

Recent Advances in the Treatment of Metastatic Soft Tissue Sarcoma

Authors:	*Elizabeth J. Davis, Vicki L. Keedy Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA *Correspondence to Elizabeth.j.davis@vumc.org
Disclosure:	The authors have declared no conflicts of interest.
Received:	28.08.18
Accepted:	02.10.18
Keywords:	Eribulin, ipilimumab, nivolumab, olaratumab, pembrolizumab, soft tissue sarcoma (STS), trabectedin.
Citation:	EMJ Oncol. 2018;6[1]:91-101.

Abstract

Soft tissue sarcomas (STS) are a rare group of heterogeneous malignancies with >50 histologic subtypes that have varying biological behaviour and responsiveness to systemic therapy. The mainstay of therapy for metastatic STS in recent decades has been doxorubicin. To improve survival outcomes, numerous agents have been combined with doxorubicin; however, no combination has led to a survival benefit over doxorubicin alone until the recent use of olaratumab, a monoclonal antibody targeting platelet-derived growth factor- α . In addition to olaratumab, several other new drugs have surfaced as promising treatment options. Marine-derived chemotherapy agents, eribulin and trabectedin, are active in selecting STS subtypes. Both agents are effective in liposarcoma, while trabectedin also has activity in leiomyosarcoma. Further understanding of the importance of STS subtype-directed therapy, as well as the genomic complexities of STS, has led to development of several small molecule inhibitors for specific STS histologies. Agents targeting vascular endothelial growth factors, platelet-derived growth factors, and cyclin-dependent kinases 4 and 6 have all shown some efficacy in various STS subtypes. Similar to the selective activity of cytotoxic agents and small molecule inhibitors, immunotherapy, which has revolutionised management of numerous cancers, has also demonstrated activity in select STS subtypes. Collectively, these novel therapies highlight the importance of histology-directed approaches and of a greater understanding of the genomic landscape of STS. This review describes advances in chemotherapy, molecularly targeted, and immunotherapy agents for STS.

INTRODUCTION

Soft tissue sarcomas (STS) are a rare group of heterogeneous malignancies with >50 histologic subtypes that have varying biological behaviour and responsiveness to systemic therapy. Doxorubicin has been the mainstay of treatment in numerous subtypes of metastatic STS for decades, achieving response rates

(RR) of 12–29% and average life expectancies of 12–18 months (Table 1).^{1–7} Until recently, numerous agents have been combined with doxorubicin with limited benefit. Olaratumab, a fully human IgG1 monoclonal antibody that targets platelet-derived growth factor receptor (PDGFR)- α , combined with doxorubicin resulted in a near doubling of overall survival (OS) compared with doxorubicin alone.⁴ Aside

from doxorubicin-based regimens, novel chemotherapy agents, eribulin and trabectedin, have demonstrated efficacy in the L-sarcomas, liposarcoma (LPS), and leiomyosarcoma (LMS), highlighting the role of histology-directed therapy for these malignancies.

Further understanding of the importance of subtype-directed therapy and the genomic complexities of STS has led to the development of small molecule inhibitors for certain STS histologies (Table 2).⁸⁻¹³ Tyrosine kinase inhibitors (TKI) (imatinib, sunitinib, and regorafenib) have dramatically changed the treatment landscape and outcomes for gastrointestinal stromal tumour (GIST), one of the most common STS subtypes.¹⁴⁻¹⁶ Imatinib, cediranib, and pexidartinib have also demonstrated activity in some of the rarest, chemo-refractory STS subtypes, including dermatofibrosarcoma protuberans,^{17,18} alveolar soft part sarcoma (ASPS),¹⁹ and tenosynovial giant cell tumour.^{20,21} The increased efficacy of these agents is due to the complex STS genomic landscape, including alterations to KIT, PDGFR- β , vascular endothelial growth factor receptors (VEGFR), and colony stimulating factor-1. Other more common STS also demonstrate potentially targetable aberrations in VEGFR, PDGFR- α and β , and cyclin-dependent kinases (CDK), suggesting a need for study of additional targeted therapies.

Similar to the selective activity of cytotoxic agents and small molecule inhibitors, immunotherapy, which has revolutionised the management of numerous cancers, has also demonstrated activity in select STS subtypes. Immunotherapy trials have shown activity in undifferentiated pleomorphic sarcoma (UPS) and LPS (Table 3).²²⁻²⁵ Factors such as tumour microenvironment, tumour mutational burden, and the transcriptome have been associated with response to immunotherapy; however, the data for these factors in STS are limited.^{26,27} Correlative work to understand the relevant factors for predicting response in STS is ongoing. Numerous studies, including combinations of immunotherapy agents or immunotherapy combined with radiotherapy and/or chemotherapy, are also in progress.

As in other cancers, the understanding of the genomic complexity of STS has expanded over the past decade and spurred development of novel agents. The treatment paradigm for STS has shifted from treating all subtypes similarly towards a more histology-directed approach. In this review, the authors summarise recent developments in the treatment of non-GIST STS, as well as ongoing studies within the realms of chemotherapy, targeted therapies, and immunotherapy.

Table 1: Chemotherapy studies in advanced soft tissue sarcoma.

