Metastatic soft tissue sarcomas: update on new agents and clinical studies

Attila Kollár[1], Bernd Kasper[2]

Abstract
Soft tissue sarcomas are rare tumors of mesenchymal origin comprising about 1% of all adult malignant diseases. Systemic therapy for locally advanced and metastatic disease was restricted for decades to a few effective and approved agents, such as doxorubicin or ifosfamide. However, numerous clinical trials and new drug developments such as trabectedin, pazopanib, olaratumab or eribulin have recently enriched the therapeutic armamentarium in the treatment of patients with advanced soft tissue sarcomas and will be presented in the following review.

Key words: soft tissue sarcoma, chemotherapy, clinical studies

Background

Soft tissue sarcomas (STS) are a rare group of tumors of mesenchymal origin comprising about 1% of all malignancies in the adulthood. According to the updated WHO classification (2013), STS represent a highly heterogeneous tumor entity of more than 50 subtypes based on their histological, molecular and certainly clinical characteristics [1]. Conventional chemotherapy with doxorubicin and/or ifosfamide still represents the backbone of systemic treatment in the locally advanced and metastatic setting sequentially or in combination [2]. Since the early 80's many trials have been published investigating the addition of new drugs to doxorubicin in order to improve overall survival (OS). However, no statistically significant benefit could be proven regarding this matter. Even in the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) 62012 trial that included 455 patients and compared single agent doxorubicin with a combination regimen with ifosfamide in a randomized fashion, the primary endpoint of improvement in OS was not met. Whereas the response rate was higher (27% *vs* 14%) and the progression-free survival (PFS) could be prolonged in the combination arm (7.4 *vs* 4.6 months), the doxorubicin/ifosfamide combination did not lead to a statistically significant improvement in OS (14.3 *vs* 12.8 months) [3]. For the first time after 40 years of standard first-line anthracycline therapy, the approval of olaratumab, a platelet-derived growth factor receptor (PDGFR) inhibitor, in combination with doxorubicin, has revolutionized the first-line treatment of advanced STS [4]. In a randomized phase II trial, olaratumab combined with doxorubicin was able to prolong OS for almost one year when compared to doxorubicin alone.

With the successful launching of trabectedin, pazopanib and eribulin for specific subtypes of STS, the treatment landscape in the further-line setting has been broadened and promising systemic treatment options can be offered to patients [5-8]. Furthermore, taxanes have shown a beneficial response in angiosarcomas, and leiomyosarcomas seems to be highly sensitive to gemcitabine alone or combined with docetaxel [9-10]. With the rapidly evolving knowledge on sarcoma pathogenesis and increasing clinical trial data on treatment of sarcoma subtypes, histology-driven chemotherapy is already well-established in the present and represents the future. A simplified treatment algorithm illustrating potential systemic treatment options for locally advanced and metastatic STS is depicted in Figure 1.

[1]Department of Medical Oncology, Sarcoma Unit,
Bern University Hospital, Bern, Switzerland.
[2]Sarcoma Unit, Interdisciplinary Tumor Center Mannheim,
Mannheim University Medical Center, University of Heidelberg,
Mannheim, Germany.
Correspondence to:
Attila Kollár, MD,
Department of Medical Oncology, Sarcoma Unit,
Bern University Hospital, Freiburgstrasse, 3010 Bern, Switzerland.
Phone: +41 (0)31 632 4114 – Fax: +41 (0)31 632 4119
E-mail: attila.kollar@insel.ch
CANCER BREAKING NEWS 2017;5(2):5-11
DOI: 10.19156/cbn.2017.0042

The prognosis of locally advanced and metastatic STS is unfavorable [11, 12].

The median OS at this stage has been approximately 12 months, but has increased up to 19 months in recent years. However, there is still an unmet need for new, innovative drugs and treatment strategies [13]. The prolongation of survival and the improvement in quality of life, in particular, should be the main treatment goals in this advanced tumor situation.

New agents

In recent years, several promising agents have been investigated in large, multicenter, international registration trials. Few of them have demonstrated proven efficacy, been approved by the corresponding medical health authorities and reached marketing authorization.

