUCTION

Soft-Tissue Sarcoma **(STS)** is a heterogeneous group of more than 50 different subtypes, representing about 2% of all solid tumors in adults [1] and about 5 new cases per 100.000 per year in Europe [2]. Sarcomas can arise in any part of the organism, can be both visceral and somatic, and surgery (and adjuvant radiotherapy when indicated) is the mainstay of therapy in the localized setting [3]. In spite of correct local treatment, about one third of patients will eventually develop metastasis and ultimately die due to disease progression. Anthracycline-based regimes (in combination with ifosfamide in many cases) have been the backbone in soft-tissue sarcomasystemic therapy in the last thirty years, being the drugs used in the adjuvant setting, if advised, and in the first line of advanced disease. At present, there is no demonstration of the superiority of multiagent chemotherapy over single agent chemotherapy with doxorubicin alone in terms of Overall Survival **(OS)** in advanced disease [4]. However, the combination seems to be superior in terms of volumetric response, being a valuable option when tumor shrinkage is needed to palliate symptoms or to facilitate a surgery.

Besides anthracyclines and ifosfamide, other cytotoxic drugs have been for a long time used in STS as dacarbazine, gemcitabine and taxanes. In the last decade, trabectedin and pazopanib have been emerged in the therapeutic armamentarium. Currently, the median of overall survival for metastatic STS is no longer 12 months but around 18 months. This beneficial change in efficacy could be attributed to new active second lines in STS [5].

The increase of knowledge on molecular pathogenic basis, especially in some uncommon STS, has enabled us to offer targeted successful therapies, which ended up good tumor control.

Gemcitabine Combinations

Gemcitabine is a nucleoside analogue, widely used in the treatment of sarcomas. Several small clinical trials have assessed the efficacy of gemcitabine alone or in combination with docetaxel or dacarbazine, showing its activity [6] (Table 1).

Table 1: Gemcitabine- based studies in soft-tissue sarcoma.

Type of study	Population	n	Shedule	RECIST RR (%)	3-month PFS (%)	6-month PFS (%)	Median OS (months)	Ref
Phase II	STS	39	Gem 1000 mg/m2 30' weekly 7/8 weeks	18	NS	NS	NS	Patel
Phase II	Pretreated uterine LMS	48	Gem 900 mg/m2 90' d1,8 + Docetaxel 100 mg/m2 d8, 21d	27.1	72.9	52	14.7	Hensley
Rand Phase II	Pretrated STS	49 73	Gem 1200 mg/m2 120' d1,8 vs Gem 900 mg/m2 90' d1,8 + Docetaxel 100 mg/m2 d8, 21d	8 17	NS	NS	11.5 17.9	Maki
Rand Phase II	Pretreated LMS Uterine	21 21	Gem 1000 mg/m2 100' d1,8,15 vs Gem 900 mg/m2 90' d1,8 + Docetaxel 100 mg/m2 d8, 21d	19 24	57 71	48 48	20 23	Pautier
	Non- uterine	22 19	Gem 1000 mg/m2 100' d1,8,15 vs Gem 900 mg/m2 90' d1,8 + Docetaxel 100 mg/m2 d8, 21d	14 5	68 53	50 47	15 13	
Phase II	First line uterine LMS	42	Gem 900 mg/m2 90' d1,8 + Docetaxel 100 mg/m2 d8, 21d	35.7	NS	19	16	Hensley
Phase II	Pretreated STS	26	Gem 1800 mg/m2 180' + Dacarbazine 500 mg/m2, 14d	4	48	28	8.6	Lossa
Rand Phase II	Pretreated STS	54 58	Dacarbazine 1200 mg/m2, 21d vs Gem 1800 mg/m2 180' + Dacarbazine 500 mg/m2, 14d	4 12	37 56	NS NS	8.2 16.8	Garcia del Muro

PFS: Progression-Free Survival; **OS:** Overall Survival; **STS:** Soft-Tissue Sarcoma; **Gem:** Gemcitabine; **LMS:** Leiomyosarcoma; **NS:** Not Specified; **Rand:** Randomized

