Oncology

EOR | VOLUME 5 | NOVEMBER 2020
DOI: 10.1302/2058-5241.5.200069
www.efortopenreviews.org

EFORT open reviews

Treatment options in unresectable soft tissue and bone sarcoma of the extremities and pelvis – a systematic literature review

Maria Anna Smolle[1]
Joanna Szkandera[2]
Dimosthenis Andreou[3]
Emanuela Palmerini[4]
Marko Bergovec[1]
Andreas Leithner[1]

- In patients with metastatic or unresectable soft tissue and bone sarcoma of extremities and pelvis, survival is generally poor. The aim of the current systematic review was to analyse recent publications on treatment approaches in patients with inoperable and/or metastatic sarcoma.
- Original articles published between 1st January 2011 and 2nd May 2020, using the search terms 'unresectable sarcoma', 'inoperability AND sarcoma', 'inoperab* AND sarcoma', and 'treatment AND unresectable AND sarcoma' in PubMed, were potentially eligible. Out of the 839 initial articles (containing 274 duplicates) obtained and 23 further articles identified by cross-reference checking, 588 were screened, of which 447 articles were removed not meeting the inclusion criteria. A further 54 articles were excluded following full-text assessment, resulting in 87 articles finally being analysed.
- Of the 87 articles, 38 were retrospective (43.7%), two prospective (2.3%), six phase I or I/II trials (6.9%), 22 phase II non-randomized trials (27.6%), nine phase II randomized trials (10.3%) and eight phase III randomized trials (9.2%). Besides radio/particle therapy, isolated limb perfusion and conventional chemotherapy, novel therapeutic approaches, including immune checkpoint inhibitors and tyrosine kinase inhibitors were also identified, with partially very promising effects in advanced sarcomas.
- Management of inoperable, advanced or metastatic sarcomas of the pelvis and extremities remains challenging, with the optimal treatment to be defined individually. Besides conventional chemotherapy, some novel therapeutic approaches have promising effects in both bone and soft tissue subtypes. Considering that only a small proportion of studies were randomized, the clinical evidence currently remains moderate and thus calls for further large, randomized clinical trials.

Keywords: inoperable sarcoma; advanced sarcoma; treatment approach; novel therapeutics

Cite this article: *EFORT Open Rev* 2020;5:799-814.
DOI: 10.1302/2058-5241.5.200069

Introduction

Soft tissue sarcomas (STS) and bone sarcomas constitute rare mesenchymal neoplasms, with an incidence of 4.7 and 0.8 per 100 000 patients per year in Europe, respectively.[1,2] The majority of these tumours are located in the extremities and pelvis.[1] Complete surgical resection is the gold standard in multimodal treatment plans with curative intent.[3] Most STS of the extremities are resectable at initial presentation, while patients with locally advanced tumours involving important anatomical structures or those with distant spread may not be suitable for curative surgery. Survival in the case of metastatic disease is rather poor, with median survival times of 14 to 17 months.[4,5] Likewise, about 70% of bone sarcomas can be treated by surgery with or without chemotherapy (CTX), depending on their histology, with curative intent, whereas in the metastatic setting, five-year survival is less than 25%.[6–8]

In locally advanced, unresectable and/or metastatic sarcomas, treatment options are generally limited. Systemic options include conventional CTX and – in recent years – targeted treatments, tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors. For local control (LC), unresectable or metastatic tumours may be treated with standard radiotherapy (RTX), particle therapy, embolization or isolated limb perfusion (ILP). Treatment plans are discussed in multidisciplinary team meetings in order to achieve the best outcomes possible. In recent years,

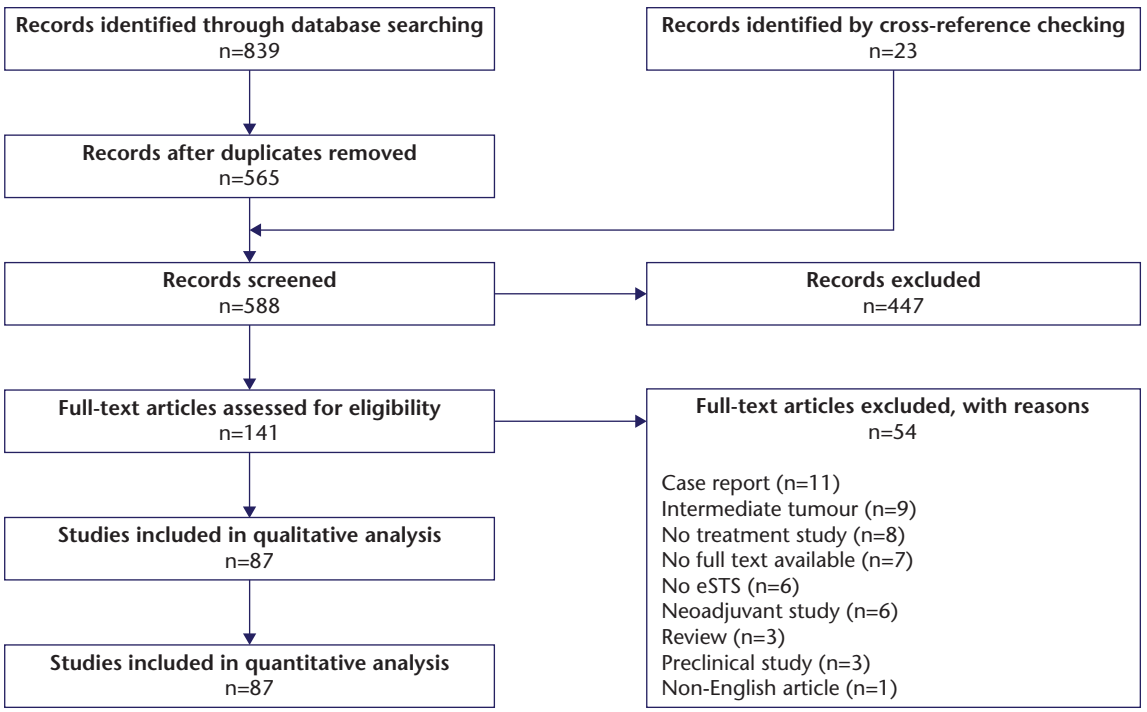

Fig. 1 PRISMA flow chart.

several studies have been published investigating innovative treatment options in patients with locally advanced, recurrent or metastatic sarcomas not amenable to local surgery. Because sarcomas comprise a heterogeneous group with variable treatment responses, however, therapeutic approaches for different subtypes may significantly differ.

Therefore, the aim of the present systematic review was to summarize recent knowledge on treatment of patients with locally advanced, unresectable or metastatic soft tissue and bone sarcomas of the extremities and pelvis, providing an overview on which treatment modalities per histological subtype are potentially available.

Methods

All original articles published in English language between 1st January 2011 and 2nd May 2020 on inoperable primary or recurrent as well as metastatic sarcoma of the extremities and pelvis were potentially eligible. Case reports and review articles were excluded from this review, as were non-English publications, those with full-text articles not available in electronic form and studies predominantly dealing with sarcomas of the trunk, abdomen, retroperitoneum and/or head and neck region.

PubMed was searched for original articles published between 1st January 2011 and 2nd May 2020 using the following search terms: 'Unresectable sarcoma', 'inoperability AND sarcoma', 'inoperab* AND sarcoma', and 'treatment AND unresectable AND sarcoma' (last retrieval date: 2 May 2020; Fig. 1). Further articles were included by cross-reference checking if not retrievable from the literature search. The systematic literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] After removing duplicates, titles and abstracts were screened. Thereafter, full-text articles were assessed for eligibility. All original articles investigating the effect of various treatments apart from surgery in metastatic or unresectable sarcomas could be included. Due to the heterogeneity of studies analysed, no meta-analysis was conducted. Therefore, descriptive statistics were performed only. Treatment effects were separated into poor, moderate and promising, based on the conclusions drawn by the authors of the respective studies. Furthermore, study limitations, levels of evidence according to the Oxford Centre for Evidence Based Medicine Levels of Evidence Scale,[10] and clinical efficacy in distinct histological subtypes were documented.

Results

From the initial 839 articles, 274 duplicates were removed. Thereafter, 23 articles were added following cross-reference checking, resulting in 588 articles being screened. Of these, 447 articles not meeting the inclusion criteria were excluded. Thereafter, 141 articles were assessed for eligibility, with 54 publications excluded for several reasons, resulting in 87 studies finally included in qualitative analysis (Fig. 1).

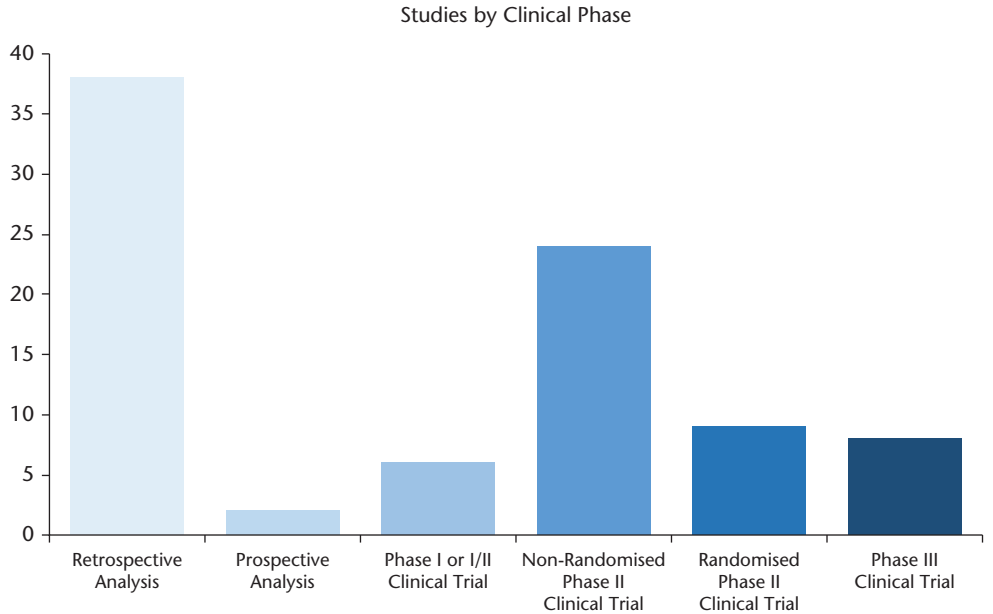

Fig. 2 Studies analysed in the systematic review, separated by clinical phase.

Altogether, 38 retrospective analyses (43.7%), two prospective analyses (2.3%), six phase I or phase I/II clinical trials (6.9%), 22 phase II non-randomized clinical trials (27.6%), nine phase II randomized trials (10.3%), and eight phase III clinical trials (9.2%) could be finally included in qualitative and quantitative analysis (Fig. 2). Of those, 41 studies had an evidence level IV (47.1%), 29 an evidence level III (33.3%) and 17 an evidence level II (19.5%).

Bone sarcomas

With five-year post-relapse survival rates of less than 30%, prognosis in advanced bone sarcomas is generally poor.[11] Yet, throughout the past years, several studies investigating novel treatment options have been published, with sometimes promising results (Table 1). Besides conventional RTX as the standard of care for local treatment of some histological subtypes such as Ewing's sarcoma,[12] particle therapy with protons or heavy ions may be used in unresectable or incompletely resected bone sarcoma – including relatively radio-resistant tumours as osteosarcoma – achieving adequate LC rates, especially in small tumours and single-site disease.[13,14] Furthermore, chemoembolization with N-2-btyl-cyanoacrylate (NBCA) has been shown to be effective for symptom palliation in unresectable or recurrent bone sarcomas of the shoulder girdle or pelvis.[15]

With regards to systemic therapy, conventional CTX with gemcitabine and docetaxel or high-dose ifosfamide monotherapy may lead to durable treatment responses in selected cases of refractory bone sarcomas.[16,17] On the other hand, combination therapy with topotecan and cyclophosphamide, an established treatment protocol in paediatric bone sarcoma patients, has only limited effectiveness in adults.[18] Also, several phase II trials demonstrated activity of targeted agents as tyrosine kinase inhibitors[19,20] and the mammalian target of rapamycin (mTOR) inhibitor ridaforolimus.[21,22] In particular, a progression free survival (PFS) of 3.5 to 3.9 months in patients with advanced sarcoma (both bone and soft tissue) was demonstrated for ridaforolimus, with manageable toxicity profile.[21,22] Moreover, immune checkpoint inhibitors, such as pembrolizumab or nivolumab in combination with ipilimumab, can lead to substantial and durable antitumour responses in selected advanced bone sarcoma patients.[23–25] Yet, the median achieved PFS of 1.7 to 4.1 months is worse than the one seen in STS.[23–25]

Chondrosarcoma

Most chondrosarcomas are low grade, thus only growing very slowly, and have a favourable prognosis.[26] However, a small proportion are high grade, with high risk of metastatic spread and consecutive poor prognosis.[27] In order to improve outcome of patients with advanced chondrosarcoma, various local and systemic treatment modalities may be applied, with differing outcomes (Table 2).

Particle therapy with carbon ions has been shown to be effective in patients with chondrosarcoma not deemed resectable, leading to a median LC rate of 39.6 months.[28] Of note, the LC rate significantly varies depending on grading and histological subtype, with naturally better rates for grade I conventional chondrosarcoma (median LC rate: 66 months) in comparison to grade III conventional chondrosarcoma (median LC rate: 25 months) or

Table 1. Treatment options for bone sarcomas in general (sorted by level of evidence)

Treatment	Effect	Comments	Level	Ref.
Nivolumab	Poor		II, IV	23, 24
Pembrolizumab	Moderate		III	25
Ridaforolimus	Promising		III	21, 22
Conventional RTX	Promising		IV	12
Particle therapy (carbons, protons)	Promising		IV	13, 14
Chemo-embolization (NBCA)	Promising	Pain relief	IV	15
Gemcitabine + docetaxel	Promising		IV	16
Topotecan + cyclophosphamide	Poor	Regimen effective in children, but not in adult patients; mixed cohort of paediatric-type sarcomas	IV	18
Ifosfamide	Promising		IV	17
Nivolumab + ipilimumab	Moderate		IV	23

dedifferentiated chondrosarcoma (median LC rate: 9 months).[28]

Systemic treatment with first-line anthracycline- or non-anthracycline-based CTX in patients with locally advanced or metastatic chondrosarcoma is of limited efficacy, with an overall objective response rate (ORR) of 15%. Notably, patients with mesenchymal and dedifferentiated chondrosarcoma seemed to have a greater benefit from CTX than those with conventional chondrosarcoma.[29] Moreover, therapy with gemcitabine and docetaxel leads to rather low response rates in chondrosarcoma.[30] Notably, one retrospective study suggested that first-line doxorubicin monotherapy might be more efficacious as compared with doxorubicin-based combination therapy in dedifferentiated chondrosarcoma, though reasons for this observation remained unclear.[27] The same study suggested that first-line anti-hormonal therapy might have a promising anti-tumour activity in unresectable conventional chondrosarcoma.[27] In unresectable or metastatic extraskeletal myxoid chondrosarcoma, the TKI pazopanib can lead to a clinically meaningful tumour response after failed response to first-line anthracycline-based CTX, with a median PFS of 19 months (95% confidence interval (95% CI): 11 months to 27 months).[31] Pazopanib was also shown to be active in metastatic or unresectable conventional chondrosarcoma, with a manageable toxicity profile.[32,33] Also, the monoclonal antibody ramucirumab, targeting vascular endothelial growth factor receptor 2 (VEGFR2), has been tested in metastatic chondrosarcoma, achieving partially long-lasting stable disease.[33] Nevertheless, there is a broad variation in treatment effects between patients with similar chondrosarcoma subtypes and identical treatments, and uniform guidelines for this histological subtype in the advanced setting are yet to be defined.

Osteosarcoma

In the curative setting, osteosarcoma patients younger than 40 years are usually treated according to the European and American Osteosarcoma Studies (EURAMOS) protocol with neoadjuvant methotrexate, doxorubicin and cisplatin (MAP), followed by surgery and further MAP therapy.[34] In patients older than 40 years, neoadjuvant CTX protocols most commonly consist of cisplatin, doxorubicin and ifosfamide.[35] Considering that 30% to 40% of patients treated with curative intent for primarily localized osteosarcoma will develop local or systemic relapses, second- and third-line treatments in the advanced setting are required (Table 2).[6,36]

Besides chemo-embolization with N-butyl-cyanoacrylate (NCBA), local treatments leading to promising LC rates include particle therapies with carbons, protons or protons and photons.[37–39] With carbon ion radiotherapy, five-year PFS rates of 23% to 35% can be achieved, with small and low-grade pelvic osteosarcomas showing better response rates.[37,38] Although even higher five-year LC rates have been reported for proton- or proton-photon-based particle therapy in unresectable osteosarcoma, these results have to be interpreted carefully, considering that extremity-, pelvis- and axial tumours had been collectively analysed.[39]

Combination CTX with gemcitabine and docetaxel may be considered as a systemic treatment option in pre-treated, unresectable and metastatic osteosarcoma.[11,30,40] Although only moderate response rates with this combination treatment are observed, four-month PFS rates of 46% can be achieved, particularly in patients with a good performance status.[11] In case of inoperable high-grade primary osteosarcomas, combination of conventional multi-agent CTX and RTX does not only palliate symptoms, but may even lead to long-term LC rates in selected patients.[41]

The multikinase inhibitor sorafenib was the first TKI to show activity in osteosarcoma.[19] Second- or third-line monotherapy with sorafenib leads to a median PFS of four months (95% CI: two months to five months), with an acceptable toxicity profile.[19] Only recently, several studies with regorafenib, apatinib and pazopanib confirmed the role of TKIs in osteosarcoma.[42–46] For example, second- or third-line treatment with regorafenib significantly delays disease progression in advanced osteosarcoma in comparison to placebo, while OS rates are comparable.[42,43] Moreover, the TKI apatinib leads to encouraging response rates in advanced osteosarcoma progressive upon CTX, with a recommended daily dose of 500 mg.[44,45] According to a retrospective analysis, pazopanib also has some clinical efficacy and tolerable toxicity.[46]

Table 2. Treatment options divided by histological subtypes of bone sarcomas (sorted by level of evidence)

Chondrosarcoma

Treatment	Effect	Comments	Level	Ref.
CTX	Poor	As first line, including all chondrosarcoma subtypes	IV	29
Gemcitabine + docetaxel	Poor		III	30
Carbon ions	Promising	Conventional and dedifferentiated chondrosarcoma	IV	28

Dedifferentiated chondrosarcoma

Treatment	Effect	Comments	Level	Ref.
CTX	Moderate	As first line	IV	29
Doxorubicin	Promising		IV	27
Combination CTX with doxorubicin	Poor		IV	27

Conventional chondrosarcoma

Treatment	Effect	Comments	Level	Ref.
Pazopanib	Promising		III	32, 33
Ramucirumab	Promising	Based on two clinical cases	IV	33
Antihormone therapy	Promising		IV	27

Extraskeletal myxoid chondrosarcoma

Treatment	Effect	Comments	Level	Ref.
Pazopanib	Promising		III	31

Osteosarcoma

Treatment	Effect	Comments	Level	Ref.
Regorafenib	Promising	Improved PFS in comparison to placebo (but similar OS rates)	II	42, 43
Robatumumab	Poor		II/III	48
Pembrolizumab + cyclophosphamide	Poor		III	49
Sorafenib	Promising		III	19
Sorafenib + everolimus	Promising	P-ERK1/2 positive osteosarcoma	III	20
Gemcitabine + sirolimus	Promising	P-ERK1/2 positive osteosarcoma	III	47
Gemcitabine + docetaxel	Promising		III, IV	11, 30, 40
Apatinib	Promising	Recommended daily dose of 500 mg	III, IV	44, 45
Chemo-embolization (NCBA)	Promising	Pain relief	IV	119
Particle therapy (carbon ions, protons ± photons)	Promising		IV	37–39
CTX + RTX	Promising		IV	41
Pazopanib	Promising		IV	46

Ewing's sarcoma

Treatment	Effect	Comments	Level	Ref.
Robatumumab	Promising		III	48
Gemcitabine + docetaxel	Poor		III	30
Carbon ion radiotherapy + high-dose CTX	Promising		IV	54
Irinotecan + temozolomide	Promising	Effective in both paediatric and adult patients	IV	55

Chordoma

Treatment	Effect	Comments	Level	Ref.
Sorafenib	Promising		III	57
Imatinib	Promising	PDGFB or PDGFRB-positive chordoma	III, IV	58, 59
Particle therapy (carbons, protons)	Promising	Better outcome if planned target volume < 500 mm^3	IV	14
Pazopanib	Promising		IV	53
Sunitinib	Promising		IV	53

Combination therapy of sorafenib with mTOR-inhibitor everolimus in the same clinical setting results in a median PFS of five months (95% CI: two months to seven months), with tumours overexpressing both P-ERK1/2 (phosphoextracellular signal-regulated kinases 1/2) and P-RPS6 (phosphor-ribosomal protein 6) showing better response rates.[20] Likewise, combination therapy of gemcitabine and mTOR-inhibitor sirolimus is particularly effective in patients with metastatic

osteosarcomas positive for P-ERK1/2.[47] On the other hand, monotherapy with the IGF-1R (insulin-like growth factor receptor 1) inhibitor robatumumab is of limited clinical benefit in metastatic and unresectable osteosarcoma.[48] Also, the combination of immune checkpoint inhibitor pembrolizumab with cyclophosphamide has only limited activity in advanced osteosarcoma.[49]

Ewing's sarcoma

In primary localized Ewing's sarcoma, two chemotherapeutic approaches are today most commonly used, one developed by the Children Oncology Group (COG), and the other by an European collaboration within the Euro-E.W.I.N.G-99 and EWING-2008 studies. The COG-based regimen uses interval compressed vincristine, doxorubicin and cyclophosphamide, alternately given with ifosfamide and etoposide.[50] The European approach recommends vincristine, ifosfamide, doxorubicin and etoposide (VIDE), followed by vincristine, actinomycin D and cyclophosphamide or ifosfamide (VAC/VAI) in low-risk patients, or high-dose chemotherapy with busulfan and melphalan followed by autologous stem cell rescue in high-risk patients.[51]

While cytotoxic CTX is considered essential to achieve long-term remission in patients with localized Ewing's sarcoma and patients with primary pulmonary metastases only, it is far less effective for patients with primary extrapulmonary metastases, local recurrences or secondary metastases (Table 2).[52–54] Several chemotherapeutic agents are used in the setting of relapsed disease, including temozolomide and irinotecan, as well as the combination of gemcitabine and docetaxel.[30,55] While temozolomide and irinotecan achieve a disease control rate of over 70% in recurrent Ewing's sarcoma, combined therapy with gemcitabine and docetaxel achieves only moderate clinical response rates.[30] The IGF-1R inhibitor robatumumab shows a limited efficacy in a minority of patients with metastatic Ewing's sarcoma, with some patients remaining in long-term remission of > four years, however median overall survival amounted to only seven months.[48]

Chordoma

About 30% to 40% of chordomas will develop distant metastases, although the greater morbidity results from locoregional recurrence and destruction of adjacent structures.[56] Cytotoxic CTX is not recommended in advanced chordoma, as being of very limited efficacy only.[53] Yet, some alternative treatment options have been investigated in this setting (Table 2). For example, in unresectable or incompletely resected pelvic chordoma, particle therapy with carbon ions or protons leads to promising PFS and OS rates.[14] Notably, chordoma patients show better OS rates than patients with other sarcoma subtypes.[14] Furthermore, according to a small case series, treatment of chordomas with vascular endothelial growth factor (VEGF)-inhibitors pazopanib or sunitinib results in promising clinical response rates.[53] Even more, VEGF inhibitor sorafenib could effectively slow down tumour progression in advanced chordomas, with a nine-month PFS rate of 73%.[57] In platelet-derived growth factor beta (PDGFB) or platelet-derived growth factor beta receptor (PDGFRB) positive chordomas, the TKI imatinib – primarily used in the treatment of gastrointestinal stromal tumour (GIST) – can stabilize previously progressive advanced chordomas in up to 70% of cases.[58,59]

Soft tissue sarcomas

In the curative setting of high-risk extremity STS, systemic treatment consists of anthracyclines (doxorobucin or epirubicin) with or without ifosfamide.[60] Moreover, RTX is frequently applied before or following surgical resection, aiming at reducing local recurrence rates and thus improving patients' prognosis.[61] Prognosis in metastatic STS is generally poor, with median survival rates of approximately 18 months.[62] Thus, several local and systemic treatment options in recurrent, unresectable or metastatic STS have been tested over the past years, aiming at improving patients' outcome (Table 3).

Transarterial chemo-embolization can be used in locally unresectable STS, leading to a reduction in pain scores, promising local response rates and median OS rates of 21 months (range: 11 months to 30 months)[63] to 23.7 months (± 2.1 months).[64] Other therapeutic measurements to achieve LC in unresectable STS include – similar to bone sarcomas – conventional RTX[12,65] and particle therapy.[13,14,66] Definite RTX in patients with unresectable non-rhabdomyosarcoma STS was shown to result in median disease-free survival rates of 12 months (range 0.1 years to 9.4 years).[12,65] Likewise, particle therapy seems to be effective in unresectable STS, although studies identified in the current systematic review either reported on few STS cases only[13,14], or collectively analysed pelvic STS with retroperitoneal, chest wall- and abdominal wall-STS.[65] Of note, carbon ion radiotherapy seems to be more effective regarding LC in liposarcoma and undifferentiated pleomorphic sarcoma (UPS) as compared with malignant peripheral nerve sheath tumour or synovial sarcoma.[65,66]

Another locoregional treatment modality constitutes ILP with tumour necrosis factor alpha (TNFa) and melphalan. According to a study involving 17 patients, this treatment leads to near complete response/complete response and partial response in 12% and 58% of locally advanced, unresectable or metastatic STS of the extremities, respectively.[67] On the other hand, ILP with doxorubicin appears to be less effective.[67] Furthermore, isolated limb infusion, a less invasive alternative to ILP, can be performed – even repeatedly – in unresectable, recurrent extremity STS and achieve promising LC rates.[68]

Table 3. Treatment options for soft tissue sarcomas in general (sorted by level of evidence)

Treatment	Effect	Comments	Level	Ref.
Pazopanib	Promising	Non-adipocytic STS	II	79
Regorafenib	Promising	Non-adipocytic STS	II	78
Gemcitabine + dacarbazine	Promising	Better PFS and OS than for dacarbazine alone	II	74
Dacarbazine	Poor	Worse PFS and OS in comparison to combination therapy with gemcitabine	II	74
Nivolumab	Poor	Except for UPS, liposarcoma	II	23
Nivolumab + ipilimumab	Promising	Angiosarcoma, leiomyosarcoma, myxofibrosarcoma, liposarcoma, UPS	II	23
Doxorubicin + ifosfamide	Moderate	First line; may be chosen in case tumour shrinkage is main goal	II	4
Doxorubicin + evofosfamide	Moderate	First line; not superior to doxorubicin monotherapy	II	69
Aldoxorubicin	Promising	First line; superior to doxorubicin monotherapy	II	71
Doxorubicin	Promising	First-line therapy	II	4, 70
Gemcitabine + docetaxel	Moderate	Manageable toxicities; worse outcome than with doxorubicin	II, IV	70
Olaratumab + doxorubicin	Poor	Not superior to doxorubicin monotherapy	II, III	77, 85
Ridaforolimus	Promising	Particularly effective in patients previously benefiting from CTX	II, III	21, 22, 87
Isolated limb perfusion (TNF + melphalan)	Promising		III	67
Isolated limb perfusion (doxorubicin)	Moderate		III	67
Pembrolizumab	Poor	Except for UPS, dedifferentiated liposarcoma	III	25
Retaspimycin Hydrochloride	Promising		III	80
Axitinib + pembrolizumab	Promising	Particularly alveolar soft part sarcoma	III	82
Conatumumab + doxorubicin	Moderate	Not superior to doxorubicin monotherapy	III	84
Tasisulam sodium	Poor		III	5
Larotrectinib	Promising	TRK fusion-positive STS	III	76
(Chemo-)embolization	Promising		IV	63, 64
RTX	Promising		IV	12, 65
Isolated limb infusion	Promising	Repeated administration possible	IV	68
Particle therapy (carbons, protons)	Promising	Axial STS (pelvis, gluteal region, retroperitoneum, abdominal/chest wall)	IV	13, 14, 66
Topotecan + cyclophosphamide	Poor	Previous long-lasting response to CTX associated with improved prognosis	IV	18
Cyclophosphamide	Promising	Particularly effective in Irradiation-induced STS	IV	72

With regards to systemic treatment, the efficacy of various chemotherapeutic agents has been analysed in unresectable STS, including doxorubicin[4,69–71], aldoxorubicin,[71] cyclophosphamide,[72] topotecan in combination with cyclophosphamide,[18] trabectedin,[73] ifosfamide,[17] gemcitabine in combination with docetaxel,[16,70] dacarbazine,[74] and gemcitabine in combination with dacarbazine.[74]

The combination therapy of topotecan and cyclophosphamide has only limited activity in adult patients with relapsed or refractory paediatric-type STS.[18] However, patients with previous long-lasting response to induction CTX can achieve prolonged survival rates upon this combined regimen.[18] Furthermore, oral metronomic cyclophosphamide monotherapy may be applied in elderly patients with unresectable STS, especially in the case of irradiation-induced tumours.[72] One of the most hotly debated issues in first-line treatment concerns the efficacy of combining doxorubicin with an alkylating agent compared to single-agent doxorubicin treatment. Available studies have failed to demonstrate an overall survival advantage for the combination of doxorubicin with ifosfamide in patients with advanced STS compared with doxorubicin monotherapy, however the latter regimen may be chosen in case tumour shrinkage is a specific treatment goal.[4] Similarly, first-line combination of doxorubicin and evofosfamide was not shown to be associated with a treatment benefit in unresectable, metastatic STS in comparison to doxorubicin monotherapy.[69] On the other hand, first-line CTX with aldoxorubicin, a pro-drug of doxorubicin designed to improve concentrations of the agent within the tumour,[71,75] is associated with superior efficacy over doxorubicin with regards to tumour response and PFS in untreated, locally advanced, unresectable or metastatic STS.[71] Yet, OS rates are comparable for both treatment arms.[72] A randomized phase III study (Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft tissue sarcomas – GeDDiS) revealed that doxorubicin should be favoured as standard treatment in CTX-naïve, advanced STS instead of gemcitabine and docetaxel.[70] Also, combination CTX of dacarbazine with gemcitabine leads to significantly better PFS and OS in comparison with dacarbazine monotherapy in patients with pre-treated, advanced STS.[74] On the other hand, only modest anti-tumour activity is observed upon second- or third-line treatment of advanced STS with tasisulam sodium, an acylsulfonamide.[5] Thus, despite partially encouraging effects observed with novel chemotherapeutics, the agent of choice in advanced STS remains doxorubicin.[4,70,71]

In recent years, novel systemic anti-tumour therapeutics have been developed and – after showing promising results in various carcinomas – tested in STS, including TKIs,[76–79] immune checkpoint inhibitors,[23–25] mTOR-inhibitors[21] and other small molecules.[5,80] After partially dramatic effects in melanoma, renal cell cancer and bronchial carcinoma, immune checkpoint inhibitors were also tested in STS. Combination immunotherapy with nivolumab and ipilimumab, inhibiting immune checkpoints PD-1 and CTLA-4,

respectively, led to PFS and OS of 4.1 and 14.3 months, thus being comparable to currently available treatment options in patients with pre-treated, unresectable or metastatic STS.[23] On the other hand, nivolumab monotherapy was shown to be of only limited efficacy in most STS subtypes, except for UPS and liposarcoma.[23] Likewise, most STS subtypes show only moderate response to PD-1 inhibitor pembrolizumab, while clinically meaningful responses are seen in metastatic UPS and dedifferentiated liposarcoma.[25]

Due to the activity of TKIs imatinib and sunitinib in gastrointestinal stromal tumours, several kinase inhibitors have extensively been studied in advanced STS.[79] According to the Pazopanib expLorEd in SofT Tissue Sarcoma (PALETTE) and Regorafenib in patients with advanced soft tissue sarcoma (REGOSARC) trials, the multitarget TKIs pazopanib and regorafenib show clinically meaningful effects in non-adipocytic metastatic STS.[78,79] Notably, patients with adipocytic STS had been excluded from the PALETTE trial, based on conclusions of the phase II European Organisation for Research and Treatment of Cancer (EORTC) study 62043 revealing a low response rate upon pazopanib treatment.[81] Furthermore, the combination of the TKI axitinib with PD-1 inhibitor pembrolizumab is effective in advanced STS, with a three-month PFS of 65.6% exceeding the historical benchmark of 19% indicative of a clinically meaningful effect.[82,83]

Notably, studies combining doxorubicin with novel therapeutic agents in advanced STS have been published over the past years, aiming at improving tumour response. For example, the first-line combination of doxorubicin with the monoclonal antibody conatumumab, targeting tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), did not improve disease control in comparison to doxorubicin monotherapy.[84] Similarly, the phase III Doxorubicin Plus Olaratumab vs Doxorubicin Plus Placebo in Patients with Advanced Soft Tissue Sarcoma (ANNOUNCE) trial showed that the combination therapy of the monoclonal antibody olaratumab (platelet-derived growth factor receptor alpha (PDGFRa) inhibitor) with doxorubicin did not improve OS in patients with anthracycline-naïve advanced STS as compared with doxorubicin monotherapy,[85] despite promising preliminary results in a preceding phase II trial.[77] Notably, olaratumab received a conditional marketing authorization by the European Medicines Agency after the results of the phase II trial that was subsequently revoked following the publication of the phase III trial results.[85] On the other hand, the heat-shock protein 90 (HSP90) inhibitor retaspimycin hydrochloride targets PDGFRa and other molecules indirectly by blocking their conformational maturation, stability and activation.[80,86] Although only preliminary results are available, there is evidence that this molecular agent has some anti-tumour activity in pre-treated STS.[80] Another molecular targeted agent that has been investigated in pre-treated, advanced STS is the mTOR-inhibitor ridaforolimus, resulting in six-month PFS rates of around 23%, easily surpassing the six-month PFS threshold of 14% recommended by the EORTC to identify active treatments in pre-treated sarcomas.[21,22,83,87]. Patients previously showing response to conventional CTX seem to particularly benefit from subsequent treatment with ridaforolimus, delaying tumour progression in comparison to placebo.[87]

One of the most recent novel therapeutics investigated in advanced STS is the tropomyosin receptor kinase (TRK) inhibitor larotrectinib.[76] While TRK-fusions are found in over 90% of infantile fibrosarcomas and are even pathognomic in secretory breast carcinoma, they may be present in less than 5% of non-GIST STS.[88,89] Larotrectinib leads to 75% overall response rates in patients with pre-treated, advanced, TRK fusion-positive tumours, including STS.[77] Notably, adverse events are generally manageable, with grade III or IV adverse events occurring in merely 5% of patients.[76]

Although some already established chemotherapeutics as well as novel agents show promising results in advanced, unresectable, partially pre-treated STS, their administration in elderly, often multimorbid, patients is questionable. However, in elderly patients with advanced STS, any CTX has been shown to be associated with improved OS in comparison to best supportive care.[90] Nevertheless, considering that the positive influence of CTX in this study was lost in multivariate analysis and that many patients had been denied systemic treatment due to anticipated toxicities and co-morbidities, further studies are warranted to define the best treatment approach in this elderly population.[90]

Leiomyosarcoma

While CTX with high-dose ifosfamide has been shown to be of limited efficacy in advanced leiomyosarcoma,[17] second-line gemcitabine monotherapy achieved results similar to combination therapy of gemcitabine with docetaxel in relapsed or metastatic leiomyosarcoma (Table 4).[91] Considering the lower toxicity rate observed upon gemcitabine monotherapy, this approach should be favoured.[91] Furthermore, eribulin, a microtubule-dynamics inhibitor[92,93], led to better OS in advanced, pre-treated leiomyosarcoma in comparison to dacarbazine, while PFS was similar.[93] Moreover, trabectedin, a marine-derived drug,[73, 94] was associated with significantly improved PFS in patients with advanced leiomyosarcoma experiencing progression to previous CTX as compared with dacarbazine, whereas OS was comparable.[94]

Besides distinct chemotherapeutic agents, some TKIs and immune checkpoint inhibitors have also shown encouraging results in advanced leiomyosarcoma. Combination immunotherapy with ipilimumab and nivolumab led to an objective response rate of 16% in pre-treated,

Table 4. Treatment options for different histological subtypes of soft tissue sarcomas (sorted by level of evidence)

Leiomyosarcoma

Treatment	Effect	Comments	Level	Ref.
Gemcitabine	Promising	Second line	II	91
Gemcitabine + docetaxel	Moderate	Second line; similar efficacy to gemcitabine monotherapy, but increased toxicity rate	II	91
Nivolumab + Ipilimumab	Promising		II	23
Regorafenib	Promising	Better PFS in comparison to placebo	II	78
Sunitinib	Promising		III	95
Eribulin	Promising	Better OS in comparison to dacarbazine	II, IV	92, 93
Trabectedin	Promising	Better PFS in comparison to dacarbazine	II, IV	73, 94
Ifosfamide	Poor		IV	17

Liposarcoma

Treatment	Effect	Comments	Level	Ref.
Nivolumab + Ipilimumab	Promising		II	23
Regorafenib	Poor		II	78
Eribulin	Promising	Better OS in comparison to dacarbazine	II, IV	92, 93
Trabectedin	Promising	Better PFS in comparison to dacarbazine	II, IV	73, 94
Pembrolizumab	Promising	Dedifferentiated liposarcoma	III	25
Pazopanib	Moderate		III	99
Sunitinib	Promising		III	95
Amrubicin	Promising	TLS-CHOP translocated myxoid liposarcoma	III	98
Carbon ion radiotherapy	Promising		IV	66

Synovial sarcoma

Treatment	Effect	Comments	Level	Ref.
Pazopanib	Promising		II	79
Regorafenib	Promising		II	78
Gemcitabine + docetaxel	Poor		III	102
Carbon ion radiotherapy	Poor		IV	66
Ifosfamide	Promising		IV	17
Trabectedin	Moderate		IV	73

Alveolar soft part sarcoma

Treatment	Effect	Comments	Level	Ref.
Cediranib	Promising	Active in adults, but not in paediatric patients	III	104, 105
Crizotinib	Promising	TFE3 rearranged MET+ ASPS	III	106
Axitinib + pembrolizumab	Promising		III	82
Sunitinib	Promising		IV	103

Undifferentiated pleomorphic sarcoma

Treatment	Effect	Comments	Level	Ref.
Nivolumab + ipilimumab	Promising		II	23
Sunitinib	Moderate	Results based on small case number	III	95
Pembrolizumab	Promising		III	25

Angiosarcoma

Treatment	Effect	Comments	Level	Ref.
Paclitaxel	Promising	Similar anti-tumour effects as paclitaxel + bevacizumab combination therapy, but lower toxicity	II	96
Paclitaxel + bevacizumab	Moderate	Higher toxicity rates than with paclitaxel monotherapy	II, III	96, 111
Gemcitabine	Promising		IV	110
Pazopanib	Promising		IV	112

Malignant Solitary Fibrous Tumour

Treatment	Effect	Comments	Level	Ref.
Pazopanib	Promising		III	114
Sorafenib	Moderate		IV	113

Epithelioid Sarcoma

Valproic acid + bevacizumab + gemcitabine + docetaxel	Moderate	Epithelioid sarcoma, carcinosarcoma	III	118
Gemcitabine + docetaxel	Promising		IV	117

metastatic leiomyosarcomas, being comparable to the rates usually achieved with standard CTX as gemcitabine and docetaxel, or doxorubicin.[23] Furthermore, the multikinase inhibitor sunitinib is likewise effective in heavily pre-treated, advanced leiomyosarcoma.[95] As mentioned above, the multikinase inhibitor regorafenib was associated with a clinically relevant treatment effect in pre-treated, advanced, non-adipocytic STS, including leiomyosarcoma.[78]

Liposarcoma

In advanced or metastatic liposarcoma, cytotoxic CTX is generally of limited efficacy, with response rates of about 10%.[94,96,97] Thus, alternative treatment options have been investigated in different liposarcoma subtypes (Table 4). Carbon ion radiotherapy has shown good LC rates in patients with unresectable axial STS (besides pelvis, also including STS of the abdominal wall, chest wall and retroperitoneum).[66] Amrubicin, a synthetic 9-aminoanthracycline, may be administered as first-line therapy in unresectable or metastatic myxoid liposarcoma, leading to tumour response rates comparable to those achieved with doxorubicin, while having a lower toxicity profile.[98] Similar to leiomyosarcoma, both eribulin[92,93] and trabectedin[73,94] are associated with improved tumour response in comparison to dacarbazine in pre-treated, advanced or metastatic liposarcoma.[93,94] Moreover, immune checkpoint inhibitor therapy with nivolumab and ipilimumab can achieve anti-tumour effects in advanced liposarcoma comparable to those obtained with standard CTX regimens.[23]

Additionally, PD-1 inhibitor pembrolizumab is effective in pre-treated, metastatic dedifferentiated liposarcoma, leading to partial response and stable disease in 20% and 40% of patients, respectively.[25] According to a phase II study of patients with adipocytic tumours excluded from the PALETTE trial,[25] the multitarget TKI pazopanib was also effective in advanced liposarcoma, with PFS rates comparable to those observed in patients with non-adipocytic STS in the PALETTE trial.[99] Moreover, the multitarget TKI sunitinib has shown three-month PFS rates of more than 40% in advanced liposarcoma.[95] On the other hand, regorafenib, another multitarget TKI, was not shown to improve PFS or OS in patients with advanced, pre-treated liposarcoma, as compared with placebo.[78]

Synovial sarcoma

Synovial sarcomas constitute a rare, highly aggressive STS subtype, with a five-year cancer-specific survival probability of 66%.[100,101] In unresectable, recurrent or metastatic synovial sarcomas, various treatment options have been investigated (Table 4).

Particle therapy with carbon ions seems to be less effective in synovial sarcomas as compared with UPS or liposarcoma.[66] Systemically, combination CTX with gemcitabine and docetaxel shows little efficacy in advanced and metastatic synovial sarcoma.[103] Moreover, only modest response rates are observed with trabectedin.[73] On the other hand, high-dose ifosfamide has promising efficacy not only as a first line, but also as a second- and third-line systemic treatment in patients with refractory synovial sarcoma.[17] Furthermore, both the multikinase inhibitors pazopanib[79] and regorafenib lead to significantly improved PFS in synovial sarcoma patients previously treated with doxorubicin or other anthracyclines.[78]

Alveolar soft part sarcoma (ASPS)

Alveolar soft part sarcomas (ASPS) develop predominantly in young patients and often present with multiple metastases at initial diagnosis. Therefore, systemic treatment is required in order to improve patients' prognosis (Table 4). Besides the TKI sunitinib,[103] cediranib,[104,105] crizotinib[106] and axitinib,[82] have also been tested in ASPS, with encouraging results. In adult patients with metastatic ASPS, cediranib exhibits substantial single-agent activity.[104] In the paediatric population, on the other hand, response rates to cediranib are relatively lower.[105] This could, at least in part, be caused by the 30% dose reduction necessary in young patients.[105] In ASPS, TKI sunitinib can achieve partial response and stable disease in 28.6% and 71.4%, respectively, although prospective, randomized studies are needed to confirm the effects seen in the retrospective setting.[103]

One of the most recent studies investigating novel therapeutic approaches in STS analysed the activity and safety of the protein kinase inhibitor crizotinib in transcription factor binding to IGHM enhancer 3 (TFE3)-rearranged advanced or metastatic ASPS.[106] According to the Cross-tumoral Phase 2 With Crizotinib (CREATE) phase II clinical trial, a median PFS of 8.1 months (95% CI: 4.1 months to 12.8 months) could be achieved under crizotinib treatment, specifically in patients with MET+, TFE3-rearranged ASPS.[106] This is distinctly longer than the median PFS of 4.6 months (95% CI: 2.9 months[4] to 5.6 months and 95% CI: 3.7 months to 4.8 months)[79] usually observed in patients with advanced STS treated with doxorubicin or pazopanib.[4,79] Moreover, the combination of CTLA-4 inhibitor pembrolizumab and TKI axitinib (targeting VEGF-R) was shown to achieve three-month PFS rates of 72.7% with a manageable toxicity profile.[82,83] Yet, it should be noted that ASPS have a different biological behaviour as compared with other STS subtypes, wherefore response rates may not be directly comparable.[106]

Undifferentiated pleomorphic sarcoma

Metastases develop in 30% to 35% of patients treated with curative intent for primary localized UPS.[107,108] Thus, active treatments in advanced setting are required (Table 4). The multikinase inhibitor sunitinib has shown some anti-tumour activity in UPS according to a phase II study,

with a median PFS and OS of 2.5 (95% CI: 1.4 months to 5.5 months) and 13.6 months (95% CI: 3.1 months to not reached), respectively. However, the results have to be interpreted carefully due to the small number of cases included (n = 14).[95] Combination therapy of nivolumab and ipilimumab leads to clinically meaningful response rates in pre-treated, metastatic UPS, comparable to those observed for liposarcoma.[23] Moreover, pembrolizumab is likewise effective in metastatic UPS with an objective response rate of 40%, while other STS subtypes – except for dedifferentiated liposarcoma – show objective response rates between 0% and 10% for leiomyosarcoma and synovial sarcoma, respectively.[25]

Angiosarcoma

About 40% of patients with initially localized angiosarcoma will develop metastatic disease, being associated with a poor prognosis.[109] Clinically active systemic treatments have been investigated over the past years in advanced angiosarcoma, aiming at improving patients' prognosis (Table 4). Gemcitabine-based CTX is active in both RTX-induced and primary advanced angiosarcoma, with an overall response rate of 68% according to one retrospective analysis.[110] Moreover, the anti-microtubule agent paclitaxel in combination with VEGF-inhibitor bevacizumab has clinically meaningful anti-tumour activity in unresectable, locally advanced or metastatic angiosarcoma.[96,111] However, combination therapy of bevacizumab and paclitaxel is not superior to paclitaxel monotherapy, while being associated with higher toxicity rates.[111] Thus, paclitaxel monotherapy should be favoured in advanced or metastatic angiosarcoma.[96] Moreover, according to a retrospective case series, the TKI pazopanib slows disease progression and may even lead to the stabilization of taxane-resistant, unresectable cutaneous angiosarcoma.[112]

Malignant solitary fibrous tumour

It is expected that 35% to 45% of primarily localized malignant solitary fibrous tumours will develop metastatic disease during the course of their disease. In order to improve the outcome of patients in the advanced setting, some novel systemic therapies apart from conventional CTX have been investigated over the last few years (Table 4). For example, the TKIs sorafenib[113] and pazopanib[114] have been analysed for clinical efficacy in malignant or dedifferentiated solitary fibrous tumours. According to a small prospective case series, sorafenib exerts anti-tumour activity in this tumour entity, with two of five patients with previously progressive disease showing stabilization under sorafenib treatment.[113] Moreover, the results of a phase II single-arm study show that pazopanib leads to a partial response in up to 50% of patients with advanced malignant solitary fibrous tumours.[114]

Epithelioid sarcoma

Other than in most STS subtypes, lymphogenic metastases are frequently observed in epithelioid sarcomas, with a rather poor prognosis.[115,116] A retrospective analysis examining the efficacy of gemcitabine and docetaxel in patients with advanced epithelioid sarcoma demonstrated a clinical benefit rate of 83% and a median PFS of eight months.[117] Furthermore, the combination of the weak histone deacetylase inhibitor valproic acid, together with the VEGF-inhibitor bevacizumab and gemcitabine/docetaxel has also been investigated in advanced STS, including epithelioid sarcoma, aiming at modifying the tumour microenvironment to enhance anti-angiogenetic effects of bevacizumab.[118] According to the preliminary results of a phase I/II study, this combination therapy may be administered especially in epithelioid sarcoma and carcinosarcoma subtypes, showing moderate response rates.[118]

Discussion and conclusion

Despite improvements in treatment approaches, unresectable and/or metastatic bone and soft tissue sarcomas remain a therapeutic challenge. Only 17 of the 87 studies (19.5%) in the current systematic review were randomized and produced level II evidence, while 41 (47.1%) constituted evidence level IV studies (Fig. 3 and Fig. 4). Thus, the overall clinical evidence with regards to treatment options in advanced sarcoma may be only moderate. The relatively low number of randomized studies can in part be attributed to the rarity of sarcomas in general, but also to their heterogeneity, precluding generalization of treatment effects to all histological subtypes. Nevertheless, treatment plans should be individually tailored depending on the histological subtype, tumour location, systemic involvement and patient's general condition. Studies investigating immune checkpoint inhibitors in STS and bone sarcoma have discovered encouraging anti-tumour effects in advanced STS but only minor effects in bone sarcoma. Moreover, efficacy appears to be generally lower than in carcinomas, and further in-depth research on which patients might eventually benefit from immunotherapy is warranted. Targeted therapeutics and TKIs, on the other hand, lead to promising anti-tumour activity in both advanced bone and soft tissue sarcoma. Notably, some studies have demonstrated that molecular aberrations within the individual tumours are associated with higher response rates to specific treatments. Thus, future clinical trials may focus even more on molecular changes rather than the histological subtype only. For this purpose, already available data may be used to identify patients with advanced bone or soft tissue sarcoma who might potentially benefit from specific treatment options, using big-data approaches, machine learning and artificial intelligence.

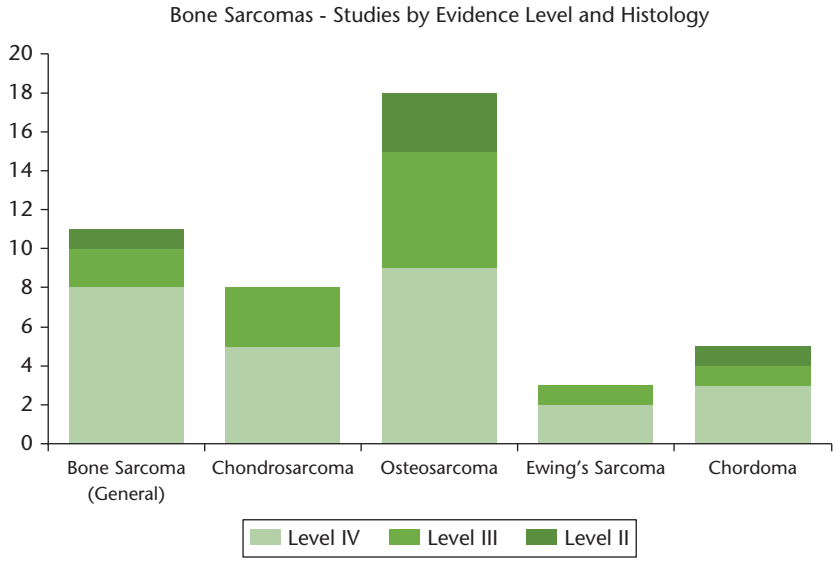

Fig. 3 Studies retrieved in the systematic review dealing with bone sarcomas, separated by entities and clinical evidence level (multiple entries possible).

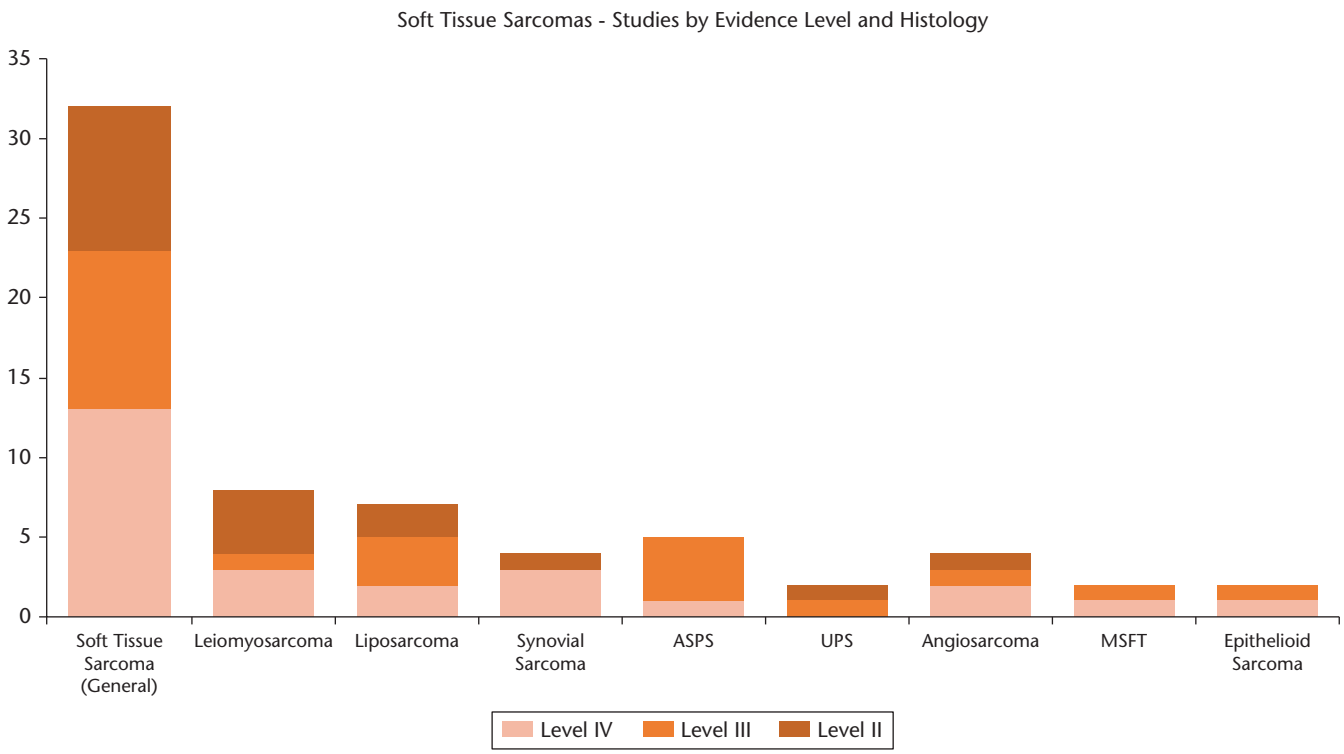

Fig. 4 Studies analysed in the systematic review investigating treatments in advanced soft tissue sarcomas, divided by histological subtypes and clinical evidence level (multiple entries possible).

AUTHOR INFORMATION

[1]Department of Orthopaedics and Trauma, Medical University of Graz, Graz, Austria.
[2]Division of Clinical Oncology, Internal Medicine, Medical University of Graz, Graz, Austria.
[3]Division of Orthopaedic Oncology and Sarcoma Surgery, Helios Klinikum Bad Saarow, Sarcoma Center Berlin-Brandenburg, Berlin, Germany.
[4]Chemotherapy Unit, IRCCS Istituto Ortopedico Rizzoli, Bologna University, Bologna, Italy.

Correspondence should be sent to: Andreas Leithner, Department of Orthopaedics and Trauma, Medical University of Graz, Auenbruggerplatz 5, 8036 Graz, Austria. Email: andreas.leithner@medunigraz.at

ICMJE CONFLICT OF INTEREST STATEMENT

DA reports payment for lectures including service on speaker's bureaus from Lilly GmbH and travel/accommodations/meeting expenses unrelated to activities listed from Implantcast GmbH, outside the submitted work.
EP reports Amgen, Daiichi Sankyo, Lilly, Eusa Pharma and Deciphera, support for travel to meetings for the study or other purposes from Lilly, Pharmamar and Takeda, provision of writing assistance, medicines, equipment, or administrative support from Daiichi Sankyo and Amgen, preclinical research study drug funding from Bristol Myers Squibb, Pfizer and PharmaMar, related to the work.
AL reports grants/grants pending and institutional educational grants from Johnson & Johnson, Alphamed, Globus and Implantec, outside the submitted work.
The other authors declare no conflict of interest relevant to this work.

FUNDING STATEMENT

Although none of the authors has received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article, benefits have been or will be received but will be directed solely to a research fund, foundation, educational institution, or other non-profit organization with which one or more of the authors are associated.

REFERENCES

1. Stiller CA, Trama A, Serraino D, et al; RARECARE Working Group. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. *Eur J Cancer* 2013;49:684–695.

2. Wibmer C, Leithner A, Zielonke N, Sperl M, Windhager R. Increasing incidence rates of soft tissue sarcomas? A population-based epidemiologic study and literature review. *Ann Oncol* 2010;21:1106–1111.

3. Tunn PU, Kettelhack C, Dürr HR. Standardized approach to the treatment of adult soft tissue sarcoma of the extremities. *Recent Results Cancer Res* 2009;179:211–228.

4. Judson I, Verweij J, Gelderblom H, et al; European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. 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;15:415–423.

5. Ryan CW, Matias C, Agulnik M, et al. A phase II study of tasisulam sodium (LY573636 sodium) as second-line or third-line treatment for patients with unresectable or metastatic soft tissue sarcoma. *Invest New Drugs* 2013;31:145–151.

6. Meyers PA, Schwartz CL, Krailo MD, et al; Children's Oncology Group. Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival—a report from the Children's Oncology Group. *J Clin Oncol* 2008;26:633–638.

7. Verma V, Denniston KA, Lin CJ, Lin C. A comparison of pediatric vs. adult patients with the Ewing sarcoma family of tumors. *Front Oncol* 2017;7:82.

8. Geller DS, Gorlick R. Osteosarcoma: a review of diagnosis, management, and treatment strategies. *Clin Adv Hematol Oncol* 2010;8:705–718.

9. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.

10. Group OLoEW. *The Oxford 2011 levels of evidence*. Oxford: Oxford Centre for Evidence-Based Medicine; 2011.

11. Palmerini E, Jones RL, Marchesi E, et al. Gemcitabine and docetaxel in relapsed and unresectable high-grade osteosarcoma and spindle cell sarcoma of bone. *BMC Cancer* 2016;16:280.

12. Doi H, Oh RJ, Miura H, Masai N, Shiomi H, Inoue T. Outcomes and toxicity of radiotherapy for refractory bone and soft tissue sarcomas. *Mol Clin Oncol* 2016;4:83–88.

13. Hayashi K, Yamamoto N, Shirai T, et al. Sequential histological findings and clinical response after carbon ion radiotherapy for unresectable sarcoma. *Clin Transl Radiat Oncol* 2017;2:41–45.

14. Demizu Y, Jin D, Sulaiman NS, et al. Particle therapy using protons or carbon ions for unresectable or incompletely resected bone and soft tissue sarcomas of the pelvis. *Int J Radiat Oncol Biol Phys* 2017;98:367–374.

15. Mavrogenis AF, Rossi G, Altimari G, et al. Palliative embolisation for advanced bone sarcomas. *Radiol Med* 2013;118:1344–1359.

16. Takahashi M, Komine K, Imai H, et al. Efficacy and safety of gemcitabine plus docetaxel in Japanese patients with unresectable or recurrent bone and soft tissue sarcoma: results from a single-institutional analysis. *PLoS One* 2017;12:e0176972.

17. Lee SH, Chang MH, Baek KK, et al. High–dose ifosfamide as second- or third-line chemotherapy in refractory bone and soft tissue sarcoma patients. *Oncology* 2011;80:257–261.

18. Hartmann JT, Issels RD, Nicolo KS, et al. Topotecan plus cyclophosphamide in adults with relapsed or refractory pediatric-type sarcoma: a retrospective analysis from the German Sarcoma Medical Oncology Group (AIO). *Invest New Drugs* 2015;33:1115–1122.

19. Grignani G, Palmerini E, Dileo P, et al. A phase II trial of sorafenib in relapsed and unresectable high-grade osteosarcoma after failure of standard multimodal therapy: an Italian Sarcoma Group study. *Ann Oncol* 2012;23:508–516.

20. Grignani G, Palmerini E, Ferraresi V, et al; Italian Sarcoma Group. Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial. *Lancet Oncol* 2015;16:98–107.

21. Chawla SP, Staddon AP, Baker LH, et al. Phase II study of the mammalian target of rapamycin inhibitor ridaforolimus in patients with advanced bone and soft tissue sarcomas. *J Clin Oncol* 2012;30:78–84.

22. Mita MM, Poplin E, Britten CD, et al. Phase I/IIa trial of the mammalian target of rapamycin inhibitor ridaforolimus (AP23573; MK-8669) administered orally in patients with refractory or advanced malignancies and sarcoma. *Ann Oncol* 2013;24:1104–1111.

23. D'Angelo SP, Mahoney MR, Van Tine BA, 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;19:416–426.

24. Paoluzzi L, Cacavio A, Ghesani M, et al. Response to anti-PD1 therapy with nivolumab in metastatic sarcomas. *Clin Sarcoma Res* 2016;6:24.

25. Tawbi HA, Burgess M, Bolejack V, 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;18:1493–1501.

26. Rozeman LB, Hogendoorn PC, Bovée JV. Diagnosis and prognosis of chondrosarcoma of bone. *Expert Rev Mol Diagn* 2002;2:461–472.

27. van Maldegem A, Conley AP, Rutkowski P, et al. Outcome of first-line systemic treatment for unresectable conventional, dedifferentiated, mesenchymal, and clear cell chondrosarcoma. *Oncologist* 2019;24:110–116.

28. Imai R, Kamada T, Araki N. Working Group For B, Soft-Tissue S. Clinical efficacy of carbon ion radiotherapy for unresectable chondrosarcomas. *Anticancer Res* 2017;37:6959–6964.

29. Italiano A, Mir O, Cioffi A, et al. Advanced chondrosarcomas: role of chemotherapy and survival. *Ann Oncol* 2013;24:2916–2922.

30. Fox E, Patel S, Wathen JK, et al. Phase II study of sequential gemcitabine followed by docetaxel for recurrent Ewing sarcoma, osteosarcoma, or unresectable or locally recurrent chondrosarcoma: results of Sarcoma Alliance for Research Through Collaboration Study 003. *Oncologist* 2012;17:321.

31. Stacchiotti S, Ferrari S, Redondo A, et al. Pazopanib for treatment of advanced extraskeletal myxoid chondrosarcoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2019;20:1252–1262.

32. Chow W, Frankel P, Ruel C, et al. Results of a prospective phase 2 study of pazopanib in patients with surgically unresectable or metastatic chondrosarcoma. *Cancer* 2020;126:105–111.

33. Jones RL, Katz D, Loggers ET, Davidson D, Rodler ET, Pollack SM. Clinical benefit of antiangiogenic therapy in advanced and metastatic chondrosarcoma. *Med Oncol* 2017;34:167.

34. Smeland S, Bielack SS, Whelan J, et al. Survival and prognosis with osteosarcoma: outcomes in more than 2000 patients in the EURAMOS-1 (European and American Osteosarcoma Study) cohort. *Eur J Cancer* 2019;109:36–50.

35. Bacci G, Ferrari S, Donati D, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremity in patients in the fourth and fifth decade of life. *Oncol Rep* 1998;5:1259–1263.

36. Whelan JS, Davis LE. Osteosarcoma, Chondrosarcoma, and Chordoma. *J Clin Oncol* 2018;36:188–193.

37. Matsunobu A, Imai R, Kamada T, et al; Working Group for Bone and Soft Tissue Sarcomas. Impact of carbon ion radiotherapy for unresectable osteosarcoma of the trunk. *Cancer* 2012;118:4555–4563.

38. Mohamad O, Imai R, Kamada T, Nitta Y, Araki N; Working Group for Bone and Soft Tissue Sarcoma. Carbon ion radiotherapy for inoperable pediatric osteosarcoma. *Oncotarget* 2018;9:22976–22985.

39. Ciernik IF, Niemierko A, Harmon DC, et al. Proton-based radiotherapy for unresectable or incompletely resected osteosarcoma. *Cancer* 2011;117:4522–4530.

40. Lee JA, Paik EK, Seo J, et al. Radiotherapy and gemcitabine-docetaxel chemotherapy in children and adolescents with unresectable recurrent or refractory osteosarcoma. *Jpn J Clin Oncol* 2016;46:138–143.

41. Hernberg MM, Kivioja AH, Böhling TO, Janes RJ, Wiklund TA. Chemoradiotherapy in the treatment of inoperable high-grade osteosarcoma. *Med Oncol* 2011;28:1475–1480.

42. Duffaud F, Mir O, Boudou-Rouquette P, et al; French Sarcoma Group. Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study. *Lancet Oncol* 2019;20:120–133.

43. Davis LE, Bolejack V, Ryan CW, et al. Randomized double-blind phase II study of regorafenib in patients with metastatic osteosarcoma. *J Clin Oncol* 2019;37:1424–1431.

44. Tian Z, Gu Z, Wang X, et al. Efficacy and safety of apatinib in treatment of osteosarcoma after failed standard multimodal therapy: an observational study. *Medicine (Baltimore)* 2019;98:e15650.

45. Xie L, Xu J, Sun X, et al. Apatinib for advanced osteosarcoma after failure of standard multimodal therapy: an open label phase II clinical trial. *Oncologist* 2019;24:e542–e550.

46. Longhi A, Paioli A, Palmerini E, et al. Pazopanib in relapsed osteosarcoma patients: report on 15 cases. *Acta Oncol* 2019;58:124–128.

47. Martin-Broto J, Redondo A, Valverde C, et al. Gemcitabine plus sirolimus for relapsed and progressing osteosarcoma patients after standard chemotherapy: a multicenter, single-arm phase II trial of Spanish Group for Research on Sarcoma (GEIS). *Ann Oncol* 2017;28:2994–2999.

48. Anderson PM, Bielack SS, Gorlick RG, et al. A phase II study of clinical activity of SCH 717454 (robatumumab) in patients with relapsed osteosarcoma and Ewing sarcoma. *Pediatr Blood Cancer* 2016;63:1761–1770.

49. Le Cesne A, Marec-Berard P, Blay JY, et al. Programmed cell death 1 (PD-1) targeting in patients with advanced osteosarcomas: results from the PEMBROSARC study. *Eur J Cancer* 2019;119:151–157.

50. Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. *J Clin Oncol* 2012;30:4148–4154.

51. Whelan J, Le Deley MC, Dirksen U, et al; Euro-E. W.I.N.G.99 and EWING-2008 Investigators. High-dose chemotherapy and blood autologous stem-cell rescue compared with standard chemotherapy in localized high-risk Ewing sarcoma: results of Euro-E.W.I.N.G.99 and Ewing-2008. *J Clin Oncol* 2018 Sept 6. doi: 10.1200/JCO.2018.78.2516 [Epub ahead of print].

52. Balamuth NJ, Womer RB. Ewing's sarcoma. *Lancet Oncol* 2010;11:184–192.

53. Lipplaa A, Dijkstra S, Gelderblom H. Efficacy of pazopanib and sunitinib in advanced axial chordoma: a single reference centre case series. *Clin Sarcoma Res* 2016;6:19.

54. Iwata S, Yonemoto T, Ishii T, et al. Efficacy of carbon-ion radiotherapy and high-dose chemotherapy for patients with unresectable Ewing's sarcoma family of tumors. *Int J Clin Oncol* 2013;18:1114–1118.

55. Palmerini E, Jones RL, Setola E, et al. Irinotecan and temozolomide in recurrent Ewing sarcoma: an analysis in 51 adult and pediatric patients. *Acta Oncol* 2018;57:958–964.

56. Fletcher CD, