

Molecular targets and novel therapeutic avenues in soft-tissue sarcoma

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ABSTRACT

Soft-tissue sarcoma (STS) represents a heterogeneous group of rare tumours, and a significant number of affected patients will develop metastatic disease. Outcomes in the population with metastatic disease are generally poor, especially after progression on standard chemotherapy. The advent of personalized medicine has permitted oncologists to offer targeted treatment, thus addressing the limited treatment options and poor prognosis after progression on first-line chemotherapy. In this review, we delineate the existing data and therapeutic successes with respect to existing and emerging molecular targets in STS and options for immunotherapy in STS. Our review also summarizes emerging clinical trials that are currently recruiting patients.

Key Words Sarcoma, chemotherapy, targeted therapy, immunotherapy

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INTRODUCTION

Soft-tissue sarcoma (STS) represents a heterogeneous group of rare tumours¹. Of patients with early-stage disease treated with locoregional modalities such as surgery and radiation, approximately 40% will develop metastatic disease; and of patients presenting for the first time with STS, 10% will be diagnosed with metastatic disease². Goals of treatment in the metastatic setting are to palliate symptoms and improve quality of life and survival. Doxorubicin with or without ifosfamide is the first-line standard of care for the treatment of metastatic STS. Angiosarcomas are also sensitive to anthracycline-based chemotherapy³, but taxane-based chemotherapy also has significant activity⁴⁻¹⁰.

For patients with metastatic disease, outcomes are generally poor, with overall survival ranging between 12 and 19 months, and little improvement in outcomes has been observed since the start of the 2000s². There is therefore an unmet clinical need to develop and implement novel treatment modalities that will improve outcomes for patients with metastatic STS.

The advent of personalized medicine has permitted oncologists to offer targeted treatment, addressing the limited treatment options and poor prognosis after progression on first-line chemotherapy. In this review, we delineate the existing data and therapeutic successes with respect to existing and emerging molecular targets in STS. The STSs with targetable molecular abnormalities in the

adult population reviewed in detail here include desmoid tumours, tenosynovial giant-cell tumours, *SMARCB1*-deficient sarcomas, and *TRK* fusion sarcomas. Next-generation sequencing (NGS) has allowed for the identification of driver mutations and potentially targetable molecular abnormalities in patients with limited treatment options, and recent data using NGS in the STS setting are also discussed in the review.

REVIEW

Desmoid Tumours

Desmoid tumour, also known as aggressive fibromatosis, is a rare disease of fibroblastic proliferation, characterized by mutations of the *CTNGB1* (beta-catenin) or *APC* (familial adenomatous polyposis) gene. Although this neoplasm lacks metastatic potential, it is often locally aggressive and is characterized by infiltrative growth of adjacent tissues into the mesentery, neurovascular structures, and visceral organs¹. Patients diagnosed before the age of 40 are more likely to be women, and the most common site of onset in these patients is the abdominal wall. After the age of 40, these tumours develop in men and women equally, and no predilection for a particular tumour site is observed in older adults. Desmoid tumours are treated initially with active surveillance^{11,12}, because about 20% of patients can experience spontaneous regression¹³. Upon progression, or in the presence of life-threatening symptoms or of significant

symptoms that cannot be controlled with pain control measures, active therapy is offered. If the patient is a candidate for surgery and the desmoid tumour is located in the abdominal wall, surgery is generally the next step. It is important to note that rates of local recurrence are high¹. If the desmoid tumour arises in other sites, such as the head-and-neck area, the extremities, or the intra-abdominal or pelvic areas, systemic therapy is usually offered. Typically given for 6–12 months, common cytotoxic chemotherapy regimens include low-dose vinblastine (or vinorelbine) and methotrexate for patients who have low burden-of-disease symptoms¹⁴, and liposomal doxorubicin for patients having more severe symptoms or experiencing progression after a prior regimen¹⁵.

Targeted Therapy in Desmoid Tumours

Imatinib: Imatinib has a limited role in patients with desmoid tumours. A phase II study in which 38 patients with unresectable desmoid tumour received imatinib reported an overall response rate of 19%¹⁶, but no control group was used. A retrospective case series reviewed the response rate to imatinib combined with radiation therapy in 4 patients with unresectable or recurrent desmoid tumours; all patients either experienced a partial response or had stable disease¹⁷. Given the paucity of prospective data, the use of imatinib in patients with desmoid tumours cannot be recommended at this time.