Study	Number of participants	Histology	Regimen	RR (%)	Median PFS (months)	Median OS (months)
Judson et al., ¹ 2014	228 227	STS	Doxorubicin 75.0 mg/m ² Doxorubicin 75.0 mg/m ² , ifosfamide 10.0 g/m ²	*14.0 *26.0	*4.6 *7.4	12.8 14.3
Tap et al., ² 2017	323 317	STS	Doxorubicin 75.0 mg/m ² Doxorubicin/evofosfamide 75.0/300.0 mg/m ²	*18.0 28.0	6.0 6.3	19.0 18.4
Ryan et al., ³ 2016	221 226	STS	Doxorubicin 75.0 mg/m ² Doxorubicin/palifosfamide 75.0/450.0 mg/m ²	*19.0 *27.0	5.2 6.0	16.9 15.9
Tap et al., ⁴ 2016	67 66	STS	Doxorubicin 75.0 mg/m ² Doxorubicin 75.0 mg/m ² , olaratumab 15.0 mg/kg	11.9 18.2	4.1 6.6	*14.7 *26.5
Demetri et al., ⁵ 2016	345 173	LPS/LMS	Trabectedin 1.5 mg/m ² Dacarbazine 1,000.0 mg/m ²	9.9 6.9	*4.2 *1.5	12.4 12.9
Schöffski et al., ⁶ 2016	228 224	LPS/LMS	Eribulin 1.4 mg/m ² Dacarbazine 850.0-1,200.0 mg/m ²	4.0 5.0	2.6 2.6	*13.5 *11.5
Demetri et al., ⁷ 2017	71 72	LPS	Eribulin 1.4 mg/m ² Dacarbazine 850.0-1,200.0 mg/m ²	1.0 0.0	*2.9 *1.7	*15.6 *8.4

*Statistically significant.

LMS: leiomyosarcoma; LPS: liposarcoma; OS: overall survival; PFS: progression-free survival; RR: response rate; STS: soft tissue sarcoma.

Table 2: Targeted agents in soft tissue sarcoma.

Study	Number of participants	Histology	Regimen	RR (%)	Median PFS (months)	Median OS (months)
van der Graaf et al., ⁸ 2012	246 123	STS (non-LPS)	Pazopanib 800 mg daily Placebo	6.0 0.0	*4.6 *1.6	12.5 10.7
Chi et al., ⁹ 2018	166	STS	Anlotinib 12 mg daily on Day 1-14 of a 21-day cycle	13.0	5.6	12.0
Mir et al., ¹⁰ 2016	28 28 20 23 13 14 27 27	LPS LMS SS Other	Regorafenib 160 mg Placebo Regorafenib 160 mg Placebo Regorafenib 160 mg Placebo Regorafenib 160 mg Placebo	0.0 0.0 0.0 4.0 8.0 0.0 11.0 0.0	1.1 1.7 *3.7 *1.8 *5.6 *1.0 *2.9 *1.0	4.7 8.8 21.0 9.1 13.4 6.7 12.1 9.5
Dickson et al., ¹¹ 2013	30	DDLPS/WDLPS	Palbociclib 200 mg daily on Day 1-14 of a 21-day cycle	3.0	4.5	NR
Dickson et al., ¹² 2016	60	DDLPS/WDLPS	Palbociclib 125 mg daily on Day 1-21 of a 28-day cycle	1.7	4.5	NR
Gounder et al., ¹³ 2018	26 30	DDLPS	Selinexor 60 mg twice a week Placebo	0.0 0.0	5.5 2.7	NR NR

*Statistically significant.

DDLPS: dedifferentiated liposarcoma; LMS: leiomyosarcoma; LPS: liposarcoma; NR: not reported; OS: overall survival; PFS: progression-free survival; RR: response rate; SS: synovial sarcoma; STS: soft tissue sarcoma; WDLPS: well-differentiated liposarcoma.

NOVEL CHEMOTHERAPY AGENTS AND COMBINATIONS

Doxorubicin has been the backbone of treatment for advanced STS for >40 years. The addition of ifosfamide (and its analogues evofosfamide and palifosfamide) and dacarbazine has resulted in improved RR but lacked a significant survival benefit and with increased toxicities.^{1,3,28-30} Olaratumab, a monoclonal antibody that targets PDGFR- α , was the first agent to be combined with doxorubicin and demonstrated an OS benefit in patients with metastatic STS. Olaratumab targets PDGFR- α by blocking the binding of PDGF ligands and preventing receptor activation. PDGFR- α is overexpressed in some STS subtypes^{31,32} and preclinical work in LMS cell lines has demonstrated antitumour efficacy,³³ providing rationale for investigation in STS patients. A Phase I/II study⁴ enrolled varied STS subtype patients and randomised them 1:1 to doxorubicin with olaratumab versus doxorubicin alone. The progression-free survival (PFS) was 4.1 months and 6.6 months in the monotherapy and combination arms, respectively ($p=0.0615$), and

the OS nearly doubled following combination therapy (26.5 months compared with 14.7 months with doxorubicin alone [$p=0.0003$]). The reason for the survival improvement with olaratumab remains unclear and preliminary analysis of the PDGFR- α expression status suggested no association with outcomes. Further investigation of the mechanism of action of olaratumab is needed to understand how the drug alters the tumour microenvironment and potentially improves the efficacy of doxorubicin. Olaratumab-doxorubicin combination therapy increased rates of neutropenia (58% versus 35%), mucositis (53% versus 35%), nausea (73% versus 52%), vomiting (45% versus 18%), and diarrhoea (34% versus 23%) compared with doxorubicin alone. However, despite increased neutropenia, there was no difference in the rates of febrile neutropenia or infection between the study arms. Infusion reactions, including two Grade 4 events, occurred in 13% of patients treated with combination therapy, but no cases were reported in those treated with doxorubicin alone.⁴ This study led to conditional approval of olaratumab in 2016 by the European Medicines Agency (EMA) and accelerated approval by the U.S. Food and Drug Administration (FDA) for the

treatment of patients with STS not amenable to curative treatment with radiotherapy or surgery and with a histologic subtype for which an anthracycline-containing regimen is appropriate.