Gemcitabine in monotherapy has been tested both non-selected STS and metastatic leiomyosarcoma. Several schedules, with different doses and infusion times have been administered, ranging from 200mg/m^2 to 1.250mg/m^2 in 30-360 minutes, in weekly basis [6]. The most frequently used schedule consists in 1.000mg/m^2 over 30minutes days 1,8,15 every 28 days. Fixed-Dose Rates **(FDR)** of infusion of gemcitabine at 10 mg/m^2/min showed higher efficacy in carcinomas compared to short infusions [7,8] and cellular concentration of gemcitabine is higher with prolonged infusions [9], thus, many clinical trials on sarcoma used FDR of gemcitabine with prolonged infusion times. 1.000mg/m^2 at FDR of gemcitabine in leiomyosarcoma resulted in 3-month PFS rates **(PFR)** of 57% and 68% in non-uterine and uterine leiomyosarcoma respectively [10].

Combinations of gemcitabine have also been tested. The activity of the combination of gemcitabine 900mg/m^2 on days1 and 8 plus docetaxel 100 mg/m^2 on day 8 has been assessed in pretreated advanced uterine and soft-tissue leiomyosarcoma in several small phase II trials. This regimen was considered active (in accordance to EORTC definition of PFS rate at 3 months higher than 40% [11]) for leiomyosarcoma arising at all locations, although in those patients with uterine leiomyosarcomathe benefit seemed to be greater:the3-month PFR for patients with uterine leiomyosarcoma was 70–75% [10,12] in contrast to 52% in non-uterine leiomyosarcoma [10]. Data regarding the superiority of gemcitabine in combination with docetaxel versus gemcitabine

alone are conflicting. In one phase II randomized trial, conducted in all STS subtypes, patients on the combination arm showed significantly more objective responses (16% vs 8%), prolonged PFS (6.2 vs 3 months), and longer OS (17.9 vs 11.5m) [13]. However, in another phase II trial, enrolling only advanced leiomyosarcoma patients, differences were not found in terms of efficacy and the combination arm exhibited clearly more secondary side effects [10].

Another interesting, and synergistic in preclinical experiments, active combination is gemcitabine plus dacarbazine. Two phase II studies developed by the Spanish Sarcoma Group for Research on Sarcoma **(GEIS)** tested the combination of FDR gemcitabine 1800mg/m^2 and dacarbazine 500mg/m^2 every 2 weeks [14,15]. The first study showed the activity of this regimen, showing a 3-month PFR of 48% and a median PFS of 3.9 months. After this study a randomized phase II trial included 113 pretreated advanced STS patients, randomized to receive dacarbazine in monotherapy 1.200mg/m^2 every 21 days or the combination of gemcitabine 1800mg/m^2 and dacarbazine 500mg/m2 every 2 weeks. Efficacy outcome significantly favored patients on the combination arm, with 3-month PFR of56% vs 37%, median PFS of 4.2 vs 2 months and median Overall Survival **(OS)** of 16.8 vs 8.2 months.

Gemcitabine-docetaxel has also been tested in first line [16] in metastatic uterine leiomyosarcoma, showing a median PFS of 4.4months and leading to the use of gemcitabine-docetaxel in USA as upfront line (not pretreated with anthracycline) in many soft-tissue sarcomas. Recently, the study GeDDiS did not show superiority of first-line gemcitabine-docetaxel over doxorubicin alone, neither in terms of PFS nor in OS in a randomized phase III trial [17].

Despite the fact there are lacking confirmatory phase III trials, gemcitabine combinations represent an interesting therapeutic option in patients with pretreated soft-tissue sarcomas, especially in leiomyosarcomas, and probably also in other subtypes, such as undifferentiated pleomorphic sarcoma. Due to the fact of better tolerance and the absence of conflicting results incomparative trials, gemcitabine plus dacarbazine is the most frequently used gemcitabine-based combination in our country.

