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# Treatment of advanced, metastatic soft tissue sarcoma: latest evidence and clinical considerations

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***Abstract*:** Soft tissue sarcoma (STS) is a biologically heterogeneous malignancy with over 50 subtypes. Historically, there have been few systemic treatment options for this relatively rare disease. Traditional cytotoxic agents, such as anthracyclines, alkylating agents, and taxanes have limited clinical benefit beyond the first-line setting; across all high-grade STS subtypes, median overall survival remains approximately 12–18 months for advanced metastatic disease. The development of targeted therapies has led to recent US Food and Drug Administration approval of four new treatments for high-grade STS in the advanced metastatic setting. Among these, olaratumab is most notable for its improvement in overall survival for patients with anthracycline-naïve disease. Further progress in STS management will rely on novel trial design, subtype-specific therapies and validation of biomarkers to tailor therapy. Immunotherapy has shown promise as a new, but yet undiscovered frontier in the management of STS.

***Keywords:*** eribulin, high-grade, immunotherapy, metastatic, olaratumab, pazopanib, sarcoma, soft tissue, trabectedin

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## Introduction

Soft tissue sarcomas (STSs) remain one of the most challenging diseases to treat for the medical oncologist. STSs are mesenchymal neoplasms that can arise from any site within the body, including the extremity, trunk, retroperitoneum, and head and neck. These are biologically heterogeneous diseases, with over 50 subtypes that vary by molecular, histological, and clinical characteristics. The most common subtypes of high grade STS include undifferentiated pleomorphic sarcoma (UPS), liposarcoma (LPS), leiomyosarcoma (LMS), synovial sarcoma (SS), and malignant peripheral nerve sheath tumors (MPNSTs). Collectively, STSs are rare, accounting for <1% of adult cancers, with an estimated 12,310 new cases in 2016 in the United States.[1] Unfortunately, up to 50% of high-risk patients with high-grade STS develop metastases and die from their disease.[2] Among the young adult and pediatric population under 20-years old, STS is one of the top five causes of cancer-related death.[1] The median overall survival (OS) for advanced, metastatic STS has historically been in the range of 12 months, while more recent randomized studies have noted survival approximating 18–19 months.[3–10] Nonetheless, improvements in the management of high-grade STS are needed.

Because of the relatively low annual incidence and heterogeneous nature of these neoplasms, positive studies using newer active systemic agents for sarcomas are few. In recent years, the understanding and management of STS have been improved by the molecular and histological subclassification of STS, as well as development of novel drugs for these subtypes. In the age of personalized medicine, the medical oncologist is challenged with the task of properly tailoring and sequencing therapies for STS in an individualized manner. In this review, we provide an update of systemic options for high-grade STS, including a

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discussion of how best to incorporate their use amongst the growing arsenal of active agents. Specifically, we focus on the subtypes mentioned above: UPS, LPS, LMS, SS and MPNST. While there have been advances in treatment of other sarcoma subtypes, including dermatofibrosarcoma protuberans and gastrointestinal stromal tumors, a discussion of these and other sarcoma subtypes is beyond the scope of this paper and should be sought elsewhere.

## Anthracycline-based therapy: first-line therapy across all subtypes

As of 2016, anthracyclines (e.g. doxorubicin) remain the standard of care for first-line therapy in high-grade STS, regardless of subtype, presentation and patient characteristics. Anthracyclines intercalate into deoxyribonucleic acid (DNA), thereby blocking DNA and ribonucleic acid (RNA) synthesis, while also interfering with topoisomerase II, leading to DNA breakage.[11] Doxorubicin has single-agent activity in high-grade STS, and demonstrates a dose–response relationship, with doses lower than 60 mg/m$^2$ associated with inferior efficacy.[12,13] Because of its toxicity profile however, most dose-intensive treatment schedules administer doxorubicin at 75 mg/m$^2$ for otherwise fit patients.[14,15] Alkylating agents (e.g. ifosfamide) exert their antineoplastic effects by cross-linking strands of DNA.[16] Ifosfamide also has single-agent activity in STS,[17] and while they are not synergistic with anthracyclines, the two are often combined on the basis of improved response rates (RRs), progression-free survival (PFS) and palliation.[13,14,18] In the first-line setting, the combination of doxorubicin and ifosfamide (AI) achieves an RR up to 12–34%, dependent on subtypes, and disease control rates (DCRs) as high as 45–77%.[14,15,18–21] There has been no definitive improvement in survival, however, with median OS still between 12 and 18 months.[13–15,18,22,23] This remains an area of active investigation, with one particular criticism being the lower doses of anthracyclines that may have confounded results in earlier studies.[24]

The phase III, multi-institutional EORTC 62012 study was designed to address this continuing debate.[14] The investigators compared doxorubicin 75 mg/m$^2$ in combination with ifosfamide 10 g/m$^2$ every 3 weeks for six cycles (AI) versus doxorubicin 75 mg/m$^2$ every 3 weeks for six cycles in 455 patients with advanced or metastatic high-grade STS. Patients younger than 60-years old with good performance status were eligible. The AI combination showed a higher RR, 26.5% *versus* 13.6% ($p < 0.0006$), respectively, compared with doxorubicin alone. AI significantly improved PFS from 4.6 months to 7.4 months [hazard ratio (HR) 0.74, $p = 0.003$], as well. However, there was no significant difference between AI and doxorubicin alone in terms of OS (14.3 months *versus* 12.8 months, HR 0.83, $p = 0.076$). Despite its efficacy, there was higher toxicity when using the combination, with 18% of patients receiving AI and 3% of patients receiving doxorubicin alone being unable to complete the planned six cycles of therapy due to adverse events. It should be noted the most common grade 3–4 toxicities when administering AI are related to bone marrow suppression,[15,18,19] which highlights the need for regular blood-count monitoring, supportive transfusions and growth factor support. Cardiotoxicity is a rare, but significant toxicity related to anthracyclines that occurs in a dose-dependent manner, with increased risk of cardiomyopathy occurring with cumulative doses above 550 mg/m$^2$.[25–27]

