

Metastatic Soft Tissue Sarcomas: A Review Of Treatment and New Pharmacotherapies

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ABSTRACT

Soft tissue sarcomas represent a group of heterogeneous mesenchymal tumors that occur rarely in adults. While a variety of histological subtypes exist, some of the most common are leiomyosarcoma and liposarcoma. For eligible patients, standard first-line treatment of metastatic disease has typically comprised anthracycline-containing regimens. While traditional cytotoxic chemotherapy has been the mainstay of treatment in metastatic soft tissue sarcoma, emerging targeted and novel therapies are creating new frontiers of treatment for a variety of histological subtypes. Olaratumab (Lartruvo, Eli Lilly) in combination with doxorubicin represents a new potential first-line treatment option. Second-line therapy is often histology-driven, and novel treatment options include trabectedin (Yondelis, Janssen) and eribulin (Halaven, Eisai). This review discusses the diagnosis, role of chemotherapy in unresectable and metastatic disease, and role of emerging therapies in the treatment of metastatic soft tissue sarcoma.

INTRODUCTION

Adult sarcomas are a rare class of malignant tumors that account for approximately 1% of adult malignancies, and about 80% of these originate from soft tissue.¹ In the United States in 2017, there were an estimated 12,390 new cases and 4,990 deaths due to sarcoma in adults.²

Most of these tumors arise in the limbs; however, they can occur in any part of the body, including the abdominal cavity, retroperitoneum, thoracic, and head and neck regions. The incidence of *de novo* metastatic disease in this group of tumors is around 10%, with 83% of these metastases located in the lung. An additional 25% of cases will develop metastatic disease after the initial treatment for curative intent of the primary tumor.^{3,4}

Few patients with resectable oligometastatic lung disease will have the potential for cure, or they will alternatively enter a prolonged remission period with reported five-year survival rates ranging from 25% to 40%.^{5,6} The vast majority of patients who present with metastatic soft tissue sarcoma (STS) will unfortunately succumb to complications of the disease. For this group of patients, systemic therapy offers palliation to diminish symptoms and improve quality of life.

In this review, we will summarize the palliative systemic treatment options for disseminated metastatic STS with information pertaining to regimens newly approved by the Food and Drug Administration (FDA).

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GENERAL PRINCIPLES

STS comprises a group of heterogeneous tumors with more than 50 different histological subtypes that can be classified according to the soft tissue of origin. The most common subtypes found in adults are described in Figure 1.

In the case of unresectable disseminated disease, a biopsy should be performed before initiating treatment. A core biopsy is preferred; a fine-needle aspiration (FNA) is not recommended for initial diagnostic purposes because multiple studies have shown inferior diagnostic accuracy for FNA compared with the core biopsy.^{7,8} Of note, definitive diagnosis may require flow cytometry, cytogenetics, or molecular analyses for chromosomal translocations, all of which may require an incisional biopsy to be performed.

Some patients with metastatic STS may remain asymptomatic for a prolonged period even without active treatment. This group of patients may be watched closely, particularly if they have a low burden of disease.

With multiple histological types, STS has varied responses to therapy. Selection of a treatment regimen must be based on several factors, including histology, disease biology, and patient preferences. Moreover, prognostic factors for longer survival are different than the factors predicting response to systemic therapy.⁹ This may indicate that survival is associated more with disease biology than with type or response to systemic therapy.

TREATMENT PRINCIPLES

A majority of existing studies do not address the variety of histological subtypes of STS during the analysis of the data, including reported response rates and outcomes. Only recently have various studies started to recognize the concept of histology-directed treatment. One should recognize that different histological subtypes exhibit different patterns of response to chemotherapy; therefore, the choice of treatment in these types of tumors should be histologically driven.

For many years, cytotoxic therapy consisting of doxorubicin and ifosfamide was among the few options to treat this type of solid tumor. However, recent advances in molecular pathogenesis and the subsequent development of novel and targeted therapies have added to the armamentarium of treatment options in the management of advanced STS in adults.