Trabectedin

Trabectedinis an alkaloid originally derived from the marine tunicate Ecteinascidia turbinate and now produced synthetically. Several mechanisms of action have been postulated for trabectedin. The most studied is in relation with its binding covalently to G nucleotides in the minor groove of DNA, bending DNA helix towards the major groove. This causes a widening of the DNA minor groove and stimulates the Nucleotide Excision Repair Machinery **(NER)** which cause single no reversible strand breaks instead of reparation. Additionally, as new NER proteins try to repair the DNA, a more toxic complex is formed resulting in double strand breaks [18]. Other mechanisms, as the detachment of prescription factors to their target genes are described in myxoid liposarcomas. On the other hand, antitumoral effects of trabectedin also include indirect anti-inflammatory and anti-angiogenic activity via tumor-associated macrophages [19]. Many

different schedules were used during its clinical development [20,21], being 1.5 mg/m^2 in 24h continuous infusion every 21 days, 1.3mg/m^2 in 3-hour infusion every 3 weeks and 0.58mg/m^2 weekly in 3-hour infusion, 3 weeks out of 4 consecutive weeks, the chosen regimens for phase II studies. The principal studies are summarized in Table 2. In phase II trials in pretreated sarcoma patients trabectedin showed a manageable toxicity profile, being neutropenia and elevation of transaminases the most reported G3-4 toxicities. Objective response rate by RECIST was as low as 4-8% for trabectedin [22,23,24], but interestingly,patients achieving disease stabilization were able to show a long-lasting tumor control in an early phase II trial enrolling 54 heavily pretreated sarcoma,3-month and 6-month PFR of 39% and 24% were respectively reported [22]. In another phase II EORTC studyenrolling104 previously treated patients, progression free survival at 3 and 6 months were remarkable52% and 29%, respectively [24]. Then, a randomized study comparing two schedules of trabectedin on pretreated patients with L-sarcomas (leiomyosarcoma and liposarcoma) was carried out. One hundred and thirty-four patients received 1.5mg/m^2 in 24h every 3 weeks and one hundred thirty-six patients received 0.58mg/m^2 per week. Again, the objective response rate by RECIST was low (5.6% in the every 3-weeks arm and 1.6%responses in the weekly schedule), but themedian ofPFS was significantly better in the 3-weekly arm: 3.3 months vs. 2.3 months (p=0.041). Toxicity profiles were different between the two regimens, seeing more neutropenia and liver toxicity in 3-weekly arm, but in any case, these adverse events were manageable [25].

Table 2: Trabectedin- based studies in soft-tissue sarcoma.

Type of study	Population	n	Schedule	RECIST RR (%)	3-month PFS (%)	6-month PFS (%)	Median OS (months)	Ref
Phase II	Pretreated STS	36	1.5 mg/m2, 21d	8	NA	NA	12.1	Garcia Carbonero
Phase II	Pretreated STS	54	1.5 mg/m2, 21d	4	39	24	12.8	Yovine
Phase II	Pretreated STS	104	1.5 mg/m2, 21d	8	52	29	9.2	Le Cesne
Rand Phase II	Pretreated L-sarcoma	136 134	1.5 mg/m2, 21d vs 0.58 mg/m2/w (3/4)	5.6 1.6	51.5 44.7	35.5 27.5	13.9 11.8	Demetri
Phase III	Pretreated L-sarcoma	345 173	T: 1.5 mg/m2, 21d vs DTIC:1000 mg/ m2, 21d	9.9 6.9	56 34	37 14	12.4 12.9	Demetri
Rand Phase II	Pretreated TRS	37 36	T: 1.2 mg/m2, 21d vs Best supportive care	8 0	70.3 0	44 0	NR 8	Kawai
Phase III	First-line TRS	61 60	T: 1.5 mg/m2, 21d vs Doxo 75 mg/m2	5.9 27	75 70	60 65	38.9 27.3	Blay
Phase II	First-line LMS (Uterine and ST)	47 (U) 61 (ST)	Doxo 60 mg/m2, 21d + T vs 1.1 mg/m2 3h,	59.6 39.4	87.2 91.8	72.3 90.2	20.2 34.5	Pautier

PFS: Progression-Free Survival; **OS**: Overall Survival; **STS**: Soft-Tissue Sarcoma; **TRS**: Translocation-Related Sarcoma; **T**: Trabectedin; **LMS**: Leiomyosarcoma; **NA**: Not Achieved; **Rand**: Randomized.