Retrospective studies indicate that young age and good performance status are good prognostic factors for survival,[28,29] while a study by Van Glabbeke noted that young age may also be predictive of response to anthracycline-based therapy.[30] Meanwhile, higher histological grade is associated with better RR to chemotherapy but worse OS,[28,30] likely reflecting that higher-grade tumors are more chemosensitive, but will also relapse and progress quickly. Other characteristics, such as gender, location of primary tumor, location of metastases, and histology subtype have also been investigated as additional prognostic and predictive factors, and warrant further investigation. Negative phase III trials of other anthracycline-based combinations (e.g. evofosfamide, palifosfamide),[10,31] indicate the need for better patient selection, and putative biomarkers will be crucial towards improving future clinical trials.

In consideration of these findings, our practice is to offer AI combination therapy in the front-line setting to select patients who are fit and highly appropriate based on burden of disease, particularly with the goals of tumor shrinkage and resectability, or potentially life-threatening disease. We recommend the dose of doxorubicin 75 mg/m$^2$ (25 mg/m$^2$ per day on days 1, 2, and 3) in combination with ifosfamide 7.5 g/m$^2$ (2.5 g/m$^2$

**Table 1.** Proposed treatment sequence for advanced or metastatic, high-grade soft tissue sarcoma.

| Sarcoma subtype | First line | Second line | Third line | Fourth line[e] |
|---|---|---|---|---|
| UPS | [a]Anthracycline-based regimen | Gemcitabine + docetaxel | Pazopanib | |
| LPS | [a]Anthracycline-based regimen | [b]Trabectedin | Eribulin | |
| LMS | [a]Anthracycline-based regimen | [c]Gemcitabine + docetaxel | Trabectedin | Pazopanib |
| SS | [a]Anthracycline-based regimen | [d]High-dose ifosfamide | Pazopanib | |
| MPNST | [a]Anthracycline-based regimen | Pazopanib | | |

[a]Anthracycline-based regimens include: single-agent doxorubicin, doxorubicin and ifosfamide, doxorubicin and olaratumab, or liposomal doxorubicin.
[b]Trabectedin particularly effective for myxoid/round cell LPS.
[c]Gemcitabine + docetaxel particularly effective for uterine LMS.
[d]High-dose ifosfamide only recommended for select patients with good performance status and preserved renal function.
[e]Clinical trials are recommended for eligible patients.
UPS, undifferentiated pleomorphic sarcoma; LPS, liposarcoma; LMS, leiomyosarcoma; SS, synovial sarcoma; MPNST, malignant peripheral nerve sheath tumor.

per day on days 1, 2 and 3) with granulocyte colony-stimulating factor, every 3 weeks for a maximum of six cycles. For total doses of doxorubicin above 450 mg/m$^2$, use of cardioprotectants (e.g. desroxazone) and cardiac monitoring should be considered. For less fit patients, in whom the risks of toxicity outweigh the benefits of AI combination chemotherapy, alternatives may include single-agent doxorubicin, single-agent ifosfamide, or liposomal doxorubicin (Doxil).[32–34] As of November 2016, the US Food and Drug Administration (FDA) granted accelerated approval for olaratumab, an anti-PDGF R (as in anti-PDGFR) monoclonal antibody, for use in combination with anthracyclines; this will be discussed in further detail below.

It should be noted that other than the five primary STS subtypes mentioned above (UPS, LPS, LMS, SS, MPNST), there are a number of other less common subtypes which are anthracycline resistant, and for which AI therapy is not recommended first line. For these subtypes, specific-histology-based treatment is discussed elsewhere,[35–40] and the reader is encouraged to also consider clinical trials and genomic profiling.

### *Second-line therapy and beyond: the basis for treating by histology subtypes*

Beyond first-line therapy, we recommend that treatment be tailored to histology and molecular subtype, as well as patient characteristics. While a number of second-line regimens exist, any one agent has not proven superior across all subtypes. We will discuss these options, and provide our recommendations for when they should be appropriately sequenced (Table 1).

### High-dose ifosfamide

For SS (i.e. harboring the t(x;18) or SYT (synaptotagmin) / SSX (synovial sarcoma, X breakpoint) translocation) patients, who are fit and have good performance status, our practice is to rechallenge with high-dose ifosfamide (HDI) as second-line therapy. As previously mentioned, ifosfamide has single-agent activity in front-line and relapsed STS, with RR ranging from 25% to 50%. Ifosfamide demonstrates a dose–response relationship, particularly at doses from 5 to 12 g/m$^2$,[41–44] while at doses above 16 g/m$^2$, there are higher rates of toxicity without any further efficacy, and worse pharmacokinetics.[4,43,45–47] The primary toxicities associated with ifosfamide include nausea, vomiting, myelosuppression, hemorrhagic cystitis, nephrotoxicity (renal tubular acidosis, salt-wasting nephropathy), asthenia and encephalopathy.[4,43,45–48] Ifosfamide can be administered as a prolonged infusion with mesna via portable pumps with good physicochemical stability.[49] As such, a number of studies have explored the potential for HDI in salvaging refractory STS patients, especially those who progressed on prior anthracycline-based regimens, including AI combination therapy.