CYTOTOXIC SYSTEMIC CHEMOTHERAPY

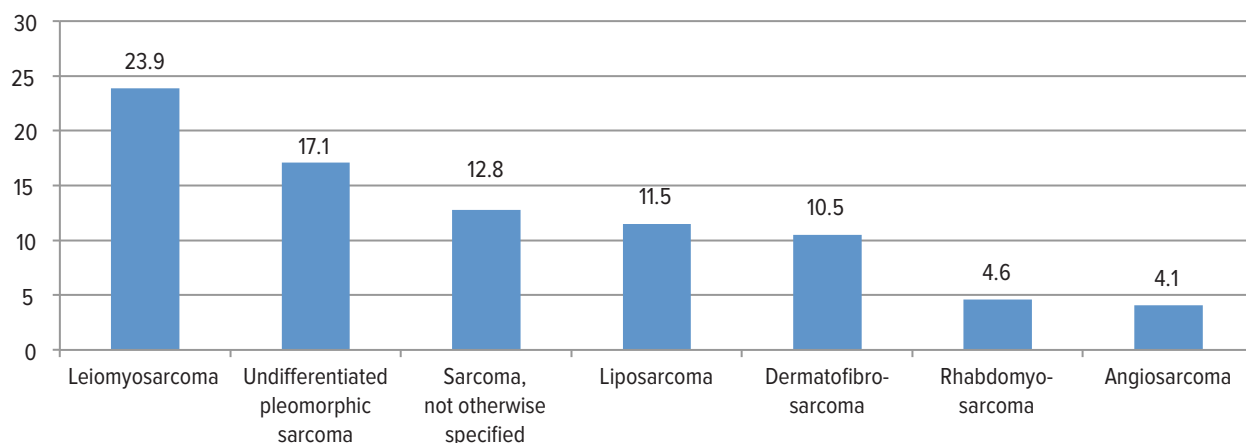
Single-Agent Regimens

Few single-agent chemotherapies have shown a reasonable response rate with acceptable toxicity to justify their use in the treatment of metastatic STS. Two of the most commonly used single agents are doxorubicin and ifosfamide.

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Figure 1 Incidence of Most Common Adult Soft Tissue Sarcoma Histologies (%)⁵⁰



Doxorubicin is considered to be the oldest drug therapy used for metastatic STS, with the first data published in the 1970s.¹⁰ Doxorubicin is an anthracycline antibiotic that exerts its antineoplastic activity by inhibition of topoisomerase, which prevents DNA religation during DNA replication, resulting in DNA strand breaks.¹¹ Most of the trials evaluating single-agent doxorubicin in adult STS showed response rates in the 10% to 25% range, and the dose shown to be effective with acceptable toxicity is 60 mg/m².^{12–16} Adverse events associated with doxorubicin include myelosuppression, mucositis, nausea/vomiting, and cardiotoxicity.¹¹ Pegylated liposomal doxorubicin has a better toxicity profile compared with unencapsulated doxorubicin because it is less cardiotoxic. When the two regimens were compared in the treatment of adults with advanced or metastatic STS of varying subtypes, 50 mg/m² of pegylated liposomal doxorubicin demonstrated similar efficacy to unencapsulated doxorubicin, with response rates of 14% and 12%, respectively, when gastrointestinal stromal tumors (GISTs) were excluded.¹²