Data from the ANNOUNCE study,³⁴ a Phase III trial comparing outcomes of STS patients treated with doxorubicin and olaratumab or doxorubicin alone, are expected in late 2019, and the results will determine whether the survival benefit withstands in a larger population. The results may also identify subtypes that have the greatest benefit and the mechanism of this survival benefit. Other ongoing studies are investigating neoadjuvant olaratumab as well as combinations with other sarcoma chemotherapy (gemcitabine-docetaxel,³⁵ doxorubicin-ifosfamide,³⁶ and doxorubicin-trabectedin³⁷) and immunotherapy (pembrolizumab)³⁸ agents, which may identify additional roles for olaratumab in STS. Trabectedin is a synthetically derived tetrahydroisoquinoline alkaloid originally isolated from the marine ascidian *Ecteinascidia turbinata*. Trabectedin binds to the minor groove of DNA, resulting in a conformational change of the DNA, bending towards the major

groove and altering transcription regulation.³⁹ The first Phase II studies of trabectedin in patients with advanced STS demonstrated a RR of 4-17%, median PFS of 1.9 months, and median OS of 9.2-12.8 months.⁴⁰⁻⁴³ Given the paucity of treatment options for STS and the clinical activity and tolerability, the drug received approval by the EMA in 2007 for the treatment of patients with advanced STS after failure of anthracyclines and ifosfamide or for those who were unfit to receive these agents.

In these initial Phase II studies, patients with L-sarcomas, particularly LMS and myxoid round cell LPS, showed the greatest benefit.⁴⁰⁻⁴⁴ Therefore, a multicentre Phase III trial⁴⁵ compared trabectedin 1.5 mg/m² every 3 weeks to dacarbazine 1,000 mg/m² every 3 weeks in L-sarcoma patients after prior anthracycline treatment and at least one additional regimen. The median PFS was improved, measuring 4.2 months versus 1.5 months (p<0.001) with trabectedin and dacarbazine, respectively. In addition, the median PFS improvement was greatest in the myxoid round cell LPS group, totalling 5.6 months versus 1.5 months with trabectedin and dacarbazine, respectively.

Table 3: Immunotherapy studies in sarcoma.

Study	Number of participants	Histology	Regimen	RR (%)	Median PFS (months)	Median OS (months)
Tawbi et al., ²² 2017	80	STS/bone	Pembrolizumab (200 mg q3wk)	18 (UPS, LPS) 5 (CS, OST)	4.1 1.9	11.4 12.0
Ben-Ami et al., ²³ 2017	12	LMS/uterine	Nivolumab (3 mg/kg q2wk)	0	1.8	NR
D'Angelo et al., ²⁴ 2018	85	STS/bone	Nivolumab (3 mg/kg q2wk) Ipilimumab/nivolumab (1 mg/kg/3 mg/kg q3wk for 4 cycles, nivolumab q2wk for 2 years)	5 (ASPS, LMS) 16 (LMS, MFS, UPS, AS)	1.7 4.1	10.7 14.3
Toulmonde et al., ²⁵ 2018	57	LMS UPS Other GIST	Cyclophosphamide (50 mg bid qow) and pembrolizumab (200 mg q3wk)	0 0 7 (SFT) 0	1.4 1.4 1.4 1.4	9.2 5.6 7.1 NYR

AS: angiosarcoma; ASPS: alveolar soft part sarcoma; bid: twice daily; CS: chondrosarcoma; GIST: gastrointestinal stromal tumour; LMS: leiomyosarcoma; LPS: liposarcoma; MFS: myxofibrosarcoma; NR: not reported; NYR: not yet reached; OS: overall survival; OST: osteosarcoma; PFS: progression-free survival; q: every; qow: every other week; RR: response rate; SFT: solitary fibrous tumour; STS: soft tissue sarcoma; UPS: undifferentiated pleomorphic sarcoma; wk: week.

There was no difference in RR or OS. Trabectedin was also well tolerated, with the most common serious adverse events (AE) being myelosuppression and transient liver function test elevation.⁵ This study led to FDA approval for trabectedin in 2015 for the treatment of patients with unresectable or metastatic LPS or LMS who had received a prior anthracycline-containing regimen. Trabectedin became the third FDA-approved drug for STS treatment after doxorubicin (1974) and pazopanib (2012).⁴⁵ The approval of trabectedin, based on improvement in PFS, demonstrates the acceptance of disease stability as a meaningful endpoint in metastatic STS and highlights that disease response by Response Evaluation Criteria in Solid Tumors (RECIST) is uncommon in STS, underscoring the need for novel systemic therapies.

Eribulin mesylate is a synthetically derived analogue of halichondrin B, which was originally derived from a marine sponge. It is a non-taxane microtubule inhibitor that prevents mitotic spindle formation, inducing cell cycle arrest.⁴⁶ Eribulin was initially FDA-approved to treat advanced or metastatic breast cancer. Similar to trabectedin, a Phase II study⁴⁷ of eribulin in multiple STS subtypes demonstrated activity solely in the L-sarcomas. The proportion of LMS and LPS patients who were progression-free at 12 weeks was 31.6% and 46.9%, respectively, which compared favourably to historical controls.⁴⁷ Due to the activity in L-sarcomas, a Phase III study⁶ compared the efficacy of eribulin 1.4 mg/m² on Days 1 and 8 of a 21-day cycle with dacarbazine 850–1,200 mg/m² every 3 weeks only in these patients. The OS was improved, totalling 13.5 months versus 11.5 months with eribulin and dacarbazine, respectively (p=0.0169), and there was no difference in PFS or RR.⁶ In a preplanned subgroup analysis, the primary benefit of eribulin was in LPS, with improved OS (15.6 months versus 8.4 months, respectively [p<0.001]) and PFS (2.7 months versus 1.9 months, respectively [p=0.0015]) in the eribulin group compared to the dacarbazine group. Notably, there was no difference in RR.⁷ In both cohorts, eribulin was associated with a greater incidence of AE Grade ≥3 (67%) than dacarbazine (56%). Most severe AE were haematologic; however, the incidence of neutropenic fever was low.⁶ Collectively, these

data led to the approval of eribulin by the EMA and FDA in 2016 for patients with unresectable or metastatic LPS after a prior anthracycline-based regimen, but not for patients with LMS. This agent provides a reasonable second-line option for treating advanced LPS because it demonstrated a 2-month survival benefit and was reasonably well tolerated.