This led on September 2007 to the approval of trabectedin by EMA for adult patients with pretreated advanced soft-tissue sarcoma. Recently,data from a large phase III trial comparing trabectedin versus dacarbazine in advanced L-sarcoma, showed significantly better PFS favoring trabectedin arm (4.2 vs 1.5 months) with similar OS (12.4 vs 12.9 months) [26]. This data made possible the FDA approval for trabectedin in L-sarcomas since October 2015.

Regarding the duration of therapy with trabectedin, a phase II trial from the French sarcoma group randomized patients achieving disease control after 6 cycles of trabectedin, to continue or to stop the drug. Those patients progressing after interrupting trabectedin were allowed to restart the drug. After randomization, PFS at 6 months was 51.9% (95% CI 31.9-68.6) in the continuation group versus 23.1% (95% CI 9.4-40.3) in the stopping group (p=0.02) [27]. Based on these results, therapy with trabectedin should be maintained up to progression or intolerance. Remarkably, trabectedin has no cumulative toxicity and can offer a long lasting disease control in the scenario of advanced or metastatic STS disease. In this sense, it is not uncommon to have experiences of long-durable responses for more than one year.

As said it was mentioned before, trabectedin could interfere with transcription factors. Many sarcomas are characterized by genetic translocations resulting in fusion proteins, which could work as transcription factors. The activity of trabectedin in translocation-related sarcomas was shown in retrospective series with myxoid-liposarcoma [28]. A randomized phase II trial on japanese patients with pretreated translocation-related sarcomas showed a clear benefit from trabectedin compared with best supportive care (PFS 5.6 vs 0.9 months, HR: 0.07) [29]. Similarly, a randomized phase III study of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in patients with translocation-related sarcoma showed no significant differences in PFS between the two groups, but this study was underpowered due to a high proportion of patients being censored [30].

Trabectedin in combination in the first-line of advanced disease has also been explored with conflicting results. A phase II developed by the French Sarcoma Group enrolled 109 not pretreated patients with advanced leiomyosarcoma (uterine and soft-tissue). Patients received up to 6 cycles of doxorubicin 60mg/m^2 followed by trabectedin 1.1mg/m^2 in 3-hour infusion. The doses and schedules were determined in a previous phase I trial [31]. The trial showed impressive results in terms of median PFS (8.2 months for uterine leiomyosarcoma and 12.9 for soft-tissue leiomyosarcoma) and response rate (59.6% and 39.4% for uterine and soft-tissue leiomyosarcoma respectively) [32]. On the other hand, a randomized phase II trial developed for the Spanish Group for Research on Sarcoma (GEIS) comparing trabectedin-doxorubicin versus doxorubicin could not find differences between groups and the trial had to be stopped at the interim analyses after the inclusion of 115 patients [33]. Remarkably, in the second study, the sequence of the drugs was the inverse (first trabectedin and then doxorubicin), suggesting a role of the sequence on the activity of the combination.

Taking all these results together, trabectedin represents an effective and safe second-line option for all sarcoma subtypes, especially interesting in L-sarcoma but not limited to these histotypes. The efficacy of trabectedin in mono therapy or in combination in the first line setting still needs further studies.