In a phase I dose-escalation study by Elias *et al.*, 20 patients with refractory STS were treated with a 4-day continuous infusion of ifosfamide, with doses escalated from 8 up to 18 g/m$^2$ total, and supportive mesna at an equivalent dose.[50]

Dose-limiting toxicities at the 18 g/m$^2$ dose, including renal insufficiency, myelosuppression, and mucositis, were all dose dependent, while severe CNS toxicity appeared even at lower doses. Among 20 patients, there were six partial responses (PRs) and one complete response (CR) for an overall RR of 35%. A number of additional phase II and retrospective studies further support the role of salvage HDI in STS, with RRs ranging from 25% to 53.8% for pretreated patients.[5,42,43,48,51,52] However, many dose-dense regimens, such as 6-day ifosfamide with 2 g/m$^2$ per day every 3 weeks, or 4-day ifosfamide with 3 g/m$^2$ per day every 3 weeks, resulted in significant myelosuppression, sometimes as high as 40–75% grade 3–4, despite use of growth factor support.[42,43,48,53]

Investigators at the Royal Marsden Hospital, UK, explored a schedule of 14-day ifosfamide dosing, with 1 g/m$^2$ per day, continuous infusion every 4 weeks as first- or second-line therapy.[54] There were seven patients with PR (20%), as well as 10 patients with stable disease (SD) (29%) for a DCR of 49%. Although there was significant encephalopathy, including 34% among all grades and 17% grade 3–4, myelosuppression was significantly improved with 46% all grades and only 5.7% grade 3–4. Another retrospective analysis at the Royal Marsden Hospital rechallenged 67 patients with STS using HDI, either following prior adjuvant AI or front-line palliative ifosfamide-based regimens.[55] This regimen showed significant activity, including responses in the second-line, third-line and fourth-line settings. Although the clinical benefit was greater for the SS subtype, responses were also seen in LPS and LMS, as well.

Despite its toxicities, as well as its costly and time-intensive scheduling, we endorse HDI as an appropriate second-line therapy for SS after failing anthracycline-based treatment. We recommend a 14-day continuous dosing schedule with 1 g/m$^2$ per day, every 4 weeks with granulocyte colony-stimulating factor, as this regimen is well tolerated and has good efficacy as a salvage regimen. However, we advise this regimen be reserved to tertiary, academic centers with a high level of experience and appropriate support including adequate mesna administration. Additional precaution should be taken with patients at risk of nephrotoxicity, such as those with pre-existing renal insufficiency or history of nephrectomy.[45–47] For the highly select and fit patient then, especially those who demonstrated prior sensitivity to ifosfamide, this regimen is an option for salvage therapy.

Further study is needed to elicit which subtypes may be eligible for HDI treatment. Although it is generally agreed that RRs are highest for the SS subtype,[41] there is evidence that specific subtypes of LPS, including myxoid/round cell LPS and well-differentiated/dedifferentiated LPS, also respond to HDI.[54,56] Meanwhile, LMS is poorly responsive to HDI and should not be considered in this setting.[4,41,42]

### Gemcitabine and docetaxel

For the second-line treatment of STS with either UPS or LMS histology, we recommend salvage with the combination of gemcitabine and docetaxel (GD). Gemcitabine is a nucleoside analog which inhibits DNA synthesis, and demonstrated single-agent activity in phase II studies of STS that progressed after anthracyclines or alkylators, including responses among UPS and angiosarcoma histology.[57,58] Phase II studies of gemcitabine in combination with either vinorelbine or dacarbazine, showed only limited efficacy for STS.[59–61] Meanwhile, docetaxel is a taxane with microtubule-inhibiting activity, and also has single-agent activity as second-line therapy.[62,63] Given that GD have different mechanisms of action from either anthracyclines or alkylating agents, as well as preclinical evidence of their synergy, there was rationale for combining these agents for treating STS.

The first phase II study of GD, conducted by Hensley *et al.*, treated 34 patients with unresectable LMS, including 29 uterine LMS, as well as 18 treatment-naïve patients, with gemcitabine 900 mg/m$^2$ on days 1 and 8, and docetaxel 100 mg/m$^2$ on day 8, with granulocyte colony-stimulating factor every 3 weeks.[64] Among the 34 patients, there were 3 CR and 15 PR, for an overall response rate (ORR) of 53%. There were also seven patients with SD, resulting in a DCR of 73.5%. The regimen was well tolerated, with grade 3–4 neutropenia occurring in 21% of patients and grade 3–4 thrombocytopenia in 29%.