As already mentioned, desmoid tumours are more likely to be diagnosed in women before the age of 40, often during pregnancy or within 1 year postpartum¹⁸. In support of those epidemiologic findings, immunohistochemical studies have demonstrated the presence of estrogen receptor beta in 90% of desmoid tumours¹⁹. The selective estrogen receptor modulator tamoxifen has been used in the treatment of desmoid tumours^{20,21}, but a more recent publication showed no relationship between symptomatic benefit and the magnetic resonance imaging response with the use of tamoxifen²².

Sorafenib: Sorafenib, an oral multi-targeted receptor tyrosine kinase inhibitor, has shown activity in desmoid tumours. A retrospective analysis of 26 patients evaluated the efficacy of sorafenib in desmoid tumours that were unresectable or resectable only with amputation²³. The most common primary site in the cohort was abdomen or pelvis. A significant proportion of patients (42%) received sorafenib in the first-line setting. Sorafenib was started at 400 mg daily and was decreased in cases of dose toxicity. As evaluated by the Response Evaluation Criteria in Solid Tumors (version 1.1), sorafenib was associated with a partial response rate of 25%, with 70% of patients having stable disease. Additionally, approximately 70% of patients reported a subjective decrease in pain and use of analgesics with sorafenib, with most of those clinical improvements being noted within 2 weeks of sorafenib initiation. The study also noted that the Response Evaluation Criteria in Solid Tumors might underestimate the treatment response and suggested that the signal from T2-weighted magnetic resonance imaging might be more clinically relevant and accurate.

That retrospective trial prompted Gounder *et al.*²⁴ to conduct a prospective double-blind randomized phase III

trial to evaluate the safety and efficacy of sorafenib in the treatment of desmoid tumours. The study randomized 87 adult patients with either symptomatic, recurrent, or primary desmoid tumour that was deemed unresectable to receive sorafenib at a dose of 400 mg daily or placebo. Patients who had previously received sorafenib were excluded from the trial. Crossover after progression was allowed for patients receiving placebo. The 2-year progression-free survival rate was 81% in the sorafenib group compared with 36% in the placebo group [hazard ratio for progression or death: 0.13; 95% confidence interval (CI): 0.05 to 0.31; $p < 0.001$]. Before crossover, the objective response rate was 33% in the sorafenib group (95% CI: 20% to 48%) and 20% in the placebo group (95% CI: 8% to 38%). The most frequently reported adverse effects in the sorafenib group were grade 1 or 2 rash, fatigue, hypertension, and diarrhea. Of the patients in the sorafenib group, 29% experienced a grade 3 adverse event, and the incidences of grade 4 thrombocytopenia and anemia were each 2%.

The trial demonstrated a role for sorafenib in delaying disease progression in patients with desmoid tumours, but also supported a role for observation in patients without symptoms, because 20% of the patients in the placebo group experienced spontaneous regression.

Gamma-Secretase Inhibitor PF-03084014: A phase II trial evaluated gamma-secretase inhibitor PF-03084014 (niraparacetat) in 17 patients with refractory desmoid tumours. Results were encouraging, with 5 patients (29%) experiencing a confirmed partial response, and another 5 patients having prolonged stable disease²⁵. Those findings have led to a randomized placebo-controlled phase III study of niraparacetat, which is currently ongoing (see NCT03785964 at <https://ClinicalTrials.gov/>).

Tenosynovial Giant-Cell Tumours

Tenosynovial giant-cell tumour (TGCT), previously known as pigmented villonodular synovitis, is a rare and locally aggressive neoplasm of the joint or tendon sheath¹. This neoplasm is characterized by the proliferation of synovial cells that initiate recruitment of inflammatory cells such as macrophages and histiocytes¹. The tumours can be either localized or diffuse, the latter characterized by diffuse proliferation of the entire synovium, most commonly affecting the knee joint²⁶. Although most of these neoplasms occur within the joints, a diffuse form can occur, and extra-articular forms have also been described²⁷. Rarely, TGCT can metastasize to the adjacent lymph nodes and to the lungs²⁸. Localized TGCT is curable with arthroscopic or open surgery, but the diffuse form of the disease is associated with a high rate of local recurrence²⁹.

Targeted Therapy in TGCT

Pexidartinib: The neoplastic cells in giant-cell tumours can overexpress colony-stimulating factor 1 (CSF1), with signalling between CSF1 and the CSF1 receptor (CSF1R)^{30,31}. Colony-stimulating factor 1 is often found on the membranes of immune cells. Given the recruitment of inflammatory cells by the neoplastic synovial cells implicated in the pathophysiology of TGCT, it was hypothesized that

inhibition of signalling between CSF1 and CSF1R could target the underlying cause of the disease.