Pazopanib

Pazopanib is an oral Tyrosine Kinase Inhibitor **(TKI)**, which targets vascular endothelial growth factor receptor (VEGFR-1, VEGFR-2, VEGFR-3), platelet- derived growth factor receptor(PDGFR-α and PDGFR-β), c-Kit, fibroblastic growth factor receptor (FGFR-1, FGFR-2 and FGFR-3), and Colony Growth Factor Receptor **(CSF1R).** Evidence of activity of pazopanib in sarcoma derives from a phase I trial in solid tumors, in which three patients with sarcoma obtained disease stabilizations lasting more than 6 months. The recommended dose for phase II trial was defined in 800mg daily [34]. In a subsequent phase II trial (EORTC 62043)one hundred and forty-two patients with advanced pretreated STS were included in four cohorts: adipocytic sarcomas, leiomiosarcoma, synovial sarcoma and other subtypes. The cohort of adipocytic tumors was closed because activity data did not reach the pre-specified threshold. Progression-free survival **(PFS)** rate at 12 weeks was 44% in leiomyosarcoma, 49% in synovial sarcoma and 39% in other histologic subtypes. Nine patients (5 of them synovial sarcoma) experienced a RECIST partial response. Toxicity was acceptable, being hypertension, asthenia, transaminases elevation and neutropenia the most frequent grade 3-4 toxicities, in less than 10% of patients in all the cases [35]. These results led to the phase III pivotal PALETTE study [36], including 372 advanced pretreated sarcoma patients. The trial randomized between pazopanib (800mg daily) and placebo. The study was positive for its principal objective **(PFS),** with a median PFS of 4.6months (95% CI 3.7–4.8) in the pazopanib group versus 1.6 months (95% CI% 0.9–1.8) in the placebo group (HR: 0.31, 95%CI 0.24–0.40, $p<0.0001$). No statistically significant differences in terms of overall survival were detected: 12.5 months (95%CI 10.6–14.8) in the pazopanib group versus 10.7 months (95%CI8.7–12.8) in the placebo group (HR: 0.86, 95%CI 0.67–1.11, $p=0.2514$). Fourteen (6%) patients obtained a RECIST partial response and toxicity profile was predictable, being asthenia (14%), hypertension (7%), transaminases elevation (GGT 13%, GPT 10% and GOT 8%) and anorexia (6%) the most frequent grade 3-4 adverse events. Left Ventricular Ejection Fraction **(LVEF)** decreased in 6.7% of patients (being symptomatic only in the 1%) and 5% of patients experienced deep venous thrombosis. These results enabled the FDA and EMA approval in 2012 of pazopanib for advanced pretreated soft-tissue sarcoma with the exception of liposarcoma.

Recently, pazopanib has been tested in adipocytic sarcomas in clinical trials, although the results of these trials are still preliminary [37].

Temozolomide and Dacarbazine

Both are alkylating agents, being temozolomide a prodrug of dacarbazine. Both agents have showed modest activity in pretreated STS [38,39]. Temozolomide was tested in a prolonged

schedule (75-100 mg/m^2 per dayduring 6 consecutive weeks) in 48 patients with pretreated soft-tissue sarcoma [40]. Three-month PFS rate was 39.5% and RECIST response rate was 15.5%. Interestingly, those patients responding to temozolomide maintained response for a duration median time of 12.5 months. Other study with a 5-day schedule of temozolomide in pretreated soft-tissue sarcoma, found modest activity of this drug. However, those patients with leiomyosarcoma, had a median PFS and OS of 3.9 months and 30.8 months respectively [41]. These drugs could be especially interesting in leiomyosarcoma. Solitary fibrous tumor also seem to benefit from dacarbazine and temozolomide-based regimens [42,43].

New agents

Eribulin

Eribulin mesylate is an antimitotic agent, which acts inhibiting microtubules growth [44]. Consequently, this agent inducescell-cycle arrest and tumor regression. A phase II trial was designed toassess the safety and efficacy of eribulin in pretreated advanced soft-tissue sarcoma. One-hundred twenty-eight patients were included in four strata: adipocytic sarcoma (37 patients), leiomyosarcoma (40 patients), synovial sarcoma (19 patients), and other sarcomas (32 patients). The primary end-point was PFS at 12 weeks. Patients received 1.4 mg/m^2 over 2-5 min at days 1 and 8 every 3 weeks. The study was positive for its primary end-point in the group of adipocytic sarcoma: 15 (46.9%) patients were progression-free at 12 weeks, and leiomyosarcoma (12-week PFR 31.6%) The most common grade 3-4 adverse events were neutropenia (52%), anemia (7%), fatigue (7%) and febrile neutropenia (6%) [45]. Based on these results, a phase III trial included 452 patients with advanced pretreated adipocytic sarcoma and leiomyosarcoma, which were randomized 1:1 to receive eribulin (1.4 mg/m^2, IV on day 1,8) or dacarbazine (850–1200 mg/m^2, IV on day 1) every 21 days. The study was positive for its primary end-point (overall survival): Median OS for eribulin and dacarbazine were 13.5 and 11.5 months, respectively (HR = 0.768, 95% CI 0.618–0.954; p= 0.017). In the subgroup of liposarcoma these differences were significant (15.6 months for eribulin compared to 8.4 months in the dacarbazine group) while in leiomyosarcoma cohort did not [46]. These results have recently led to the FDA approval of eribulin in advanced pretreated liposarcoma [47].