In the follow-up phase II, open-label SARC 002 study, 122 STS patients with zero-to-three prior lines of chemotherapy, were randomized to either gemcitabine 1200 mg/m$^2$ on days 1 and 8 every 3 weeks alone or to GD. Histology subtypes included LMS, LPS, UPS, as well as others not

otherwise specified. Patients on both arms received a median of four cycles of therapy, and up to a maximum of eight cycles. The GD combination resulted in higher ORR (16% *versus* 8%), higher median PFS (6.2 months *versus* 3.2 months), and higher median OS (17.9 months *versus* 11.5 months), compared with gemcitabine alone, across all subtypes, but with the best outcomes primarily among LMS and UPS.[6]

The randomized, multicenter phase II TAXOGEM study compared GD with single-agent gemcitabine for the second-line treatment of LMS.[65] A total of 90 patients were stratified as uterine LMS or nonuterine LMS, and randomized to gemcitabine or GD. For patients with uterine LMS, the ORR was 19% for gemcitabine alone *versus* 24% for GD; for nonuterine LMS, the ORRs were 14% and 5%, respectively. For uterine LMS, median PFS was 5.5 months *versus* 4.7 months, and for nonuterine LMS, median PFS was 6.3 months and 3.8 months, respectively. Given its efficacy and better tolerability, the authors also recommended that single-agent gemcitabine could be considered in second-line treatment for LMS.

In the multi-institutional European GeDDiS trial, GD failed to improve outcomes in the first-line setting compared with anthracycline-based therapy.[66] A total of 257 patients with previously untreated advanced or metastatic STS were randomized 1:1 to receive doxorubicin 75 mg/m$^2$ on day 1 every 3 weeks for six cycles *versus* GD for six cycles. Histology subtypes included uterine LMS (27%), SS (4%), UPS (12%) and other sarcomas (56%). Median PFS, OS and RR trended in favor of doxorubicin compared with GD. In addition, the anthracycline arm was less toxic, thereby corroborating that GD should not displace anthracycline as first-line therapy for STS.[66] In a retrospective analysis of 246 patients with metastatic UPS treated at Memorial Sloan Kettering, there was no statistically significant difference in median time to progression between anthracycline-based therapy or GD in the first-, second- or third-line setting. ORR was marginally higher for anthracycline-based regimens in the first line, 26% compared with 22% among GD-treated patients.[67]

As with HDI, responses to GD appear to be heavily dependent on STS histology subtype. In particular, multiple studies demonstrate the efficacy of GD in LMS, with RR of 36–53% in the first-line setting and 24–27% in the second line.[7,64,68,69] Furthermore, it appears that uterine LMS is more sensitive to GD, compared with nonuterine LMS.[6,64,70,71] Smaller studies suggest GD has activity in other less common STS subtypes including angiosarcoma and epithelioid sarcoma.[72,73]

Given its modest efficacy as second-line therapy, our practice is to use the combination of gemcitabine, 900 mg/m$^2$ on days 1 and 8, and docetaxel 100 mg/m$^2$ on day 8, with granulocyte colony-stimulating factor every 3 weeks, as second-line therapy for refractory LMS and UPS. This regimen may be particularly effective for uterine LMS, as opposed to nonuterine LMS. Although practices vary by institution, many oncologists may prefer a lower dose of docetaxel 75mg/m$^2$, based on the toxicity data from SARC002. For less robust patients, single-agent gemcitabine may also be considered an option.

### Trabectedin

Trabectedin is FDA approved for second-line treatment and beyond for LPS and LMS. Trabectedin (ecteinascidin-743) is a synthetic compound derived from the Caribbean sea squirt, *Ecteinascidia turbinata*.[74] Unlike other alkylating agents which target the DNA major groove, trabectedin binds and alkylates the minor groove, bending towards the major groove, disrupting the late S-phase and G2 phase, and induces p-53-independent apoptosis.[75–77] Other effects include modulating inflammation in the tumor microenvironment and inducing caspase-8-mediated apoptosis of tumor-associated macrophages, with reduced angiogenesis.[78,79] Preclinical studies indicate trabectedin is also effective in modulating the transcription of oncogenic fusion proteins, and thus may be particularly useful in treating translocation-associated sarcomas.[80,81]

In a phase II study of 36 STS patients with up to two prior lines of therapy, the ORR for trabectedin was 8%, including one CR and two PRs, and two patients had minimal response (MR). All of the patients with objective responses had bulky disease and either LPS or LMS histology, including one patient with myxoid/round cell LPS (MRC-LPS) who achieved CR.[82] In a second, multi-institutional phase II study of 54 STS patients with at least one prior line of therapy, there was again a low ORR of 3.7%, with only 2 PRs, as well as 4 MR and 2 SD. Outcomes did not vary with number of prior lines of therapy. The median PFS for all patients was 1.9 months, with 24% of patients progression free at 6 months.

Meanwhile, the median PFS for patients with either PR or MR was 8.5 months.[83] A third phase II study treated 104 patients with refractory STS across eight European institutions; among 99 evaluable patients there were 8 PRs and 45 SDs, for an ORR of 8% and DCR of 53.5%. Responses occurred in LMS, SS, LPS and UPS, with a median duration of response of 14 months. The median PFS for all patients was 3.8 months, with 29% of patients progression free at 6 months.[3] Despite their low objective RR, these three phase II studies demonstrated trabectedin's activity in refractory STS, and also emphasized the importance of PFS and SD as endpoints in second line and beyond.

A multi-institutional phase III study randomized 518 LPS and LMS patients 2:1 to receive either trabectedin or dacarbazine.[84] All patients had progressed after either one anthracycline-based combination or an anthracycline plus a second-line regimen. Trabectedin significantly improved median PFS compared with dacarbazine (4.2 months *versus* 1.5 months), with a 45% reduction in progression or death [hazard ratio (HR) 0.55, 95% confidence interval (CI) 0.44–0.77, $p < 0.001$]. At 6 months, 37% of patients treated with trabectedin were progression free, compared with 14% of patients treated with dacarbazine. Although there was no difference in ORR (9.9% *versus* 6.9%, $p = 0.33$), DCR was higher in the trabectedin arm at 34% *versus* 19%, $p < 0.001$. It should be noted the greatest improvement in median PFS for trabectedin occurred in the subgroup of MRC-LPS (5.6 months *versus* 1.5 months). Trabectedin was well tolerated, with the most common grade 3–4 toxicities including myelosuppression and transient liver enzyme elevations.

Two studies evaluated trabectedin as first-line therapy for STS. Garcia-Carbonero *et al.* conducted a single-arm phase II study of trabectedin that resulted in one CR, five PRs and one MR, thus indicating the drug's activity in the treatment-naïve patient.[85] However, a subsequent phase IIb that randomized treatment-naïve patients to doxorubicin *versus* trabectedin failed to show any superiority to using trabectedin.[86]

In contrast to HDI or GD, responses to trabectedin appear specific not only to L-sarcoma histology subtypes, but also to molecular subtype. MRC-LPS has proven particularly sensitive to trabectedin, with retrospective studies showing ORR up to 50%, median PFS 14–17 months and 6 month PFS 88%.[87,88] In addition, MRC-LPS patients who relapse after prior response are sensitive to rechallenge with trabectedin.[89] This unexpectedly high antitumor activity has been attributed to the ability of trabectedin to modulate transcription of oncogenic fusion proteins, such as *FUS-DDIT3*, and thereby promote lipoblast differentiation.[80] These findings led to further interest in trabectedin as a treatment option for other translocation-associated STSs, but subsequent studies showed little evidence of trabectedin having activity in SS, alveolar soft-part sarcoma or rhabdomyosarcoma.[90,91]

At our institution, we reserve trabectedin to the L-sarcomas, LMS and LPS, as second-line and beyond therapy, depending on patient characteristics and ease of administration. Trabectedin is dosed at 1.5 mg/m$^2$ once every 3 weeks.[92,93] It should be noted that trabectedin requires a continuous 24-hour infusion, and central venous access is recommended to avoid painful phlebitis. Dose-limiting toxicities include myelosuppression and reversible elevation of transaminases; patients with moderate hepatic impairment require dose reduction, while patients with severe hepatic impairment are not eligible for treatment.[94] In addition to the L-sarcomas, trabectedin may have activity in other sarcomas, but this will require further investigation.[95,96] A number of ongoing studies will assess the potential combination of trabectedin with other agents,[97,98] as well as the possibility of DNA repair-based biomarkers to predict responsiveness to trabectedin.[99,100]

## Pazopanib

Pazopanib is the only FDA approved oral agent for high grade STS, and we consider this an acceptable option for all STS subtypes after failing anthracycline, with the exception of LPS. Pazopanib is a multikinase tyrosine kinase inhibitor that targets multiple receptors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGFR), and c-KIT. VEGF is overexpressed on tissue and serum samples across multiple STS subtypes, including UPS and LMS. Moreover, high VEGF expression levels are correlated with higher histologic grade, larger tumor size, higher stage, and worse prognosis,[101–104] thus supporting this as a therapeutic target for STS.

The EORTC 62043 single-arm study treated 142 advanced STS patients, who had up to two prior lines of chemotherapy, or who were ineligible for

chemotherapy, with pazopanib 800 mg orally once daily.[105] Among four different histology cohorts, three of them, LMS, SS and other sarcomas reached the primary endpoint of PFS at 12 weeks ($PFR^{12w}$), while the LPS cohort was closed early, given it did not reach the interim analysis endpoint. Among LMS, SS and other sarcomas, the $PFR^{12w}$ rates were 44%, 49% and 39%, respectively. Among nine PRs, five occurred in patients with SS, and one with LMS, but there were no CRs.

The multi-institutional, phase III PALETTE study randomized 369 pretreated, metastatic STS patients from Europe, Asia, Australia and USA, 2:1 to pazopanib *versus* placebo.[106] Patients were allowed up to four prior lines of therapy, with 99% receiving prior anthracyclines and 56% having at least two prior lines of therapy. Histology subtypes included SS, LMS and other sarcomas; LPS was not eligible. Pazopanib improved median PFS; 4.6 months *versus* 1.6 months (HR 0.31, 95% CI 0.24–0.40, $p < 0.001$), compared with placebo. Similar to the phase II study, rates of PR were very low (6% *versus* 0%), but rates of SD were higher for pazopanib, 67% *versus* 38%, compared with placebo.[106] There was no significant difference in median OS of 12.5 months for pazopanib, compared with 10.7 months for placebo (HR 0.86, 95% CI 0.67–1.1, $p = 0.25$). The most common toxicities were hypertension, fatigue, diarrhea, nausea, and weight loss, while rare but significant toxicities associated with pazopanib included thromboembolism (5%), pneumothorax (3%) and decreased left ventricular ejection fraction (6.5%). Questionnaire-based, health-related quality of life (HRQoL) was not improved with pazopanib, although this did not correlate with significantly worse overall health status.[107]