Ifosfamide has also been used in the treatment of metastatic STS. Ifosfamide is an agent derived from nitrogen mustard that exerts its antineoplastic activity by alkylating DNA.¹¹ Common adverse events associated with ifosfamide include myelosuppression, neurotoxicity, and hemorrhagic cystitis. The agent is typically administered with mesna to decrease the potential for hemorrhagic cystitis. Ifosfamide has a response rate of 18% at 5 g/m² as a first-line therapy.¹⁷ A trial compared ifosfamide in two doses (3 g/m² infusion over four hours daily for three days, or 9 mg/m² continuous infusion over 72 hours) to doxorubicin 75 mg/m² every three weeks in patients with various STS subtypes.¹⁸ There was no difference in the primary endpoint of progression-free survival (PFS) among the three groups, but the rate of adverse events was higher with both ifosfamide doses, including grade 4 neutropenia, grade 4 febrile neutropenia, and grade 3/4 encephalopathy. As a second-line treatment after doxorubicin failure, ifosfamide has demonstrated response rates ranging from 7% to 41%, with different doses used in each trial.^{19–21} A retrospective study evaluating high-dose ifosfamide, defined as administering a total dose of 14 g/m² over six days every 21 days, in the second- and third-line treatment of patients with refractory STS revealed that this dosing scheme can have

a particular advantage in synovial sarcoma.²² Of the patients with synovial sarcoma evaluated, 40% had a partial response and 40% had stable disease. Adverse events with high-dose ifosfamide were similar to those reported with other ifosfamide doses in STS, with neutropenia and neurological toxicity being among the most commonly reported serious adverse events.

Gemcitabine, a deoxycytidine analogue that inhibits DNA synthesis,²³ has limited activity as monotherapy. A phase 2 trial evaluated intravenous (IV) gemcitabine 1,000 mg/m² over 30 minutes on days 1 and 8 every 21 days in patients with metastatic leiomyosarcoma. The median PFS and overall survival (OS) were three months and 13.9 months, respectively.²⁴ The most common grade 3/4 adverse events included neutropenia, thrombocytopenia, and alanine aminotransferase (ALT) elevation. One potential modality that has been theorized to improve the efficacy of gemcitabine is administration at a rate of 10 mg/m² per minute to maximize the formation rate of the active triphosphate metabolite of gemcitabine.²⁵ A phase 2 trial evaluating fixed-dose rate gemcitabine demonstrated a positive tumor growth control rate in patients with leiomyosarcoma, with 7% and 21% of patients demonstrating a partial response and stable disease, respectively.

As a single agent, paclitaxel can be utilized in the treatment of angiosarcoma. Paclitaxel exerts its anticancer activity by stabilizing microtubules via the inhibition of the depolymerization process during the mitotic phase of the cell cycle.²⁶ In a phase 2 study evaluating paclitaxel 80 mg/m² IV given over one hour weekly in patients with advanced or metastatic angiosarcoma, paclitaxel demonstrated two-month and four-month PFS rates of 74% and 45%, respectively.²⁷ Anemia, neutropenia, and asthenia were among the most common adverse events reported in the trial.

Other single-agent drugs that have been investigated and have shown activity in metastatic STS include dacarbazine, temozolomide, vinorelbine, cisplatin, and carboplatin.^{28–34} All are associated with response rates ranging between 5% and 20%.

Combination Chemotherapy

Many phase 2 and 3 trials have evaluated a variety of chemotherapy combinations in an effort to improve response rates and

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OS. The typical backbone of combination regimens is doxorubicin with an alkylating agent. Controversy has surrounded the clinical benefits of this approach. Some combination chemotherapy trials have produced superior response rates in the combination arm compared with the single-therapy arm. Until recently, none of the previous trials had shown a significant survival advantage over single-agent regimens. Furthermore, combination chemotherapy regimens have the potential for greater risk of serious treatment-related toxicities. The single exception is the combination of olaratumab (Lartruvo, Eli Lilly) and doxorubicin, which was reported recently in a phase 2 randomized trial to have an OS advantage over a single agent, doxorubicin, with acceptable toxicity.³⁵