A phase I study of 43 patients receiving pexidartinib, a dual inhibitor of CSF1R and the c-Kit receptor tyrosine kinase, led to a multicentre single-cohort extension study of pexidartinib administered at a dose of 1000 mg daily in 23 patients with TGCT³². Patients with such tumours were included in the study if they had shown disease progression or if the tumour was recurrent or inoperable, or had required extensive surgery for complete resection. Most patients had disease within the knee. Of the 23 patients, 12 experienced a partial response, and 7 had stable disease, representing an overall response rate of 52% (95% CI: 32% to 73%) and a rate of disease control (complete response, partial response, or stable disease) of 83% (95% CI: 67% to 98%). Treatment-related adverse events occurred in 25% of the study population, and the most common adverse events included hair colour change, fatigue, nausea, dysgeusia, and periorbital edema. The most common grade 3 adverse event was elevated serum aspartate aminotransferase or alanine aminotransferase, which occurred in 3 patients.

A phase III randomized controlled trial of pexidartinib in 174 patients with TGCT was recently published in *The Lancet*³³. The trial was conducted in two parts, the first being a randomized controlled trial comparing pexidartinib with placebo in patients with inoperable disease. Patients who completed the first part of the trial were eligible to enter the second part, in which they were offered open-label pexidartinib in an intention-to-treat analysis. Compared with 0% in the placebo group, 39% of the patients in the pexidartinib group achieved a response (95% CI: 27% to 52%; $p < 0.0001$). In a secondary endpoint analysis, patients receiving pexidartinib, compared with those in the placebo group, reported improved range of motion and physical functioning. Of the patients in the pexidartinib group, 13% experienced serious adverse events (a toxicity profile similar to that described in the phase I study outlined earlier), with elevations in liver enzymes being a frequent and important side effect.

Taken together, the data demonstrate that pexidartinib should be considered in the treatment of individuals with TGCT and functional limitation where surgery is not possible.

Emactuzumab: A phase I study in 29 patients evaluated the use of emactuzumab (an immunoglobulin G1 subclass humanized recombinant monoclonal antibody directed against CSF1R expressed on the surfaces of macrophages) in patients with unresectable TGCT³⁴. Expansion cohorts for the study are currently ongoing (see NCT01494688 at <https://ClinicalTrials.gov/>). In the safety expansion cohort, independent central review of magnetic resonance imaging was conducted for 28 of 29 patients, and independent central review of positron-emission tomography imaging, for 26 of 29 patients. Of the 28 reviewed patients, 24 (86%) achieved an objective response, and 19 (68%) achieved a partial response. Of the 26 reviewed patients, 24 (92%) achieved a metabolic response. Common adverse events after emactuzumab treatment were facial edema, fatigue, asthenia, and pruritus. Drug-induced lupus erythematosus was a rare, but important, side effect.

Nilotinib: Nilotinib is a multi-targeted tyrosine kinase inhibitor that has activity against CSF1R³⁵. Its efficacy was evaluated in a phase II study involving 51 patients with advanced or unresectable TGCT³⁶. Although a high proportion of those patients were progression-free at 12 weeks, the overall response rate was lower than had been seen with pexidartinib and emactuzumab. Nearly all patients experienced at least 1 adverse event, and 11% experienced at least 1 grade 3 adverse event (headache, hepatic enzyme abnormalities, diarrhea).

Imatinib: Imatinib has weak activity against CSF1R³⁵. In a retrospective series of 29 patients with locally advanced or metastatic TGCT, the objective response rate was 19%, and 74% of the patients reported symptomatic or functional improvement³⁷. Aside from that retrospective series, case reports have described success with imatinib, but the data are currently insufficient to recommend this agent in the treatment of TGCT.

Tazemetostat In *Ini1*-Deficient Sarcomas

Epithelioid sarcoma is a rare STS, and loss of *Ini1* occurs in more than 90% of these tumours. Because *Ini1* is a negative regulator of the oncogenic driver *EZH2*, inhibition of *EZH2* was hypothesized to potentially be able to lead to tumour regression³⁸. Tazemetostat, an inhibitor of *EZH2*, was evaluated in a phase II study enrolling 62 patients with advanced *Ini1*-deficient epithelioid sarcoma. The overall response rate was 13%. Additionally, 35 patients had a best response of stable disease. Those results came from an interim analysis and remain unpublished.