In a retrospective analysis of both EORTC 62043 and PALETTE, a total of 77 patients had long-term responses with PFS >6 months and OS >18 months, including 12 patients who remained on treatment for more than 2 years.[108] The investigators identified good performance status, low or intermediate histologic grade and normal hemoglobin as good prognostic factors. TP53 mutations may predict response to pazopanib, but further investigation is need to validate this, as well as other biomarkers.[109,110] Hypertension has not proven a reliable biomarker to predict response to pazopanib.[111]

In 2012, pazopanib was FDA approved for the treatment of STS progressed on prior anthracycline-based therapy, with the exception of LPS histology. Additional studies confirmed that pazopanib has antitumor efficacy in multiple subtypes including LMS, SS, UPS and MPNST, but has minimal activity for LPS.[112–114] There are also limited data to suggest pazopanib has single-agent activity in other less common subtypes, such as clear cell sarcoma, solitary fibrous tumor, and hemangioendothelioma.[115–118]

It is our practice to consider pazopanib in the second- or third-line setting for SS, UPS, or MPNST. For patients with LMS, we also offer pazopanib in the second, third, or even fourth line, depending on patient fitness and comorbidities. We do not use pazopanib for LPS, given its poor activity in studies thus far, although there is some interest in re-exploring the role of pazopanib for this subtype. At final analysis of EORTC 62043, an additional two LPS patients did meet the primary endpoint, with a resultant $PFR^{12w}$ of 26%, which would have met the study threshold for continuation, and based on these findings, pazopanib is approved for LPS in Japan.[119] Because pazopanib is the only oral agent approved for high-grade STS and relatively well tolerated, it is an excellent alternative to other salvage therapies for the less robust patient. An ongoing phase II trial will examine the role of first-line pazopanib as an alternative to doxorubicin for elderly patients [ClinicalTrials.gov identifier: NCT01861951].[120] Additional studies are also underway to explore the potential combination of pazopanib with PIK3/mTOR inhibitors[121] and epigenetic-modifying agents.[122,123]

## Eribulin

Eribulin is FDA approved for patients with LPS that progressed after treatment with anthracyclines. Eribulin is a synthetic analog of halichondrin B, which was isolated from the marine sponge, *Halichondria okadai*, and the *Axinella* family of sponges.[124,125] Unlike other microtubule inhibitors (e.g. taxanes, vinca alkaloids), eribulin has a unique mechanism of action that sequesters tubulin into nonfunctioning aggregates.[126] Eribulin also remodels the tumor vasculature, and reverses the epithelial–mesenchymal transition.[127,128] Eribulin has activity in multiple solid tumors, and is FDA approved for breast cancer, in addition to LPS after prior anthracyclines.

In the phase II EORTC 62052 study, 128 STS patients, who progressed after one combination or up to two prior lines of therapy, were treated with

eribulin 1.4 mg/m$^2$, on days 1 and 8 every 3 weeks.[129] There were four histology cohorts including SS, LMS, LPS, and other sarcomas. At the primary endpoint, 46.9% of LPS patients and 31.6% of LMS patients were progression free at 12 weeks, while among SS and other sarcomas, PFR$^{12w}$ was 21% and 19%, respectively. Despite the low ORR of 6% among LPS, there were 41% of patients with SD, for a DCR of 47%. The DCR for LMS, SS and other sarcomas were lower at 32%, 21%, and 19%, respectively. Median PFS for LPS, LMS, SS and other sarcomas were 2.6 months, 2.9 months, 2.6 months and 2.1 months, respectively. In a second phase II study, 51 patients in Japan with refractory STS, who failed at least one line of therapy, were treated with eribulin. At the primary endpoint, patients with LPS or LMS histology had a PFR$^{12w}$ of 60% compared with 31% in other sarcomas and 51% overall. Median PFS was 5.5 months for LPS or LMS, 2.0 months for other sarcomas, and 4.1 months overall. Meanwhile, median OS was 17 months for LPS or LMS, compared with 7.6 months in other sarcomas and 13.2 months overall.[130]

In a phase III randomized study across 22 countries, 452 patients with intermediate/high-grade LPS or LMS who had up to two lines of prior therapy were randomized to eribulin *versus* dacarbazine.[131] Eribulin significantly improved median OS; 13.5 months *versus* 11.5 months, compared with dacarbazine (HR 0.77, 95% CI 0.62–0.95; $p = 0.0169$). Although not appropriately powered for this study, the median OS benefit of eribulin compared with dacarbazine was greater for LPS (15.6 months *versus* 8.4 months), as compared with LMS (12.7 months *versus* 13.0 months). Strikingly, there was no benefit on median PFS, which was 2.6 months (95% CI 1.9–2.8) for eribulin and 2.6 months (95% CI 1.8–2.7) for dacarbazine (HR 0.88; 95% CI 0.71–1.09, $p = 0.23$). PFR$^{12w}$, DCR and HRQoL were not significantly different between treatment arms. The most common grade 3–4 toxicities related to eribulin were neutropenia (35%) and leukopenia (10%), while the most common toxicities overall included fatigue, nausea, neuropathy, elevated transaminases and alopecia.