TARGETED AGENTS

Over the past two decades, molecularly targeted agents have emerged as effective anti-cancer therapies. The success of imatinib and trastuzumab in revolutionising the treatment of chronic myelogenous leukaemia and HER-2-positive breast cancer, respectively, sparked greater analysis of cancer genomics and evaluations of how genetic abnormalities could be used in developing novel anticancer strategies. STS demonstrate overexpression and/or mutations of numerous potential therapeutic targets. For example, overexpression of VEGF has been associated with higher-grade tumours and worse outcomes in sarcoma patients, and targeting VEGF has been explored as a potential therapeutic strategy with reasonable efficacy.⁴⁸⁻⁵⁰ Increased expression of CDK4, CDK6, and PDGF, as well as mutations in PDGFR- α and β , have also been described in STS. These molecular abnormalities have provided justification for several studies, which are described in greater detail later in this review.^{4,8,32,51}

Pazopanib is an oral, synthetically derived indazole pyrimidine that inhibits VEGFR 1–3, PDGFR- α and β , and c-kit.⁵² VEGF and PDGF are factors in STS angiogenesis, providing a rationale to study pazopanib as a treatment option. An initial Phase II study evaluated daily 800 mg pazopanib in 142 advanced STS patients in a Simon two-stage design.⁵³ Patients were stratified into four cohorts: adipocytic sarcoma, LMS, synovial sarcoma (SS), and other sarcomas. The adipocytic cohort closed after the first stage, but the other three cohorts completely accrued. The PFR at 12 weeks for the LMS, SS, and other sarcomas was 44%, 49%, and 39%, respectively. PFS and OS compared favourably to historical controls; in the LMS, SS, and other sarcomas, the median PFS and OS were 91 and 354, 161 and 310, and 91 and 299 days, respectively.⁵³ These data provided the basis for the

Phase III study of pazopanib in patients with advanced STS except the adipocytic subtypes.⁸ Patients were randomised 2:1 to receive either daily 800 mg pazopanib or a placebo. The median PFS was improved with pazopanib, recorded as 4.6 months versus 1.6 months with placebo ($p < 0.0001$). However, the OS was not significantly different with pazopanib and placebo (12.5 months versus 10.7 months, respectively [$p = 0.25$]) and the RR were 6% with pazopanib and 0% in the placebo group. The most common severe AE were fatigue (13%), hypertension (7%), anorexia (6%), and diarrhoea (5%).⁵⁴ Overall quality of life was not significantly worsened by pazopanib.⁵⁴ This study led to the approval of pazopanib in 2012 by the EMA and the FDA for patients with advanced STS, except adipocytic sarcomas, who have received previous chemotherapy. This approval again demonstrates the value of stable disease in the treatment of metastatic STS.

Anlotinib is an oral multikinase inhibitor that targets VEGFR 2 and 3, fibroblastic growth factor receptor 1–4, PDGFR- α and β , c-kit, Ret, Aurora-B, c-FMS, and discoidin domain receptor 1.⁵⁵ An initial Phase II study of this agent included 166 sarcoma patients who received a daily 12 mg anlotinib dose in a 2-week-on and 1-week-off regimen.⁵ The ORR was 13%. Responses were seen in 8% (2/26) of LMS, 11% (2/18) of fibrosarcoma (FS), 17% (8/47) of SS, 46% (6/13) of ASPS, and 14% (1/7) of clear cell sarcoma patients. The overall median PFS and OS were 5.6 months and 12.0 months, respectively.⁹ A Phase III study of this agent randomised 233 patients with SS, LMS, and ASPS to either anlotinib ($n = 158$) or placebo ($n = 75$). The median PFS was 6.3 months for anlotinib versus 1.5 months for placebo (hazard ratio: 0.33; $p < 0.0001$). The PFS improvement was greatest in the ASPS cohort, recorded as 18.2 months versus 3.0 months (hazard ratio: 0.14; $p < 0.0001$) with anlotinib and placebo, respectively. The ORR was 10.1% for anlotinib versus 1.3% for placebo ($p = 0.0145$). The most common Grade ≥ 3 AE were hypertension (19%), gamma glutamyl transferase elevation (4.4%), triglyceride elevation (4.4%), low-density lipoprotein elevation (3.2%), hyponatraemia (3.2%), and neutrophil count reduction (3.2%).⁵⁶ Overall, anlotinib is well tolerated and its use is promising in multiple STS subtypes. It is currently

being evaluated in a Phase III study versus dacarbazine in LMS, SS, and ASPS patients.⁵⁷

Regorafenib is an oral TKI that targets VEGFR 1–3, PDGFR, KIT, RET, and Raf, and is EMA and FDA-approved to treat GIST, colorectal cancer, and hepatocellular cancer. REGOSARC¹⁰ was a double-blind, placebo-controlled Phase II study of four cohorts of STS: LPS, LMS, SS, and other sarcomas. Patients were randomly assigned to receive 160 mg daily regorafenib on Days 1–21 of a 28-day cycle or placebo. There were no significant differences in RR or OS; however, the median PFS was significantly improved in all cohorts except for LPS. The most common Grade 3/4 AE included asthenia (13%), hand and foot skin reaction (15%), hypertension (19%), and hypophosphataemia (13%). There was one Grade 5 hepatitis-induced liver failure that was related to regorafenib.¹⁰ This study demonstrates the activity of regorafenib in non-adipocytic STS, and further investigation in a Phase III study against an active agent is warranted.

The TKI described thus far have limited or no activity in adipocytic sarcomas, suggesting that alternative targets are needed. Palbociclib is an oral inhibitor of CDK4 and CDK6 that prevents phosphorylation of the retinoblastoma protein and can result in tumour stasis or regression.⁵⁸ CDK4 is overexpressed in two subtypes of adipocytic sarcoma, well-differentiated LPS (WDLPS) and dedifferentiated LPS (DDLPS), as compared to normal fat cells.⁵⁹ Preclinical work demonstrated the antitumour activity of palbociclib in WDLPS/DDLPS cell lines and in xenografts.⁶⁰ Two Phase II studies^{11,12} confirmed antitumour activity of palbociclib in 90 patients with WDLPS/DDLPS. The studies evaluated different dosing regimens, either 200 mg daily on Days 1–14 of a 21-day cycle (high dose) or 125 mg daily on Days 1–21 of a 28-day cycle (low dose). The primary endpoint was met in both studies, achieving a PFS at 12 weeks of 66% in the high-dose and 57% in the low-dose group. The median PFS was 18 weeks in both studies and the low dose was slightly better tolerated. Grade 3/4 AE were primarily haematologic: anaemia (17% versus 22%), thrombocytopenia (30% versus 7%), neutropenia (50% versus 36%), and febrile neutropenia (3% versus 0%) with the high and low doses, respectively.^{11,12} Correlative work from paired tumour biopsies demonstrated that benefit from palbociclib treatment was

associated with downregulation of MDM2,⁶¹ suggesting a potential biomarker that could be used to predict response to CDK4 inhibition.