Special histologic subtypes

Some infrequent subtypes of soft-tissue sarcomashow characteristically specific sensitivity for any determined targeted therapy, and, typically in these cases, cytotoxic chemotherapy does not represent the best therapeutic option. Examples are: PECOMA with mTOR inhibitors [48,49], inflammatory myofibroblastic tumor withcrizotinib [50], Dermato Fibro Sarcoma Protuberans **(DFSP)** and imatinib [51]. Likewise, antiangiogenics such as sunitinib and cediranib have shown activity in Alveolar Soft-Part Sarcoma **(ASPS)** [52,53], Extraskeletal Myxoid Chondrosarcoma **(ECM)** 54, and Solitary Fibrous Tumor **(SFT)** [55].

Other Potentially Upcoming Drugs

Palbociclib

Palbociclib is an oral inhibitor of CDK4. More than 90% of Well-Differentiated/De-Differentiated **(WD/DD)** liposarcomas harbor the amplification of CDK4. A phase II trial exploring the safety and efficacy of palbociclib in a cohort of 30 patients with pretreated WD/DD liposarcoma showed a 3-month PFR of 66%, with a median PFS of 18 weeks [56]. Neutropenia was the most frequent toxicity in these patients, being G3 in 43% of the cohort, but only one patient presented febrile neutropenia and the drug was well tolerated besides the hematological toxicity.Given these results, more studies are warranted.

Olaratumab

Olaratumab is a human antibody that binds external domain of platelet-derived growth factor receptor alfa (PDGFR-α), blocking the interaction of the receptor with its ligand. PDGFR-α overexpression has been demonstrated in sarcoma [57], suggesting that the blockage of this molecule could play a therapeutic role in soft-tissue sarcoma. Olaratumab showed its safety in a phase I trial, in which no Dose-Limiting Toxicities **(DLT's)** were described. The dose of 15mg/Kg on days 1and 8 every 21 days and 20mg/kg every 2 weeks were judged as acceptable for subsequent trials [58]. Then, a phase Ib/II trial was designed in patients with unresectable/advanced soft-tissue sarcoma, assessing the combination of doxorubicin 75mg/m^2 day 1 every 21 days with olaratumab/placebo 15mg/Kgdays 1and 8 every 21 days. The trial met its Primary Endpoint **(PFS)**, with 6.6months in the arm of olaratumab vs 4.1 months in the arm of doxorubicin alone (HR: 0.672). Strikingly, the patients on the combination arm achieved an impressive median Overall Survival **(OS)** of 25months vs 14.7 months in the doxorubicin arm (HR: 0.44, p=0.0005) [59]. At present, a phase III trial comparing doxorubicin 75mg/m^2 vs doxorubicin 75mg/m^2 plus olaratumab 15mg/m^2 is ongoing [60]. If these impressive results on OS are confirmed in this study, this will represent the greatest paradigmatic change in the last three decades in the clinical practice of STS: Doxorubicin in monotherapy would not be longer the standard upfront systemic treatment in advanced STS. Other combinations of olaratumab in sarcoma are ongoing and a phase Ib/II trial assessing the combination of this antibody with gemcitabine plus docetaxel is planned [61]. The effects of this molecule on overall survival are still unknown, being an immune modulatory effect or a stroma direct modulation plausible explanations, still to be confirmed.

In conclusion, although doxorubicin- based chemotherapy represents the first line of systemic therapy in advanced soft-tissue sarcoma, patients with metastatic sarcoma can benefit from other active agents. There are several active second-line options, and as there are lacking comparative trials addressing the best sequence, the election should be based on histologic subtype patient characteristics, toxicity profile among other factors. Nevertheless, we have a larger number of treated patients with trabectedin in comparison with other second line options. Some of these

data states that the earlier the trabectedin administration, the higher the probability of obtains better PFS and OS, and these differences were statistically significant. In any case, the clinical challenge of second and further lines is advanced STS patients is to administer all the second options in the most rational sequence for each individual patient. In the meanwhile, large studies focusing on predictive biomarkers are needed in advanced STS.

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