It remains unclear why eribulin improved OS, but failed to improve the secondary endpoints of this study, including PFS, RR and DCR. Similar findings occurred in a breast cancer study, where eribulin resulted in improved OS, but not PFS, compared with other cytotoxic therapy.[132] The investigators hypothesize that these results are due to the manner in which eribulin impacts the tumor microenvironment and induces vascular remodeling.[127,128]

We recommend eribulin 1.4 mg/m$^2$, on days 1 and 8 every 3 weeks, as third-line and beyond therapy for LPS. Given the availability of other agents in this setting (e.g. trabectedin, pazopanib), we reserve this agent only for select, appropriately fit patients. Toxicities from eribulin include mucositis, myelosuppression, elevated transaminases, and sensory neuropathy.[133] Nevertheless, eribulin is an important agent with a survival benefit in LPS, and should always remain within the consideration of the sarcoma oncologist.

## Olaratumab: a novel agent for first-line therapy

In November 2016, the FDA granted accelerated approval of olaratumab in combination with doxorubicin for the treatment of anthracycline-naïve STS, based on a phase Ib/II study. Unlike the other aforementioned agents, olaratumab combined with doxorubicin was shown to improve OS in the anthracycline-naïve setting, and as such, may change the paradigm for management of advanced high-grade STS. Results from the confirmatory phase III study will be important towards the FDA granting full approval.

Olaratumab is a fully human recombinant IgG1 monoclonal antibody that blocks PDGF-AA and PDGF-BB from binding PDGFR$\alpha$.[134] PDGFR$\alpha$ overexpression has been found in a number of malignancies, including STS,[135,136] glioblastoma,[137] ovarian carcinoma,[138] hepatocellular carcinoma,[139] and metastatic medulloblastoma.[140] PDGFR amplification and activating mutations have also been found in gliomas[137,141] and gastrointestinal stromal tumor (GIST).[142] Furthermore, PDGFR-ligand binding has been found to play a significant role in stemness, senescence and apoptosis in sarcoma, and is also associated with metastatic progression.[143] In xenograft models of LMS and glioblastoma, olaratumab demonstrated antitumor activity *via* modulation of the PDGFR pathway, as well as downstream inhibition of Akt and MAPK.[134] Olaratumab also delayed progression and reduced bone metastases in a prostate cancer xenograft.[144]

In the first-in-human phase I study, a total of 19 patients (none were STS) were treated with

olaratumab. The maximum tolerated dose (MTD) was not reached, and the recommended phase II dose was 16 mg/kg weekly and 20 mg/kg biweekly. Twelve patients (63.2%) had a best response of stable disease.[145] In a phase I study of 16 Japanese patients with advanced tumors treated with single-agent olaratumab, the best overall response was SD in seven patients (43.8%), including one patient with LMS originating in the inferior vena cava, with disease stabilization lasting 5.6 months.[146]

Olaratumab was given accelerated approval by the FDA in November 2016, based on a phase Ib/II study among anthracycline-naïve, advanced STS.[147] The phase II trial randomized patients to olaratumab 15 mg/kg on days 1 and 8 and doxorubicin 75 m/gm$^2$ on day 1, every 3 weeks, or doxorubicin alone at 75 mg/m$^2$ on day 1, every 3 weeks. After eight cycles, patients on the olaratumab arm were allowed to continue olaratumab alone, while patients on the doxorubicin alone arm could receive olaratumab monotherapy after progression. The median PFS was not significantly improved with olaratumab at 6.6 months compared with 4.1 months for doxorubicin alone (HR 0.67, 95% CI 0.44–1.02, $p = 0.0615$). However, the median OS was 26.5 months with olaratumab, compared with 14.7 months in the doxorubicin alone arm, equivalent to an improvement of 11.8 months (HR 0.46, 95% CI 0.30–0.71, $p = 0.0003$). This benefit was seen regardless of STS subtype, PDGFR expression or number of lines of prior therapy. Best response with olaratumab included two patients with CR, but the ORR was not significantly different between both arms (18.2% *versus* 11.9%, $p = 0.34$). Overall toxicities related to olaratumab included fatigue, alopecia, neuropathy and headache, while grade 3–4 toxicities included neutropenia, mucositis, nausea, vomiting and diarrhea. The confirmatory phase III of olaratumab plus doxorubicin or doxorubicin alone has completed accrual and results are pending.

Olaratumab is the first novel agent that offers a change of strategy in the treatment of high-grade, advanced or metastatic, anthracycline-naïve STS. For patients with good performance status and STS histology who do not qualify for a clinical trial, the combination of doxorubicin on day 1 with olaratumab on days 1 and 8, every 3 weeks for eight cycles, should be considered. This should be followed by continuation with olaratumab alone. We routinely premedicate patients with dexamethasone and diphenhydramine and also administer granulocyte-colony stimulating factor with each of the first eight cycles.

## The potential role of immunotherapy in STS

Although there are no approved agents using immunotherapy in sarcoma, this remains an area of active investigation and warrants mention. The role of immunotherapy in sarcoma dates back as far as the 19th century, when William Coley described a patient with the regression of sarcoma following clearance of a bacterial infection.[148] More recently, the success of checkpoint inhibitors in solid tumors has led to interest in their use for treating sarcoma. While it is generally agreed that immune recognition is critical to harnessing immunotherapy in cancer, the optimal strategy for immunotherapy in STS is yet to be determined.

Overall tumor mutational burden has been identified as a predictor of responsiveness to checkpoint inhibition in multiple malignancies;[149,150] while skeptics argue that sarcoma, as a whole, has a low mutational burden, this is likely dependent on the unique biology of each subtype.[151] Another strategy has been to identify immunogenic antigens with expression specific to sarcoma. Characteristic translocations or fusion proteins, such as those found in SS and MRC-LPS, may represent one antigen for immune recognition.[152] Another antigen is the cancer testis antigen, NY-ESO-1, which is expressed in up to 100% of MRC-LPS and 80% of SS, as well as other subtypes, including uterine LMS and osteosarcoma.[153–155] This led to a pilot study of checkpoint inhibition using the anti-CTLA-4 (cytotoxic T-lymphocyte antigen-4) antibody ipilimumab, 3 mg/kg every 3 weeks, in NY-ESO-1 expressing SS. Although no objective responses were seen among the six patients treated, ipilimumab was well tolerated with no serious adverse events reported.[156] However, in another study using NY-ESO-1-engineered T cells, four out of six responses were noted in NY-ESO-1-expressing SS patients.[157]

Tumor-infiltrating lymphocytes (TILs) play an essential role in the immune response, and have been identified in multiple STS subtypes, including LPS, LMS, SS and MPNST,[158–160] although their presence alone does not result in tumor regression. Similar to CTLA-4, the programmed cell death 1 (PD-1) receptor and its programmed

death ligand-1 (PD-L1) is another checkpoint molecule which has been unlocked with success in melanoma and non-small cell lung cancer, amongst others. PD-L1 tumor expression ranges from 12% to 58%, with notable variation by sarcoma subtype.[160,161] In a retrospective study of 82 STS patients, PD-L1 expression was seen in 100% (7/7) patients with epithelioid sarcoma, 53% (10/19) of SS, 38% (12/32) of rhabdomyosarcoma, 33% (6/18) Ewing sarcoma, and 0% (0/6) mesenchymal chondrosarcoma.[162] PD-1 positivity and PD-L1 expression in STS have been correlated with poor prognosis, advanced stage, higher histologic grade, distant metastasis, and degree of tumor differentiation and necrosis.[161]

SARC 028 is a multi-institutional, phase II study that treated 86 patients with STS and bone sarcoma with the anti-PD-1 therapy, pembrolizumab, 200 mg IV every 3 weeks [ClinicalTrials.gov identifier: NCT02301039]. Eligible subtypes included LMS, LPS, UPS and SS. Early interim analysis showed an 8-week ORR of 0% for LMS (0/10), LPS (0/9) and SS (0/10), but notably, an ORR of 22% (2/9) among UPS. PFS at 8 weeks ($PFS^{8w}$) was 50%, 63%, 30%, and 67%, for LMS, LPS, SS and UPS, respectively. Among 24 patients who were evaluated at 24 weeks, one additional LPS and one additional UPS also achieved PR.[163] Given the preliminary signal seen in dedifferentiated LPS and UPS, an expansion study is actively being planned.

A phase II, single-arm study assessed the impact of another anti-PD-1 therapy, nivolumab, in the treatment of uterine LMS with progression after at least one prior therapy.[164] Among a total of 12 women with pretreated metastatic uterine LMS who received nivolumab 3 mg/kg IV every 2 weeks, the ORR was 0% (0/12).[164] An ongoing phase II study [ClinicalTrials.gov identifier: NCT02500797] will randomize patients with advanced sarcoma to treatment with nivolumab with or without ipilimumab. Further investigation is needed to delineate the role of specific subsets of TILs in the STS microenvironment, and how to best utilize biomarkers such as NY-ESO-1 and PD-1/PD-L1, to select appropriate patients for therapy. While investigation into the role of immunotherapy for STS continues, the use of any checkpoint inhibition for STS should only be conducted in the context of a clinical trial at this time.

## Conclusion

STS remains a major challenge to the medical oncologist, despite the advent of modern systemic treatment strategies, including targeted therapy and immunotherapy. Because STS is a relatively uncommon entity, small numbers of patients have limited the ability to conduct traditional clinical trials and advance drug development. Since 2007, three novel agents including trabectedin, pazopanib and eribulin have been approved for the treatment of high-grade STS in the second-line setting after progression on anthracyclines. Trabectedin has efficacy specific for the L-sarcomas, LMS and LPS. Pazopanib is an orally active VEGF-targeting agent, but not approved for LPS. Meanwhile, eribulin is approved only for LPS, and improves OS in the post-anthracycline setting. In November 2016, the FDA granted accelerated approval for olaratumab, which improves OS in advanced and metastatic, anthracycline-naïve high-grade STS, in combination with doxorubicin.

Further advances will require an improved understanding of the biological differences between STS subtypes, specific biomarkers to elucidate responses to treatment, and mechanisms of resistance. Innovative design of clinical trials is essential to maximize the impact of studies involving this rare disease entity and to understand the unique interplay between tumor, microenvironment and therapeutic interventions. The L-sarcoma trials using eribulin and trabectedin show proof of concept that randomized studies for specific subtypes are feasible and should be further pursued. Towards this aim, correlative endpoints, such as PFS and DCR, with informative biomarkers, will be increasingly important, so that active agents can be identified and future studies will be better informed. In addition to discovering new therapeutic agents, current and future trials to evaluate novel combinations, including immunotherapy combinations, will add to the growing number of options for STS.

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## Conflict of interest statement

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