Olaratumab

Olaratumab is a recombinant human immunoglobulin G

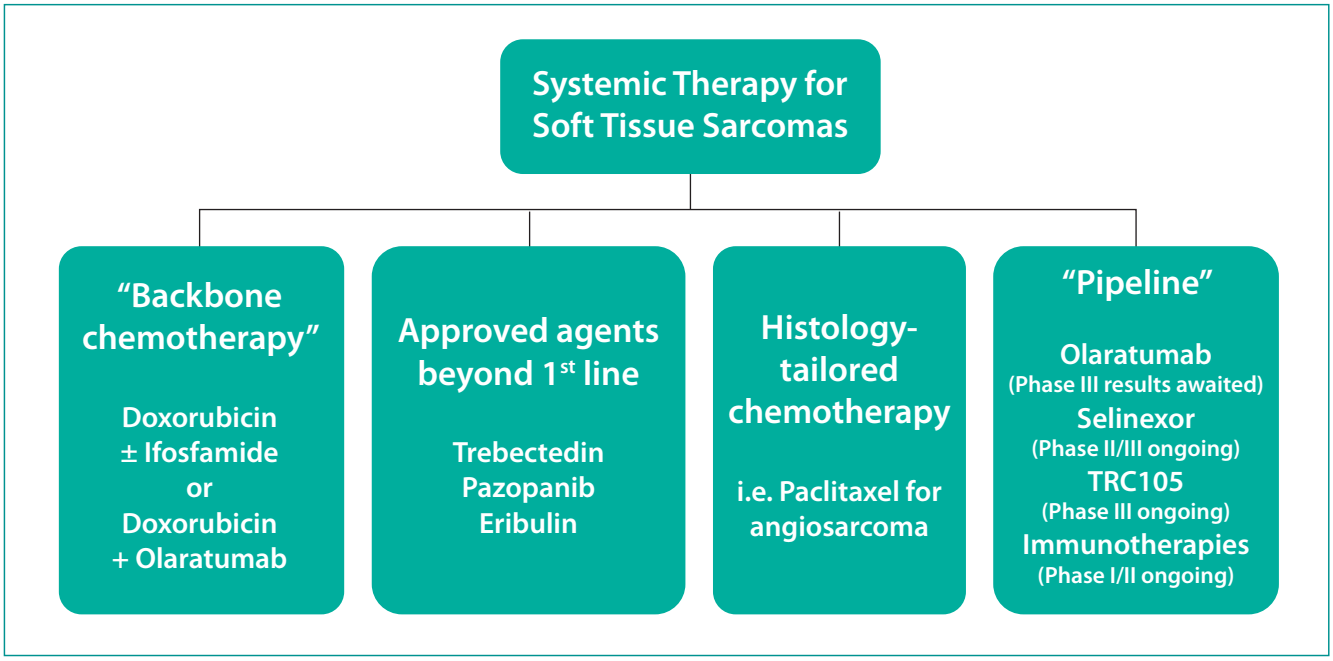

Fig. 1. Systemic treatment options for locally advanced and metastatic soft tissue sarcoma.

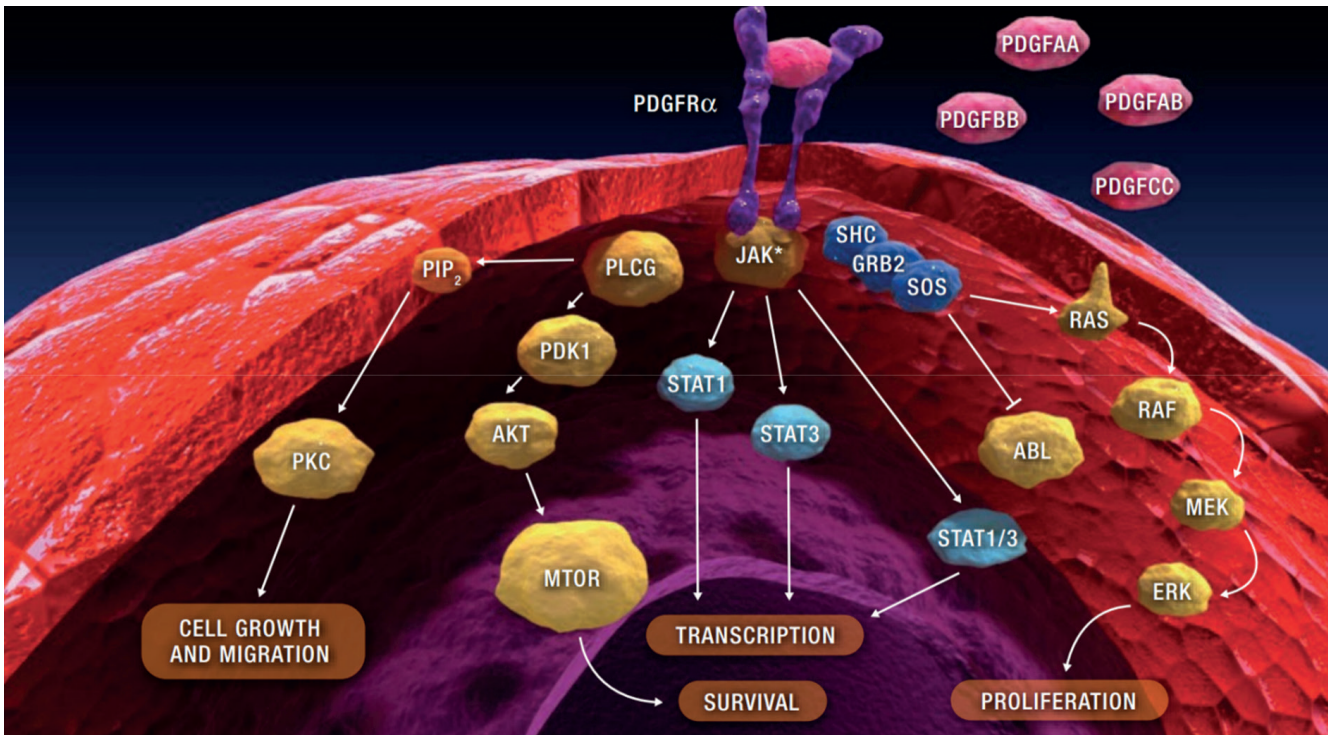

Fig. 2. Platelet-derived growth factor (PDGF) signaling pathway. Copyright © 2017 Eli Lilly and Company.

subclass (IgG1)-type monoclonal antibody that binds to PDGFRα. In normal mesenchymal biology, PDGFRα-activation via its ligand regulates cell proliferation, differentiation and survival (Figure 2). PDGFRα can be overexpressed in sarcomas. Consecutively, agents, like olaratumab, targeting PDGFRα may cause activity against sarcomas by inhibiting tumor angiogenesis and by blockage of stromal cell growth [14].

Olaratumab was first investigated in a phase Ib/II trial. Patients were randomized to treatment with doxorubicin or doxorubicin combined with olaratumab. The primary endpoint was PFS. In this study not only was the PFS significantly prolonged with the addition of olaratumab (6.6 *vs* 4.1 months; hazard ratio [HR] 0.67; p=0.0615), an impressive improvement of OS of 11.8 months (26.5 *vs* 14.7 months; HR 0.46; p=0.0003) could be detected in the combination arm for the treatment of locally advanced and metastatic STS. However, PDGFRα expression (positive or negative) did not significantly correlate with treatment outcome (OS, p=0.3209; PFS p=0.5924) [4]. Understanding the interaction between PDGFRα and its pathway and treatment effect is the focus of ongoing investigations.

Based on this promising result, the American Food and Drug Administration (FDA) as well as the European Medical Agency (EMA) health authorities recommended the granting of a conditional marketing authorization for olaratumab. Nevertheless, the suggested benefit of olaratumab within the phase II trial has to be confirmed by the results of the international, multicenter phase III ANNOUNCE-trial (ClinicalTrials.gov Identifier NCT02451943). Patient accrual had already been reached in mid-2016. However, the results, expected in 2018 at the earliest, are eagerly awaited. After many years, with the conditional approval of olaratumab in combination with doxorubicin a new first-line regimen can be used for the treatment of adult patients with advanced STS who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin. Olaratumab represents the first monoclonal antibody approved for the treatment of sarcomas.

Eribulin

Furthermore, the results of another practice-changing trial, at least in one specific histotype, were published last year. The efficacy and safety of eribulin, an inhibitor of microtubule dynamics, have been compared with dacarbazine in an international, multicenter phase III trial. A total of 450 patients with pretreated, locally advanced or metastatic leiomyosarcoma or adipocytic sarcoma were included. The inclusion of these two STS subtypes originated in the treatment benefit seen in these two strata in the previously conducted phase II trial by the EORTC/STBSG [15]. The primary endpoint was OS, which was shown to be significantly improved by two months with eribulin when compared with dacarbazine (13.5 *vs* 11.5 months; HR 0.77; p=0.0169). In particular, subgroup analysis revealed an impressive OS benefit in the liposarcoma cohort. Median OS was reported to be 15.6 months in the eribulin treatment arm and 8.4 months in the dacarbazine treatment arm (HR 0.511; p=0.0006) [8]. Based on these results, the FDA and EMA approved eribulin in early 2016 for the treatment of adipocytic sarcoma in patients who had received prior anthracycline-containing chemotherapy.

Aldoxorubicin

Aldoxorubicin, a tumor-targeted doxorubicin conjugate (with an acid sensitive linker), is currently under further investigation. Chawla et al. compared efficacy and safety parameters of aldoxorubicin and doxorubicin in a randomized phase II trial. Aldoxorubicin showed a significant prolongation of PFS (5.6 *vs* 2.7 months; p=0.02) and 6-months progression-free rate (46% *vs* 23%; p=0.02) when compared with doxorubicin for the treatment of STS in the first-line setting. Of note, no cardiotoxicity was documented in the patients treated with aldoxorubicin [16]. Additionally, aldoxorubicin was investigated in a phase III study looking at the treatment effect in the second-line setting when compared to therapy at investigator's choice (dacarbazine, pazopanib, gemcitabine plus docetaxel, doxorubicin, ifosfamide). Compared with standard treatment, aldoxorubicin showed no significant improvement in PFS (4.11 *vs* 2.96 months, p=0.087). Subgroup analysis revealed a potential benefit in lipo- and leiomyosarcoma [17].

Evofosfamide

Another drug which has been evaluated in the treatment of STS is evofosfamide (TH-302). It is an investigational prodrug which is activated only at very low levels of oxygen. Tumor hypoxia is a common phenomenon in many human solid tumors, like STS [18]. Therefore, the side effect profile is deemed to be lower when compared to its counterpart ifosfamide, which is characterized by a clinically-relevant incidence of neuro- and nephrotoxicity when given as high-dose chemotherapy.

The completed and presented phase III trial (NCT01440088) is a randomized, open-label, global, multicenter phase III study, that was designed to assess the efficacy and safety of evofosfamide in combination with doxorubicin

compared to doxorubicin alone, in patients with locally advanced, unresectable or metastatic STS previously untreated with chemotherapy. A total of 640 patients were randomized in the study. The primary endpoint of the study was OS. The response rate was slightly better in the combination arm: 28.4% *versus* 18.3%, respectively. Disappointingly, no significant difference in median OS and PFS could be seen with the combination of evofosfamide and doxorubicin when compared with doxorubicin monotherapy; 18.4 *versus* 19 months (HR 1.06) and 6.3 *versus* 6 months (HR 0.85; p=0.099), respectively. Interestingly, a significant improvement in OS was reported in the subgroup (n = 34) of synovial sarcomas; 22 *versus* 9 months, respectively (HR 0.32), underlining the sensitivity of this STS subentity to oxazaphosphorine-based chemotherapy [19].

Others (palbociclib, selinexor, carotuximab)

Several promising compounds have the potential to broaden the treatment armamentarium in the near future. Palbociclib, a selective CDK4/CDK6-inhibitor, and DS-3032b, a MDM2-inhibitor, are both investigated for the treatment of well- and dedifferentiated liposarcoma (WDLS/DDLS). Both targets act as important negative regulators of p53, a tumor suppressor gene. Several phase I and II trials have been reported and/or published so far [20-22]. Notably, palbociclib was associated with a favorable progression-free rate of 66% (90% confidence interval, 51% to 100%) in patients with CDK4-amplified WDLS/DDLS who had progressive disease despite systemic therapy (NCT01209598).

Additionally, selinexor, an oral selective inhibitor of nuclear export, has been studied in STS and bone sarcomas [23]. Recently, promising results were published for the treatment of DDLS in a phase I trial. Although no objective response by Response Evaluation Criteria In Solid Tumors (RECIST) v 1.1 was seen, 17 (33%) patients showed durable (≥4 months) stable disease (NCT01896505) [24]. A phase II/III trial (NCT02606461) is currently recruiting patients with DDLS (n=245) in order to learn more about the efficacy of selinexor in this specific cohort.

TCR105 (carotuximab) is currently under investigation for the treatment of angiosarcoma. TCR105 is a monoclonal antibody targeting endoglin (CD105) which is expressed by tumor cells in angiosarcoma and up-regulated by vascular endothelial growth factor (VEGF) inhibition [25]. Hence, TCR105 can suppress angiogenesis and might enhance the activity of, for example, bevacizumab or other tyrosine multi-kinase inhibitors such as pazopanib [26]. Based on this pathomechanism, a phase Ib/II trial combining TCR105 with pazopanib (800 mg daily) was conducted. Tumor reduction was documented in five angiosarcoma patients; two of them had progressive disease on previous pazopanib therapy. Two patients with cutaneous angiosarcoma experienced a complete remission according to RECIST criteria. Median PFS for the angiosarcoma patients was 12.9 months (NCT01975519) [27]. The corresponding phase III trial investigating the combination of TRC105 in combination with standard dose pazopanib compared to single agent pazopanib, in patients with advanced angiosarcoma, has already started recruitment (NCT02979899).

Immunotherapy

The revival of therapeutic affectation of the immune system has revolutionized patient outcome in many solid tumors in the last few years, in particular in melanoma [28]. This approach has also been evaluated in STS. The largest already-presented clinical phase II trial was performed by the Sarcoma Alliance for Research Through Collaboration (SARC) study group. In total, 80 patients with STS and bone sarcomas from 12 participating centers were treated with pembrolizumab, which is a PD1-inhibitor. The primary endpoint was the response rate. A response rate of 19% was reported for the 40 included STS patients. The heterogeneity of STS regarding biology and response to systemic treatment could be confirmed once again by showing different response rates depending on sarcoma subtype. A promising response rate of 44% was reported for undifferentiated pleomorphic sarcoma. In contrast, only 5% of bone sarcoma patients experience a tumor response [29]. Further work has to be done in order to clarify the role of immunotherapy in STS. In particular, investigating potential predictive markers on a molecular level for suggested differences in treatment sensitivity and evaluating the optimal treatment combinations of checkpoint inhibitors with chemotherapy, radiotherapy or targeted treatment options would be of major interest.

Outlook for clinical studies

The European clinical research landscape is shaped by the STBSG of the EORTC. It represents both a multinational and multidisciplinary network comprising over 600 hospitals and cancer centers in over 37 countries (www.eortc.be). Beyond that, several research groups have evolved on a national level in order to develop, conduct, coordinate, and stimulate translational and clinical research. National research groups focusing on sarcomas are active, for example, in Austria (Sarcoma Platform Austria), in France (Groupe Sarcomes Francais), in Germany (German Inter-

disciplinary Sarcoma Group (GISG) and Arbeitsgemeinschaft für Weichteilsarkome und Knochentumore AIO), in Italy (Italian Sarcoma Group), in Scandinavia (Scandinavian Sarcoma Group) and Spain (Grupo Español de Investigación des Sarcomas).

The majority of clinical trials investigate the safety and efficacy of a specific agent as monotherapy or in combination with a standard treatment in STS [30]. However, given the fact that STS represent a mixture of more than 50 subtypes, systemic treatment of specific STS subtypes are increasingly studied, requiring national and often international collaboration. Furthermore, reflecting the interdisciplinary therapy of STS, the combination of different treatment modalities (e.g. chemotherapy and radiotherapy) or their sequence represents another focus of some trials [31, 32]. An overview of the ongoing EORTC/STBSG trials is illustrated in Table 1.

Additionally, several trials are evaluating the treatment outcome in the elderly population or address patient reported outcome (PRO) parameters. Some of these trials are integrated into the trial portfolio of the GISG (www.gisg.de). One trial addressed the efficacy and safety of pazopanib compared with a standard first-line treatment with doxorubicin in patients >60 years old (GISG-05/AIO 101) [33]. Quality of life is being studied in two further trials looking at the patient benefit under pazopanib (GISG-11/PazoQoL) or trabectedin (GISG-12/YonLife) therapy. The GISG-13/E-Trab trial is also worth mentioning. An extensive geriatric assessment is being performed in an elderly patient population treated

Table 1. Ongoing European Organisation for Research and Treatment of Cancer (EORTC) / Soft Tissue and Bone Sarcoma Group (STBSG) studies.

EORTC Trial no.	Principal investigator	Phase	Title	Tumor type	NCT number
1202	L. Hayward	II	Phase II trial of cabazitaxel in metastatic or recurrent de-differentiated liposarcoma	STS	01913652
62113-55115	I. Ray-Coquard	II	A randomized double-blind phase II study evaluating the role of maintenance therapy with cabozantinib in High Grade Uterine Sarcoma (HGUtS) after stabilization or response to doxorubicin ± ifosfamide following surgery or in metastatic first line treatment	STS	01979393
1506	P. Schöffski	II	A phase II multicenter study comparing the efficacy of the oral angiogenesis inhibitor nintedanib with the intravenous cytotoxic compound ifosfamide for treatment of patients with advanced metastatic soft tissue sarcoma after failure of systemic non-oxazaphosporine-based first line chemotherapy for inoperable disease (ANITA)	STS	02808247
90101	P. Schöffski	II	Cross-tumoral phase 2 clinical trial exploring crizotinib in patients with advanced tumors induced by causal alterations of ALK and/or MET (CREATE)	STS	01524926
62092	S. Bonvalot and R. Haas	III	A phase III randomized study of preoperative radiotherapy plus surgery *versus* surgery alone for patients with retroperitoneal sarcoma (STRASS)	STS	01344018
1447	H. Gelderblom	III	Maintenance therapy with trabectedin *versus* observation after first line treatment with doxorubicin of patients with advanced or metastatic soft tissue sarcoma	STS	02929394
1402	H. Gelderblom	III	International randomised controlled trial for the treatment of newly diagnosed Ewing's sarcoma family of tumors (Euro Ewing 2012)	Ewing	92192408
1403	U. Dirksen	III	International randomised controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma (rEEcur)	Ewing	36453794
1317	P. Schöffski	II	Phase II study of cabozantinib in patients with metastatic gastrointestinal stromal tumor (GIST) who progressed during neoadjuvant, adjuvant or palliative therapy with imatinib and sunitinib (CaboGIST)	GIST	02216578
1321	J.Y. Blay	II	A randomized phase II trial of imatinib alternating with regorafenib compared to imatinib alone for the first line treatment of advanced GIST (ALT-GIST)	GIST	02365441

GIST: gastrointestinal stromal tumor; NCT number: ClinicalTrials.gov Identifier number; STS: soft tissue sarcoma

with trabectedin in the first line in order to predict safety parameters, including PROs. Among others, the geriatric assessment consists of the Instrumental Activities of Daily Living (IADL), the Mini Nutritional Assessment (MNA), the Charlson Comorbidity Index (CCI), the Geriatric Depression Scale (GDS) and Time up & Go. The predictive value of two geriatric screening tools (G8, CARG prediction tool) will be investigated with regards to unplanned hospitalizations, grade 4 toxicities and early death within the first six months [34]. The 30-item EORTC quality of life questionnaire (EORTC QLQ-C30) and the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) questionnaires are used to evaluate PROs [35]. Remarkably, this trial benefits from an international cooperation of sarcoma centers in Austria, Germany and Switzerland (A/D/CH).

Due to the variety of planned and ongoing STS trials, comprehensive trial coordination on an international level is of outmost importance. All clinical trials are registered on www.clinicaltrials.gov, which is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

Conclusions/Key Points

- Patients suffering from soft tissue tumors should be admitted to sarcoma centers early in their disease course. Treatment of STS should be concentrated in designated institutions with a high expertise in sarcoma diagnostics and therapy.
- Doxorubicin-based chemotherapy is the standard treatment of locally advanced and metastatic STS in the first-line setting.
- Olaratumab represents the first approved monoclonal antibody for the treatment of locally advanced/metastatic STS.
- With the granting of a conditional marketing authorization to olaratumab, a new first-line option for the treatment of locally advanced/metastatic STS is available.
- Trabectedin, pazopanib, eribulin and histology-driven chemotherapy in selected histotypes represent efficacious and well-tolerated treatment options beyond first line.
- Several promising new drugs (including palbociclib, selinexor, TCR105) and new therapeutic concepts are being studied in open clinical trials.
- Patients should preferably be treated within clinical trials, if available. International collaboration in this matter should be promoted.

Acknowledgments

The Authors thank Ray Hill, an independent medical writer, who provided native English editing and journal styling on behalf of HPS. This editorial assistance was funded by PharmaMar, Spain.

Conflicts of Interest

The Authors declare there are no conflicts of interest in relation to this article.

References

1. Fletcher CD, Bridge JA, Hogendoorn P et al. WHO classification of tumours of soft tissue and bone (IARC WHO Classification of Tumours), 4th edition. Lyon, France: IARC; 2013.
2. ESMO/European Sarcoma Network Working Group. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Suppl 3:iii102-12.
3. Judson I, Verweij J, Gelderblom H 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.
4. Tap WD, Jones RL, Van Tine BA 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, Chawla SP, von Mehren M et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: Results of a randomized phase II study of two different schedules. J Clin Oncol 2009;27(25):4188-96.
6. Sleijfer S, Ray-Coquard I, Papai Z 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.
7. van der Graaf WT, Blay JY, Chawla SP et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012; 379(9829):1879-86.
8. Schöffski P, Chawla S, Maki RG 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.
9. Penel N, Bui BN, Bay JO et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. J Clin Oncol 2008;26(32):5269-74.

10. Hensley ML, Maki R, Venkatraman E et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J Clin Oncol 2002;20(12):2824-31.
11. Clark MA, Fisher C, Judson I et al. Soft-tissue sarcomas in adults. N Engl J Med 2005;353(7):701-11.
12. Blay JY, van Glabbeke M, Verweij J et al. Advanced soft-tissue sarcoma: a disease that is potentially curable for a subset of patients treated with chemotherapy. Eur J Cancer 2003;39(1):64-9.
13. Penel N, Van Glabbeke M, Marreaud S et al. Testing new regimens in patients with advanced soft tissue sarcoma: analysis of publications from the last 10 years. Ann Oncol 2011;22(6):1266-72.
14. Ostman A, Heldin CH. PDGF receptors as targets in tumor treatment. Adv Cancer Res 2007;97:247-74.
15. Schöffski P, Ray-Coquard IL, Cioffi A 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.
16. Chawla SP, Papai Z, Mukhametshina G et al. First-line aldoxorubicin vs doxorubicin in metastatic or locally advanced unresectable soft-tissue sarcoma: A phase 2b randomized clinical trial. JAMA Oncol 2015;1(9):1272-80.
17. Chawla SP, Ganjoo KN, Schuetze S et al. Phase III study of aldoxorubicin vs investigators' choice as treatment for relapsed/refractory soft tissue sarcomas [Abstract]. J Clin Oncol 2017;35(15_Suppl.):11000.
18. Nordsmark M, Hoyer M, Keller J et al. The relationship between tumor oxygenation and cell proliferation in human soft tissue sarcomas. Int J Radiat Oncol Biol Phys 1996;35(4):701-8.
19. Tap W, Papai Z, Van Tine B et al. Randomized phase 3, multicenter, open-label study comparing evofosfamide (Evo) in combination with doxorubicin (D) vs. D alone in patients (pts) with advanced soft tissue sarcoma (STS): Study TH-CR-406/SARC021 [Abstract]. Ann Oncol 2016;27(suppl_6):13950.
20. Dickson MA, Tap WD, Keohan ML 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.
21. Dickson MA, Schwartz GK, Keohan ML et al. Progression-free survival among patients with well-differentiated or dedifferentiated liposarcoma ttreated with CDK4 inhibitor palbociclib: a phase 2 clinical trial. JAMA Oncol 2016;2(7):937-40.
22. Gounder MM, Bauer TM, Schwartz GK et al. A phase 1 study of the MDM2 inhibitor DS-3032b in patients (pts) with advanced solid tumors and lymphomas [Abstract]. J Clin Oncol 2016;34(15_suppl):2581.
23. Nakayama R, Zhang YX, Czaplinski JT et al. Preclinical activity of selinexor, an inhibitor of XPO1, in sarcoma. Oncotarget 2016;7(13):16581-92.
24. Gounder MM, Zer A, Tap WD et al. Phase Ib study of selinexor, a first-in-class inhibitor of nuclear export, in patients with advanced refractory bone or soft tissue sarcoma. J Clin Oncol 2016;34(26):3166-74.
25. Seon BK, Haba A, Matsuno F et al. Endoglin-targeted cancer therapy. Curr Drug Deliv 2011;8(1):135-43.
26. Rosen LS, Gordon MS, Robert F et al. Endoglin for targeted cancer treatment. Curr Oncol Rep 2014;16(2):365.
27. Sankhala K, Attia S, Barve M et al. TRC105 (Endoglin antibody) in combination with pazopanib in patients with advanced angiosarcoma [Poster #110]. CTOS 2016 Annual Meeting; November 9-12, 2016; Lisbon, Portugal.
28. Nanda V, Peng W, Hwu P et al. Melanoma and immunotherapy bridge 2015. J Transl Med 2016;14(1):65.
29. Tawbi HA-H, Burgess MA, Crowley J et al. Safety and efficacy of PD-1 blockade using pembrolizumab in patients with advanced soft tissue (STS) and bone sarcomas (BS): Results of SARC028–A multicenter phase II study [Abstract]. J Clin Oncol 2016;34(15_suppl):11006.
30. Kasper B, Reichardt P, Pink D et al. Combination of trabectedin and gemcitabine for advanced soft tissue sarcomas: results of a phase I dose escalating trial of the German Interdisciplinary Sarcoma Group (GISG). Mar Drugs 2015;13(1):379-88.
31. Jakob J, Simeonova A, Kasper B et al. Combined sunitinib and radiation therapy for preoperative treatment of soft tissue sarcoma: results of a phase I trial of the German interdisciplinary sarcoma group (GISG-03). Radiat Oncol 2016;11:77.
32. Ronellenfitsch U, Dimitrakopoulou-Strauss A, Jakob J et al. Preoperative therapy with pazopanib in high-risk soft tissue sarcoma: a phase II window-of-opportunity study by the German Interdisciplinary Sarcoma Group (GISG-04/NOPASS). BMJ Open 2016;6(1):e009558.
33. Karch A, Koch A, Grunwald V. A phase II trial comparing pazopanib with doxorubicin as first-line treatment in elderly patients with metastatic or advanced soft tissue sarcoma (EPAZ): study protocol for a randomized controlled trial. Trials 2016;17(1):312.
34. Hentschel L, Rentsch A, Lenz F et al. A questionnaire study to assess the value of the vulnerable elders survey, G8, and predictors of toxicity as screening tools for frailty and toxicity in geriatric cancer patients. Oncol Res Treat 2016;39(4):210-6.
35. Dueck AC, Mendoza TR, Mitchell SA et al. Validity and reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). JAMA Oncol 2015;1(8):1051-9.