Another potential novel treatment approach for DDLPS is selinexor, an oral selective inhibitor of nuclear export that binds to the nuclear export protein XPO1. This causes tumour suppressor proteins to accumulate in the nucleus, resulting in selective destruction of cancer cells while sparing the healthy cells. A Phase II study evaluated selinexor 60 mg twice a week in 56 patients with advanced DDLPS. The primary endpoint was PFS and selinexor demonstrated a trend towards improved PFS over placebo (5.5 months versus 2.7 months; $p=0.26$). Treatment was well tolerated, with the most common Grade 3/4 AE being hyponatraemia (19.2%), anaemia (19.2%), thrombocytopenia (11.5%), neutropenia (7.7%), and hyperglycaemia (7.7%).¹³ The Phase III portion of the study is still ongoing and is comparing selinexor to placebo in patients with advanced DDLPS.⁶²

IMMUNOTHERAPY

Immunotherapy was first described as a potential anticancer strategy in the 19th century in sarcoma patients. Streptococcal antigens (Coley's toxins) were injected into sarcomas and resulted in tumour shrinkage.⁶³ However, there was doubt about these findings, and investigation of chemotherapy and radiation took precedence over further investigation of immunotherapeutic options. More recently, immunotherapy agents targeting T cell checkpoint molecules, such as cytotoxic T lymphocyte-associated protein 4 and programmed death receptor (PD-1) and its ligand (PD-L1), have revolutionised the treatment of numerous malignancies.⁶⁴⁻⁶⁸ However, the success of immunotherapy agents in sarcoma in the modern era has been limited (Table 3).

One of the initial investigations of immunotherapy in sarcoma was SARCO28,²² a two-cohort, single-arm, open-label Phase II study of pembrolizumab, an anti-PD-1 monoclonal antibody, administered intravenously (IV) every 3 weeks at a dose of 200 mg. Forty patients were enrolled into each of the bone and soft tissue cohorts. The STS cohort was split into 10 patients with each of the following histologies: UPS, LPS, LMS, or SS. RR were

highest in the UPS and LPS cohorts, measuring 40% and 20%, respectively. No responses were seen in LMS patients. In the bone cohort, the RR were 5% (1 out of 22) in osteosarcoma, 20% (1 out of 5) in chondrosarcoma, and 0% (0 out of 13) in Ewing's sarcoma. The median PFS and OS were 18 and 49 weeks in the STS cohort, and 8 and 52 weeks in the bone cohort, respectively. Treatment was well tolerated, with treatment-related serious AE occurring in 11% of patients. AE included pneumonitis (4%), adrenal insufficiency (4%), pulmonary embolism (2%), interstitial nephritis (2%), infectious pneumonia (2%), bone pain (2%), hypoxia (2%), and pleural effusion (2%). There were no Grade 5 AE. The study concluded that pembrolizumab was promising in UPS and LPS and recently completed enrolment of additional patients into these cohorts. Select results from correlative work were included in the initial analysis. PD-L1 expression was identified in 5% (2 out of 40) of the STS samples, both cases were from UPS patients who had responded to therapy. However, responses were also noted in non-PD-L1-expressing LPS patients, suggesting that predicting response to anti-PD-1 therapy is based on more than PD-L1 expression.²² Additional correlative work from this study is pending and will offer further insight into the role of immunotherapy in sarcoma.

A smaller study²³ evaluated nivolumab, an anti-PD-1 monoclonal antibody, 3 mg/kg IV every 2 weeks in patients with metastatic uterine LMS. Twelve patients were enrolled and no responses were seen, suggesting a lack of benefit and precluding further enrolment. The median PFS was 1.8 months and a median OS was not reached. Treatment-related serious AE occurred in 25% of patients, with solitary cases of abdominal pain, elevated amylase and lipase, and fatigue. Correlative work demonstrated PD-1 and PD-L1 expression in 20% of samples, but no correlation with outcomes was observed.²³ In combination with the findings from SARCO28, this study further demonstrates the lack of efficacy of anti-PD-1 monotherapy in LMS. LMS resistance may be due to the density of tumour-associated macrophages, PTEN mutations, and reduced expression of genes encoding neoantigens.^{69,70} However, recent translational work suggests that LMS is an inflamed tumour type with high levels of T cell-related gene expression

and occasional strong expression of PD-L1, indicating that immunotherapy may be effective but that a combination strategy may be a better approach.⁷¹

Combining immunotherapy agents, such as ipilimumab, an anti-cytotoxic T lymphocyte-associated protein 4 monoclonal antibody, and nivolumab, is an effective strategy in melanoma and renal cell carcinoma.^{72,73} As a result of the potential synergy of these agents, a Phase II study evaluated two treatment strategies: nivolumab with or without ipilimumab in sarcoma. Treatment included 3 mg/kg IV nivolumab every 2 weeks or 1 mg/kg IV ipilimumab with 3 mg/kg nivolumab every 3 weeks for four doses, followed by 3 mg/kg nivolumab every 2 weeks for up to 2 years. The study was not designed to compare results between treatment arms. The RR was 5% with nivolumab and 16% with combination therapy. In the monotherapy arm, responses were seen in ASPS and non-uterine LMS, while, in the combination treatment arm, responses were seen in LMS (n=2), UPS (n=2), myxofibrosarcoma, and angiosarcoma. The median PFS and OS were 1.7 and 10.7 months and 4.1 and 14.3 months with monotherapy and combination therapy, respectively. Given that the monotherapy did not reach its target RR, nivolumab alone is considered inactive; however, the combination has activity similar to other approved sarcoma therapies and is being further investigated in UPS and LPS. Treatment-related serious AE occurred more frequently with combination therapy (26% versus 19%) than in the monotherapy arm. AE included adrenal insufficiency, elevated alanine and aspartate aminotransferase, hyponatraemia, anaemia, fatigue, pain, and pruritus with dual agent therapy, and anaemia, thrombocytopenia, anorexia, dehydration, diarrhoea, fever, elevated creatinine, and pleural effusion in the monotherapy cohort. Correlative work, including PD-L1 expression, tumour-infiltrating lymphocytes, mutational burden, neoantigen analysis, and T cell receptor clonality, is in progress.²⁴ Results of these studies will help determine factors that predict response or suggest a role for further study of combination immunotherapy in sarcoma.

Adding chemotherapy, targeted therapy, or radiation therapy to immunotherapy to augment efficacy is an area of active investigation.

Combining axitinib, a pan-VEGFR inhibitor, with pembrolizumab has showed promise in treating ASPS. The 3-month PFS rate was 90.9% (95% confidence interval: 50.8–98.7) and ORR was 45.5% (95% confidence interval: 18.1–75.4). Correlative studies found high plasma angiogenic activity, a circulating neutrophil:lymphocyte ratio <4.1, low naïve fraction CD4+ tumour-infiltrating lymphocytes, and low PD1+CD8+ peripheral blood mononuclear cell were associated with lack of progression. Overall, this combination was well tolerated and demonstrated activity in ASPS, warranting further study.⁷⁴

Given the potential immunomodulatory effects of metronomic cyclophosphamide and its activity in STS treatment, the French Sarcoma Group combined oral cyclophosphamide 50 mg twice daily every other week with 200 mg pembrolizumab IV every 3 weeks in four cohorts: LMS (n=15), UPS (n=16), GIST (n=10), and other sarcomas (n=16).²⁵ There was one partial response in a patient with solitary fibrous tumour and the median PFS was equal across cohorts at 1.4 months. The OS varied and was 9.2 months, 5.6 months, 7.1 months, and not yet reached in the LMS, UPS, other, and GIST cohorts, respectively. Correlative work demonstrated PD-L1 expression in immune cells was 23%, 64%, 29%, and 43% in the LMS, UPS, other, and GIST cases, respectively.²⁵ The only patient with immune cell PD-L1 expression >10% was also the only patient who responded to therapy. Additional translational studies evaluated expression of CD8, CD68, CD163, and IDO1. However, given the lack of reference values for these markers in sarcoma, the findings were difficult to interpret. Results were compared to a dataset derived from non-small cell lung cancer patients and revealed that CD8 densities were significantly lower in sarcoma patients compared to non-small cell lung cancer patients. Also, high infiltration by CD163+ macrophages and by macrophages that expressed IDO1 was seen in sarcomas, which potentially provides a mechanism for the PD-1 resistance seen in these tumours. An increased plasma kynurenine:tryptophan ratio correlated with increased IDO1 expression, adding further support to the IDO1 pathways as a mechanism of resistance to anti-PD-1 therapy.²⁵

CONCLUSION

STS are a highly heterogeneous group of tumours with varying responses to treatment. Given their variable genomic makeup, histology-directed therapy should be regarded as the future of treatment. Currently, combined doxorubicin and olaratumab is the first-line treatment regimen for numerous STS subtypes; however, results of the Phase III study may discern subtypes that derive the greatest benefit. Trabectedin and eribulin have demonstrated efficacy in the L-sarcomas, but further investigation is needed to understand why these subtypes have the greatest success. Targeted therapies, such as pazopanib, have an established role in treating non-adipocytic

STS. Novel agents, anlotinib, palbociclib, and selinexor, have shown promise in Phase II studies; however, larger, confirmatory Phase III studies are awaited to determine whether new options for LMS, SS, ASPS, and DDLPS will become available. The role of immunotherapy in STS remains uncertain and is currently only recommended within the context of a clinical trial. Responses in UPS and LPS are encouraging; however, additional studies evaluating more patients, combination strategies, and correlative work are needed. Collectively, the results of recent studies demonstrate the ability of the sarcoma community to enrol histology-tailored trials, which will allow for the development of more subtype-specific therapies.

References

1. Judson I et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: A randomised controlled Phase 3 trial. *Lancet Oncol.* 2014;15(4):415-23.
2. Tap WD et al. Doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARCO21): An international, multicentre, open-label, randomised Phase 3 trial. *Lancet Oncol.* 2017;18(8):1089-103.
3. Ryan CW et al. PICASSO III: A Phase III, placebo-controlled study of doxorubicin with or without palifosfamide in patients with metastatic soft tissue sarcoma. *J Clin Oncol.* 2016;34(32):3898-905.
4. Tap WD et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: An open-label Phase 1b and randomised Phase 2 trial. *Lancet.* 2016;388(10043):488-97.
5. Demetri GD et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: Results of a Phase III randomized multicenter clinical trial. *J Clin Oncol.* 2016;34(8):786-93.
6. Schöffski P et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: A randomised, open-label, multicentre, Phase 3 trial. *Lancet.* 2016;387(10028):1629-37.
7. Demetri GD et al. Activity of eribulin in patients with advanced liposarcoma demonstrated in a subgroup analysis from a randomized Phase III study of eribulin versus dacarbazine. *J Clin Oncol.* 2017;35(30):3433-9.
8. van der Graaf WT et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): A randomised, double-blind, placebo-controlled Phase 3 trial. *Lancet.* 2012;379(9829):1879-86.
9. Chi Y et al. Safety and efficacy of anlotinib, a multikinase angiogenesis inhibitor, in patients with refractory metastatic soft tissue sarcoma. *Clin Cancer Res.* 2018. [Epub ahead of print].
10. Mir O et al. Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): A randomised, double-blind, placebo-controlled, Phase 2 trial. *Lancet Oncol.* 2016;17(12):1732-42.
11. Dickson MA et al. Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma. *J Clin Oncol.* 2013;31(16):2024-8.
12. Dickson MA et al. Progression-free survival among patients with well-differentiated or dedifferentiated liposarcoma treated with CDK4 inhibitor palbociclib: A Phase 2 clinical trial. *JAMA Oncol.* 2016;2(7):937-40.
13. Gounder MM et al. Phase 2 results of selinexor in advanced dedifferentiated (DDL) liposarcoma (SEAL) study: A Phase 2/3, randomized, double blind, placebo controlled cross-over study. *J Clin Oncol.* 2018;36(Suppl 15):11512.
14. Dagher R et al. Approval summary: Imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. *Clin Cancer Res.* 2002;8(10):3034-8.
15. Demetri GD et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: A randomised controlled trial. *Lancet.* 2006;368(9544):1329-38.
16. Demetri GD et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): An international, multicentre, randomised, placebo-controlled, Phase 3 trial. *Lancet.* 2013;381(9863):295-302.
17. Stacchiotti S et al. Efficacy and biological activity of imatinib in metastatic dermatofibrosarcoma protuberans (DFSP). *Clin Cancer Res.* 2016;22(4):837-46.
18. Gooskens SL et al. Imatinib mesylate for children with dermatofibrosarcoma protuberans (DFSP). *Pediatr Blood Cancer.* 2010;55(2):369-73.
19. Kummer S et al. Cediranib for metastatic alveolar soft part sarcoma. *J Clin Oncol.* 2013;31(18):2296-302.
20. Cassier PA et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. *Cancer.* 2012;118(6):1649-55.
21. Tap WD et al. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. *N Engl*

- J Med. 2015;373(5):428-37.
22. Tawbi HA et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): A multicentre, two-cohort, single-arm, open-label, Phase 2 trial. *Lancet Oncol.* 2017;18(11):1493-501.
 23. Ben-Ami E et al. Immunotherapy with single agent nivolumab for advanced leiomyosarcoma of the uterus: Results of a Phase 2 study. *Cancer.* 2017;123(17):3285-90.
 24. D'Angelo SP et al. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): Two open-label, non-comparative, randomised, Phase 2 trials. *Lancet Oncol.* 2018;19(3):416-26.
 25. Toulmonde M et al. Use of PD-1 targeting, macrophage infiltration, and IDO pathway activation in sarcomas: A Phase 2 clinical trial. *JAMA Oncol.* 2018;4(1):93-7.
 26. Johnson DB et al. Targeted next generation sequencing identifies markers of response to PD-1 blockade. *Cancer Immunol Res.* 2016;4(11):959-67.
 27. Hugo W et al. Genomic and transcriptomic features of response to anti-PD-1 therapy in metastatic melanoma. *Cell.* 2016;165(1):35-44.
 28. Weh HJ et al. Treatment results obtained in metastatic soft-tissue sarcoma with a combination of doxorubicin and dacarbazine or doxorubicin and ifosfamide. *Cancer Chemother Pharmacol.* 1993;31(Suppl 2):S189-93.
 29. Santoro A et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: A randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *J Clin Oncol.* 1995;13(7):1537-45.
 30. Antman K et al. An intergroup Phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. *J Clin Oncol.* 1993;11(7):1276-85.
 31. Shah GD et al. Rationale for the development of IMC-3G3, a fully human immunoglobulin G subclass 1 monoclonal antibody targeting the platelet-derived growth factor receptor alpha. *Cancer* 2010;116(4 Suppl): 1018-26.
 32. Movva S et al. Multi-platform profiling of over 2000 sarcomas: Identification of biomarkers and novel therapeutic targets. *Oncotarget.* 2015;6(14):12234-47.
 33. Loizos N et al. Targeting the platelet-derived growth factor receptor alpha with a neutralizing human monoclonal antibody inhibits the growth of tumor xenografts: Implications as a potential therapeutic target. *Mol Cancer Ther.* 2005;4(3):369-79.
 34. Eli Lilly and Company. A study of doxorubicin plus olaratumab (LY3012207) in participants with advanced or metastatic soft tissue sarcoma (ANNOUNCE). NCT02451943. <https://clinicaltrials.gov/ct2/show/NCT02451943>.
 35. Eli Lilly and Company. A study of olaratumab (LY3012207) in participants with advanced soft tissue sarcoma (ANNOUNCE 2). NCT02659020. <https://clinicaltrials.gov/ct2/show/NCT02659020>.
 36. Eli Lilly and Company. A study of olaratumab (LY3012207), doxorubicin, and ifosfamide in participants with advanced or metastatic soft tissue sarcoma. NCT03283696. <https://clinicaltrials.gov/ct2/show/NCT03283696>.
 37. University of Miami. Trabectedin, doxorubicin and olaratumab in patients with metastatic or recurrent leiomyosarcoma. NCT03437070. <https://clinicaltrials.gov/ct2/show/NCT03437070>.
 38. Eli Lilly and Company. A study of olaratumab (LY3012207) plus pembrolizumab in participants with advanced or metastatic soft tissue sarcoma. NCT03126591. <https://clinicaltrials.gov/ct2/show/NCT03126591>.
 39. D'Incalci M, Jimeno J. Preclinical and clinical results with the natural marine product ET-743. *Expert Opin Investig Drugs.* 2003;12(11):1843-53.
 40. Yovine A et al. Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. *J Clin Oncol.* 2004;22(5):890-9.
 41. Garcia-Carbonero R et al. Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy. *J Clin Oncol.* 2004;22(8):1480-90.
 42. Garcia-Carbonero R et al. Ecteinascidin-743 (ET-743) for chemotherapy-naive patients with advanced soft tissue sarcomas: Multicenter phase II and pharmacokinetic study. *J Clin Oncol.* 2005;23(24):5484-92.
 43. Le Cesne A et al. Phase II study of ET-743 in advanced soft tissue sarcomas: A European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial. *J Clin Oncol.* 2005;23(3):576-84.
 44. Takahashi M et al. Efficacy of trabectedin in patients with advanced translocation-related sarcomas: Pooled analysis of two Phase II studies. *Oncologist.* 2017;22(8):979-88.
 45. Barone A et al. FDA approval summary: Trabectedin for unresectable or metastatic liposarcoma or leiomyosarcoma following an anthracycline-containing regimen. *Clin Cancer Res.* 2017;23(24):7448-53.
 46. Dybdal-Hargreaves NF et al. Eribulin mesylate: Mechanism of action of a unique microtubule-targeting agent. *Clin Cancer Res.* 2015;21(11):2445-52.
 47. Schöffski P et al. Activity of eribulin mesylate in patients with soft-tissue sarcoma: A Phase 2 study in four independent histological subtypes. *Lancet Oncol.* 2011;12(11):1045-52.
 48. Yudoh K et al. Concentration of vascular endothelial growth factor in the tumour tissue as a prognostic factor of soft tissue sarcomas. *Br J Cancer.* 2001;84(12):1610-5.
 49. Chao C et al. Vascular endothelial growth factor and soft tissue sarcomas: Tumor expression correlates with grade. *Ann Surg Oncol.* 2001;8(3):260-7.
 50. Potti A et al. Determination of vascular endothelial growth factor (VEGF) overexpression in soft tissue sarcomas and the role of overexpression in leiomyosarcoma. *J Cancer Res Clin Oncol.* 2004;130(1):52-6.
 51. Heinrich MC et al. PDGFRA activating mutations in gastrointestinal stromal tumors. *Science.* 2003;299(5607):708-10.
 52. Kumar R et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. *Mol Cancer Ther.* 2007;6(7):2012-21.
 53. Sleijfer S et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: A Phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). *J Clin Oncol.* 2009;27(19):3126-32.
 54. Coens C et al. Health-related quality-of-life results from PALETTE: A randomized, double-blind, Phase 3 trial of pazopanib versus placebo in patients with soft tissue sarcoma whose disease has progressed during or after prior chemotherapy—a European Organization for research and treatment of cancer soft tissue and bone sarcoma group global network study (EORTC 62072). *Cancer.* 2015;121(17):2933-41.
 55. Sun Y et al. Safety, pharmacokinetics, and antitumor properties of anlotinib, an oral multi-target tyrosine kinase inhibitor, in patients with advanced refractory solid tumors. *J Hematol Oncol.* 2016;9(1):105.
 56. Yihebal Chi YY et al. Anlotinib for metastatic soft tissue sarcoma: A