A meta-analysis conducted by the Cochrane Collaboration reviewed eight randomized trials reported between 1976 and 1995 comparing single-agent doxorubicin with various doxorubicin-containing combination chemotherapy regimens.³⁶ In these trials, single-agent doxorubicin was compared with a range of doxorubicin-containing combinations that included vincristine, vindesine, cyclophosphamide, streptozotocin, mitomycin-C, cisplatin, and ifosfamide. Combination regimens were consistently associated with higher rates of gastroenterological and hematologic toxicities, while the better response rates associated with combination therapy were minimal and depended on the statistical model used (fixed effects model OR_{resp} , 1.29; 95% confidence interval [CI], 1.03–1.60; $P = 0.03$; random effects model OR_{resp} , 1.26; 95% CI, 0.96–1.67; $P = 0.10$). There was no statistically significant difference in the one-year ($OR_{\text{mortality}}$, 0.87; 95% CI, 0.73–1.05; $P = 0.14$) or two-year mortality rates ($OR_{\text{mortality}}$, 0.84; 95% CI, 0.67–1.06; $P = 0.13$).

Gemcitabine plus docetaxel can be considered in patients who cannot tolerate doxorubicin because of their cardiac history. The GeDD trial compared monotherapy with doxorubicin to combination therapy with gemcitabine and docetaxel.³⁷ In this multicenter, randomized, phase 3 trial, patients with various metastatic STS histologies received either doxorubicin 75 mg/m² IV every 21 days or gemcitabine 675 mg/m² IV over 90 minutes on days 1 and 8 plus docetaxel 75 mg/m² IV over 60 minutes on day 8 every 21 days. No significant difference in PFS at 24 weeks was observed between the doxorubicin arm (46.3% [95% CI, 37.5–54.6]) and the combination therapy arm (46.4% [95% CI, 37.5–54.8]). The authors concluded that doxorubicin should remain the standard first-line treatment of metastatic STS, but gemcitabine/docetaxel can be considered an acceptable alternative in patients with cardiac dysfunction in whom doxorubicin is contraindicated.

NEW PHARMACOTHERAPIES

Olaratumab

Olaratumab is an immunoglobulin G monoclonal antibody that was approved by the FDA in 2016.³⁸ Olaratumab targets a specific subtype of the platelet-derived growth factor receptor (PDGFR) alpha receptor.³⁹ The recommended dose is 15 mg/kg infused IV over 60 minutes on days 1 and 8 of a 21-day cycle. A randomized, open-label phase 2 study compared single-agent doxorubicin therapy with the combination of doxorubicin and olaratumab in patients with locally advanced or unresectable STS not amenable to curative surgical resection or radiation therapy.³⁵ The most common histological subtypes in this study included

leiomyosarcoma (38%), liposarcoma (18%), and undifferentiated pleomorphic sarcoma (18%). Olaratumab was administered at a dose of 15 mg/kg IV on days 1 and 8 of a 21-day cycle continuously until disease progression and doxorubicin was administered at a dose of 75 mg/m² on day 1 of a 21-day cycle for up to eight cycles. The primary endpoint was PFS; OS was a secondary endpoint. Combination therapy demonstrated an increase in median PFS (6.6 months versus 4.1 months; hazard ratio [HR], 0.67) compared with doxorubicin monotherapy. Initial use of combination therapy showed a near doubling of median OS (26.5 months versus 14.7 months; HR, 0.46; 95% CI, 0.30–0.71; $P = 0.0003$), despite accounting for crossover to olaratumab in the single-agent doxorubicin arm. Combined therapy was associated with increased side effects, including infusion-related reactions (13% versus 0%), neutropenia (58% versus 35%), and mucositis (53% versus 35%). The authors concluded that the addition of olaratumab to doxorubicin in the treatment of adult STS not amenable to curative resection or radiation therapy improved OS and had an acceptable toxicity profile.

Trabectedin

Trabectedin (Yondelis, Janssen) is a newer antineoplastic agent recently approved in the United States to treat advanced liposarcoma and leiomyosarcoma in patients who have already been treated with an anthracycline-based regimen.⁴⁰ Trabectedin is a marine-derived tetrahydroisoquinolone alkaloid that binds to the minor groove of DNA, which disrupts the function of DNA binding proteins and leads to cell-cycle perturbation and apoptosis.⁴¹ It is currently approved for administration at a dose of 1.5 mg/m² IV over 24 hours on day 1 of a 21-day cycle. Administration is recommended via a central venous line because trabectedin is a vesicant.