Larotrectinib in *TRK* Fusion–Positive Sarcoma

Rarely, adults with STS have gene fusions involving *NTRK*. Larotrectinib, a selective *NTRK* inhibitor, was shown to be effective in a combined analysis of 55 patients with various *NTRK* fusion–positive solid tumours—an important subset of which consisted of patients with STS³⁹. Of 11 patients with STS showing *NTRK* fusions, 10 experienced an objective response, and 1 achieved a complete response. No patient in the study discontinued larotrectinib because of treatment-related toxicity. The most common side effects included elevations in liver enzymes, fatigue, nausea, vomiting, dizziness, diarrhea, constipation, and cough.

MET/ALK Inhibition

Thus far, combined MET and ALK inhibition using crizotinib has been evaluated in a phase II study of 20 patients with chemotherapy-refractory alveolar rhabdomyosarcoma⁴⁰. More common in children and adolescents, alveolar rhabdomyosarcoma is a rare subtype of STS in adults, accounting for only 3% of cases. Unfortunately, the crizotinib study did not reveal any meaningful activity in the adult patient population. It is important to note that most patients in the study did not harbour an *ALK* mutation. A second study evaluated the role of MET and ALK inhibition in 53 patients with alveolar soft-part sarcoma, another orphan disease in adults⁴¹. That study showed important clinical activity in patients with *MET*-positive disease, most of whom had stable disease with treatment.

Emerging Immunotherapy Regimens for STS

Pembrolizumab

Pembrolizumab, a PD-1 inhibitor, was tested in a phase II trial involving 86 patients with refractory STS⁴². The primary endpoint of overall response was not met in the study, but pembrolizumab was associated with promising response rates in patients with undifferentiated pleomorphic sarcoma and dedifferentiated liposarcoma. Results of expanded cohorts for those STS subtypes are awaited. A second phase II study, this time in multiple cohorts of patients with STS, demonstrated limited activity for pembrolizumab in combination with cyclophosphamide⁴³. The combination of nivolumab (a PD-1 inhibitor) and ipilimumab (a CTLA-4 inhibitor) showed promising results in a phase II trial involving patients with metastatic sarcoma (not limited to STS)⁴⁴.

Between 1% and 5% percent of patients with STS have high microsatellite instability, which usually predicts response to immune checkpoint inhibitors targeting PD-1 or PD-L1⁴⁵. Although not tested specifically in patients with STS, immune checkpoint inhibitors might reasonably be considered for patients with high microsatellite instability who progress on standard treatment.

New York Esophageal Squamous Cell Carcinoma 1

New York esophageal squamous cell carcinoma 1 (NY-ESO-1) is a marker on both T cells and B cells that can be targeted by CMB305, an active immunotherapy regimen that uses dendritic cell–targeting lentiviral vectors. A phase IB study that enrolled 25 patients with treatment-refractory STS demonstrated interesting response rates, with favourable progression-free and overall survival outcomes⁴⁶.

Adoptive T Cell Transfer

Adoptive transfer of T cells engineered to express NY-ESO-1 was studied as part of an ongoing phase IB trial in patients with synovial STS, demonstrating, in 50% of patients (6 of 12), antitumour responses that were characterized by tumour shrinkage over several months. In the study, correlative science demonstrated that self-regenerating pools of CD8+ NY-ESO-1 T cells produce a continuing supply of effector cells for several months⁴⁷. Two other studies examining similar treatment are currently underway (see NCT01477021 and NCT01477021 at <https://ClinicalTrials.gov/>). Other targets for adoptive cell therapy such as MAGE-A3, MAGE-A4, and MAGE-A10 are also emerging and will be studied in clinical trials in the near future⁴⁸.

Chimeric Antigen Receptor T Cell Therapy

Chimeric antigen receptors (CARs) provide another way of invigorating the immune system to kill cancer cells. In this technique, T cells are modified and equipped with CARs that redirect the antigen specificity of immune effector cells. Treatments can have important clinical activity, but sometimes cause severe adverse events by way of a cytokine storm. Use of this technique is currently being studied for many solid tumours, including a GD-2–targeting CAR in ganglioside-positive sarcomas (NCT02107963, NCT01953900)⁴⁸.

Vaccine-Based Therapies

Vaccine-based therapies have been used as another method of stimulating the anticancer immune response. As mentioned earlier, the potential for using NY-ESO-1 as a vaccine-based therapy is a promising emerging option. Another vaccine trial (of SYT–SSX breakpoint peptide vaccine) that enrolled 21 patients with synovial STS demonstrated encouraging results⁴⁹.

Targeted Therapies

Approximately one third of patients with STS have specific genetic alterations, and it is therefore important to consider targeted therapy as a potential therapeutic avenue. A large study of 584 patients that sought to characterize genomic alterations in adult patients with STS was recently published. The authors found a median of 4 genomic alterations per patient. At least 1 targetable genomic alteration was found in 239 patients (41%)⁵⁰. Another large study of 5635 patients examined the role of NGS in STS, finding meaningful clinical impacts. For example, nearly 10% of patients were found to have mutations suspicious for germline defects (including *BRCA*). In 16% of patients, treatment-linked alterations were found that are known to respond to a drug approved by the U.S. Food and Drug Administration, and in 7%, alterations were found that could make the patient eligible for a clinical drug trial. Of the patients in the study, 30% were enrolled to a clinical study, and partial and complete responses were seen in patients with alterations in *NTRK*, *IDH1*, *BRAF*, *PI3K*/mTOR, and *MDM2*, among others. Furthermore, use of NGS altered the initial pathology diagnosis in 5% of patients enrolled to the study. In another study involving 20 patients with liposarcoma for whom NGS was used, 11 subsequently received *MDM2* or *CDK4* inhibition as part of a phase I clinical trial⁵¹. Meaningful clinical activity was observed in 7 patients who experienced stable disease. Although the possibilities are exciting, the incidence of actionable mutations leading to outcome-altering treatment is unknown, and given the cost of the technique, widespread use of NGS cannot be recommended at this time.

SUMMARY AND FUTURE DIRECTIONS

A significant proportion of patients with STS present with, or develop, metastatic disease. Given the poor outcomes in STS, novel therapeutic avenues have to be developed. Many clinical trials are actively recruiting patients with advanced STS (Table 1). Promising options include the use of sorafenib in desmoid tumours, pexidartinib or emactuzumab in TGCT, tazemetostat in *Ini1*-deficient sarcomas, and larotrectinib in *TRK* fusion–positive sarcomas. Immunotherapy is also proving to be an emerging and promising avenue for patients with advanced STS. Next-generation sequencing might provide insights for personalized therapy. Altogether, novel therapies in STS are proving to be an exciting and active area of cancer research, and more data are eagerly awaited.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: TA

TABLE I Clinical trials that are actively recruiting patients with advanced soft-tissue sarcoma (STS)

ClinicalTrials.gov ID	Patients		Intervention	Primary outcome	Trial status	Location
	Population	(n)				
Targeted therapy						
NCT03104335	Advanced STS, previously treated; rhabdomyosarcoma and liposarcoma excluded	100	Apatinib	ORR	Recruiting	Peking University International Hospital, P.R.C.
NCT03526679	Advanced STS, previously treated; leiomyosarcoma, liposarcoma	30	Lenvatinib and eribulin	ORR	Recruiting	National Taiwan University Hospital, Taiwan
NCT02357810	Advanced STS, previously treated; liposarcoma excluded	136	Pazopanib hydrochloride and topotecan hydrochloride	Progression-free rate	Recruiting	Northwestern University, IL, U.S.A.
NCT02601950	Synovial sarcoma, previously treated	250	Tazemetostat	PFS, ORR	Recruiting	Multicentre, U.S.A.
Immunotherapy						
NCT04052334	Advanced STS, previously treated	5	Lymphodepletion plus adoptive cell therapy with high-dose IL-2	Safety	Recruiting	H. Lee Moffitt Cancer Center and Research Institute, FL, U.S.A.
NCT03056001	Advanced STS, previously untreated	30	Pembrolizumab and doxorubicin	Safety	Recruiting	Multicentre
NCT02496520	Metastatic or relapsed sarcoma	10	Dendritic cell–based immunotherapy	Safety	Recruiting	Clinica Universidad de Navarra, Universidad de Navarra, Spain
NCT04095208	Advanced STS, previously treated	67	Nivolumab and relatlimab	Progression-free rate	Recruiting	Institut Bergonié, France
NCT03317457	Advanced STS, previously untreated	100	Durvalumab and tremelimumab	OS	Recruiting	Multicentre
NCT03590210	Advanced STS, previously treated	74		PFS, safety	Recruiting	University Medicine Greifswald, Germany

ORR = objective response rate; PFS = progression-free survival; OS = overall survival.

has received fees as an advisory board member for Merck, Eisai, Pfizer, Novartis, and Taiho; TA's institution receives funding from Karyopharm, SpringWorks, Lilly, Deciphera for trials in which he is a co-investigator. AE has no conflicts to disclose.

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