- randomized, double-blind, placebo-controlled and multi-centered clinical trial. *J Clin Oncol.* 2018; 36(15 Suppl):11503.
57. Advenchen Laboratories, LLC. A Phase III trial of anlotinib in metastatic or advanced alveolar soft part sarcoma, leiomyosarcoma and synovial sarcoma (APROMISS). NCT03016819. <https://clinicaltrials.gov/ct2/show/NCT03016819>.
 58. Fry DW et al. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. *Mol Cancer Ther.* 2004;3(11):1427-38.
 59. Singer S et al. Gene expression profiling of liposarcoma identifies distinct biological types/subtypes and potential therapeutic targets in well-differentiated and dedifferentiated liposarcoma. *Cancer Res.* 2007;67(14):6626-36.
 60. Barretina J et al. Subtype-specific genomic alterations define new targets for soft-tissue sarcoma therapy. *Nat Genet.* 2010;42(8):715-21.
 61. Kovatcheva M et al. MDM2 turnover and expression of ATRX determine the choice between quiescence and senescence in response to CDK4 inhibition. *Oncotarget.* 2015;6(10):8226-43.
 62. Karyopharm Therapeutics Inc. Selinexor in advanced liposarcoma (SEAL). NCT02606461. <https://clinicaltrials.gov/ct2/show/NCT02606461>.
 63. Coley WB. II. Contribution to the knowledge of sarcoma. *Ann Surg.* 1891;14(3):199-220.
 64. Wolchok JD et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med.* 2013;369(2):122-33.
 65. Pembrolizumab superior to ipilimumab in melanoma. *Cancer Discov.* 2015;5(6):568.
 66. pembrolizumab has antitumor activity in advanced head and neck cancer. *Cancer Discov.* 2016;6(7):693.
 67. De Marinis F, Passaro A. [Nivolumab in second-line treatment of squamous non-small cell lung cancer.]. *Recenti Prog Med.* 2016;107(12):634-40. (In Italian).
 68. First-line atezolizumab effective in bladder cancer. *Cancer Discov.* 2016;6(8):OF7.
 69. Ganjoo KN et al. The prognostic value of tumor-associated macrophages in leiomyosarcoma: A single institution study. *Am J Clin Oncol.* 2011;34(1):82-6.
 70. George S et al. Loss of PTEN Is associated with resistance to anti-PD-1 checkpoint blockade therapy in metastatic uterine leiomyosarcoma. *Immunity.* 2017;46(2):197-204.
 71. Pollack SM et al. T-cell infiltration and clonality correlate with programmed cell death protein 1 and programmed death-ligand 1 expression in patients with soft tissue sarcomas. *Cancer.* 2017;123(17):3291-304.
 72. Nivolumab (Opdivo) plus ipilimumab (Yervoy) for metastatic melanoma. *Med Lett Drugs Ther.* 2015;57(1483):168.
 73. Motzer RJ et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med.* 2018;378(14):1277-90.
 74. Wilky BA et al. A Phase II trial of axitinib plus pembrolizumab for patients with advanced alveolar soft part sarcoma (ASPS) and other soft tissue sarcomas (STS). *J Clin Oncol.* 2018;36(Suppl 15):11547.

FOR REPRINT QUERIES PLEASE CONTACT: +44 (0) 1245 334450