A multicenter, randomized, open-label, phase 2 study evaluated the safety and efficacy of trabectedin compared with best supportive care in adults with advanced translocation-related sarcoma who did not respond to available standard chemotherapy.⁴² A variety of STS histological subtypes were eligible, including myxoid/round-cell liposarcoma, synovial sarcoma, alveolar rhabdomyosarcoma, and Ewing sarcoma. The primary endpoint was PFS. Trabectedin was administered at a dose of 1.2 mg/m² IV over 24 hours. Seventy-six patients were randomized: 39 received trabectedin, and 37 received best supportive care. Patients with primarily myxoid/round-cell liposarcoma and synovial sarcoma who received trabectedin had a significantly longer median PFS compared with best supportive care (5.6 months versus 0.9 months; HR, 0.07; 95% CI, 0.30–0.16; $P < 0.0001$). OS had not yet been reached in the trabectedin group (95% CI, 12.8–not reached [NR]) compared with eight months in patients receiving best supportive care (7.0–NR; HR, 0.42; 95% CI, 0.18–0.98; $P = 0.04$). Grade 3/4 treatment-related adverse events in patients receiving trabectedin included neutropenia (67%), febrile neutropenia (14%), thrombocytopenia (17%), ALT elevations (61%), aspartate aminotransferase (AST) elevations (41%), and creatinine phosphokinase (CPK) elevations (6%). The authors of this study concluded that trabectedin significantly improved PFS in adults with metastatic translocation-related sarcoma that had progressed with standard first-line chemotherapy compared with best supportive care.

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A multicenter, randomized, open-label, phase 3 trial compared trabectedin with dacarbazine in patients with advanced leiomyosarcoma or liposarcoma who had been treated previously with standard chemotherapy, including previous anthracycline-based chemotherapy.⁴³ Patients were randomized 2:1 to receive either trabectedin 1.5 mg/m² IV over 24 hours or dacarbazine 1,000 mg/m²; both drugs were administered on day 1 of a 21-day cycle. The primary endpoint was OS, with PFS as a secondary endpoint. Although this trial showed significantly higher median PFS (4.2 months versus 1.5 months) with trabectedin compared with dacarbazine, median OS was not significantly different (12.4 months versus 12.9 months). The most common treatment-emergent adverse events of grade 3/4 in the trabectedin group included neutropenia (37%), thrombocytopenia (17%), anemia (14%), ALT elevations (26%), AST elevations (13%), and CPK elevations (5.3%). Elevations in AST and ALT were transient, and despite the elevations in CPK only 1.2% of patients receiving trabectedin experienced rhabdomyolysis. The authors concluded that trabectedin demonstrated superior disease control compared with dacarbazine in adults with previously treated metastatic liposarcoma and leiomyosarcoma.

Eribulin

Eribulin (Halaven, Eisai) is a nontaxane microtubule inhibitor that represents another potential treatment option in metastatic STS. It was approved in the United States in 2016 for the treatment of inoperable liposarcoma in patients who had been treated previously with an anthracycline-based regimen.⁴⁴ A randomized, open-label, phase 3 trial compared the safety and efficacy of eribulin with dacarbazine in patients with advanced leiomyosarcoma or liposarcoma who had received at least two prior systemic chemotherapy regimens, including an anthracycline, unless contraindicated.⁴⁵ Eribulin was administered at a dose of 1.4 mg/m² IV on days 1 and 8 of a 21-day cycle, and dacarbazine was administered at a dose of 850 mg/m², 1,000 mg/m², or 1,250 mg/m² on day 1 of a 21-day cycle. The primary endpoint was OS; PFS was a secondary endpoint. A total of 452 patients were randomized: 228 received eribulin, and 224 received dacarbazine. Treatment benefits for eribulin in this study were limited to the subgroup of patients with liposarcoma and not those with leiomyosarcoma. The OS benefit was greater in patients receiving eribulin than in those receiving dacarbazine (15.6 months versus 8.4 months; HR, 0.51; 95% CI, 0.35–0.75) in patients with liposarcoma. Median PFS was 2.6 months in both treatment groups (HR, 0.88; 95% CI, 0.71–1.09; *P* = 0.23). Discontinuation of eribulin secondary to adverse events and dose reduction occurred in 8% and 26% of patients, respectively. Common grade 3/4 adverse events experienced by patients receiving eribulin included neutropenia (35.4%), anemia (7%), fatigue (3%), and peripheral neuropathy (1.8%). The authors concluded that eribulin improved OS compared with dacarbazine in adults with advanced STS.

Pazopanib

Pazopanib (Votrient, Novartis) is a multitargeted tyrosine kinase inhibitor (TKI) that targets and inhibits vascular endothelial growth factor receptors (VEGFR), PDGFR, fibroblast growth factor receptors, and c-Kit. It is indicated for the treat-

ment of patients with advanced STS who have received prior chemotherapy, except for patients with liposarcoma.⁴⁶ A randomized, double-blind, placebo-controlled, phase 3 study by the European Organization for Research and Treatment of Cancer compared pazopanib 800 mg orally daily until disease progression or intolerable toxicity with placebo in patients with various histological STS subtypes; patients with liposarcoma were excluded.⁴⁷ The primary endpoint was PFS, with OS as a secondary endpoint. A total of 372 patients were randomized 2:1—246 to pazopanib and 123 to placebo. Patients receiving pazopanib exhibited significantly better median PFS compared with placebo (4.6 months versus 1.6 months; HR, 0.31; 95% CI, 0.24–0.40; *P* < 0.001). However, there was no significant difference in OS (12.5 months versus 10.7 months; HR, 0.86; 95% CI, 0.67–1.11; *P* = 0.25). Common grade 3/4 adverse events experienced in patients receiving pazopanib included fatigue (13%), hypertension (7%), diarrhea (5%), and anorexia (6%). The authors concluded that pazopanib is an effective option in the management of previously treated adult nonadipocytic STS.

Regorafenib

Regorafenib (Stivarga, Bayer Healthcare) is another multitargeted TKI that exerts its antineoplastic activity by targeting and inhibiting VEGFR, c-Kit, BRAF, RET, and PDGFR.⁴⁸ While regorafenib is not yet approved by the FDA for the treatment of non-GIST STS, its safety and efficacy have been evaluated in a randomized, placebo-controlled, phase 2 trial in patients with liposarcoma, leiomyosarcoma, synovial sarcoma, or other types of STS that had been treated previously with a variety of agents.⁴⁹ Patients were randomized to receive either regorafenib 160 mg orally daily for 21 days followed by seven days off or matching placebo. A total of 181 patients were randomized to treatment; 89 received regorafenib and 92 received placebo. The primary endpoint was PFS; OS was a secondary endpoint. Compared with placebo, regorafenib demonstrated a significant benefit in PFS among patients with leiomyosarcoma (3.7 months versus 1.8 months; HR, 0.46; 95% CI, 0.46–0.80; *P* = 0.0045) and synovial sarcoma (5.6 months versus 1.0 months; HR, 0.10; 95% CI, 0.03–0.35; *P* < 0.0001). Patients with liposarcoma did not experience a benefit in PFS compared with placebo (1.1 months versus 1.7 months; HR, 0.89; 95% CI, 0.48–1.64; *P* = 0.70). Common grade 3/4 adverse events experienced by patients in the regorafenib arm included arterial hypertension (19%), hand–foot syndrome (15%), asthenia (13%), and myalgia (96%).

Table 1 summarizes key clinical characteristics of the novel and targeted agents for the treatment of STS, while Table 2 presents major findings of the studies of these agents.

CONCLUSION

The treatment of metastatic STS has seen promising advances with the approval of several novel pharmacological agents in recent years. Prior to these new drug approvals, the standard of care, first-line treatment for patients with metastatic STS was doxorubicin with ifosfamide, single-agent doxorubicin, or gemcitabine plus docetaxel. In patients with a contraindication to anthracycline-based therapy (e.g., patients with heart failure), a gemcitabine-based chemotherapy regimen could be considered for first-line therapy. Patients diagnosed

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Table 1 Novel and Targeted Agents for the Treatment of Soft-Tissue Sarcomas

Drug Name	Indicated Sarcoma Histology	Dosing	Mechanism of Action	Adverse Events*	Additional Comments
Olaratumab (Lartruvo, Eli Lilly) ^{35,38}	Any histological subtype for which an anthracycline-containing regimen is appropriate	15 mg/kg IV days 1 and 8 every 21 days	Inhibits PDGFR α	Nausea, fatigue, neutropenia, mucositis, alopecia, vomiting, anemia, constipation, diarrhea, decreased appetite, pyrexia, abdominal pain, febrile neutropenia, cardiac dysfunction [†]	<ul style="list-style-type: none"> • Premedicate with diphenhydramine 25–50 mg IV and dexamethasone 10–20 mg IV on cycle 1, day 1 of treatment to prevent infusion reaction • May cause fetal harm when administered in pregnancy
Trabectedin (Yondelis, Janssen) ^{40,42}	Leiomyosarcoma, liposarcoma	1.5 mg/m ² CIVI over 24 hours every 21 days	Alkylating agent, binds to minor groove of DNA	Nausea, decreased appetite, constipation, malaise, vomiting, anemia, myalgia, pyrexia, diarrhea, neutropenia, ALT increase, AST increase, thrombocytopenia, lymphopenia	<ul style="list-style-type: none"> • Premedicate with dexamethasone 20 mg to prevent hepatotoxicity • Vesicant, administer via central venous line • Avoid concomitant administration with CYP3A4 inhibitors and inducers • May cause fetal harm when administered in pregnancy
Eribulin (Halaven, Eisai) ^{44,45}	Liposarcoma	1.4 mg/m ² days 1 and 8 every 21 days	Nontaxane microtubule inhibitor	Neutropenia, fatigue, nausea, alopecia, constipation, pyrexia, anemia, asthenia, decreased appetite, peripheral neuropathy	<ul style="list-style-type: none"> • May cause fetal harm when administered in pregnancy
Pazopanib (Votrient, Novartis) ^{46,47}	Leiomyosarcoma	800 mg orally daily	Inhibits VEGFR, PDGFR, FGFR, c-Kit	Fatigue, diarrhea, nausea, weight loss, hypertension, anorexia, hair hypopigmentation, vomiting, dysgeusia	<ul style="list-style-type: none"> • Avoid concomitant administration with CYP3A4 inhibitors and inducers • May cause fetal harm when administered in pregnancy • Administer on an empty stomach at least 1 hour before or 2 hours after a meal
Regorafenib (Stivarga, Bayer Healthcare) ^{48,49}	Leiomyosarcoma, synovial sarcoma	160 mg orally daily for 3 weeks, then 1 week off	Inhibits c-Kit, VEGFR, PDGFR, RET, BRAF	Asthenia, pain, myalgia, anorexia, abdominal pain, diarrhea, mucositis, hand–foot syndrome, hypertension, dyspnea, hypophosphatemia	<ul style="list-style-type: none"> • Avoid concomitant administration with CYP3A4 inhibitors and inducers • May cause fetal harm when administered in pregnancy • Administer with a low-fat breakfast

* Common all-grade adverse events observed in > 20% of patients receiving drug in clinical trial.

[†] All-grade adverse events observed in > 20% of patients receiving olaratumab/doxorubicin.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CIVI = continuous intravenous infusion; CYP3A4 = cytochrome P450 3A4; FGFR = fibroblast growth factor receptor; IV = intravenous; PDGFR = platelet-derived growth factor receptor; RET = rearranged during transfection; VEGFR = vascular endothelial growth factor receptor.

with angiosarcoma may also be treated with paclitaxel as a first-line therapy. Finally, patients with a poor performance status or multiple comorbidities for whom chemotherapy is being considered can also be treated with pegylated liposomal doxorubicin or single-agent gemcitabine.

As a general initial approach to therapy, all patients with STS should be evaluated for eligibility to receive doxorubicin as first-line therapy. Patients with disease that is not amenable to curative resection or radiation therapy who are eligible to

receive doxorubicin can also be considered for combination therapy with olaratumab. It is still important to keep in mind that synovial sarcoma and myxoid/round-cell liposarcoma may be more sensitive to combination therapy with doxorubicin and ifosfamide than to doxorubicin with olaratumab, as these tumor types may be more sensitive to ifosfamide. However, there has yet to be a study comparing these two combinations.

Histology-driven therapy is now generally considered to be a second-line consideration; however, it may still be recom-

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Table 2 Studies of Novel Agents in the Treatment of Metastatic Soft Tissue Sarcoma in Adults

Study	Design	Regimen	Median PFS	Median OS	Response Rates
Tap et al. ³⁵	Phase 1b/2, randomized, open-label	Olaratumab 15 mg/kg IV days 1 and 8 and doxorubicin 75 mg/m ² day 1 every 21 days	6.6 months	26.5 months	ORR, 18.2%
Kawai et al. ⁴²	Phase 2, randomized, open-label	Trabectedin 1.2 mg/m ² CIVI over 24 hours every 21 days	5.6 months	Not reached	PR, 8% SD, 57%
Demetri et al. ⁴³	Phase 3, randomized, open-label, active-controlled	Trabectedin 1.5 mg/m ² CIVI over 24 hours every 21 days	4.2 months	12.4 months	ORR, 9.9% SD, 51%
Schöffski et al. ⁴⁵	Phase 3, randomized, open-label, active-controlled	Eribulin 1.4 mg/m ² IV days 1 and 8 every 21 days	2.6 months	13.5 months	PR, 4% SD, 52%
PALETTE ⁴⁷	Phase 3, randomized, double-blind, placebo-controlled	Pazopanib 800 mg orally daily	4.6 months	12.5 months	PR, 6% SD, 67%
REGOSARC ⁴⁹	Phase 2, randomized, double-blind, placebo-controlled	Regorafenib 160 mg orally daily for 21 days on and 7 days off	LMS: 3.7 months SS: 5.6 months	LMS: 21 months SS: 13.4 months	LMS: PR, 0%; SD, 86% SS: PR, 8%; SD, 77%

CIVI = continuous IV infusion; IV = intravenous; LMS = leiomyosarcoma; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; SD = stable disease; SS = synovial sarcoma.

mended as an initial approach to therapy for some commonly anthracycline-resistant histologies, such as alveolar soft part sarcomas, solitary fibrous tumor/hemangiopericytomas, and clear cell sarcomas. Such patients may benefit from newer treatments, such as pazopanib.

Following progression of disease on first-line therapy, a variety of treatment options may be appropriate. For example, eribulin or trabectedin can be considered for second-line treatment of liposarcomas. In addition, trabectedin can also be considered for second-line treatment of leiomyosarcomas. Pazopanib can be considered for second-line therapy for a variety of STS subtypes, except liposarcoma. Regorafenib, while it has been studied and demonstrated a benefit in patients with leiomyosarcoma and synovial sarcoma, is not yet FDA-approved for this indication.

Overall, the recent approval of several new agents has expanded the number of options available for the treatment of metastatic STS in adults.

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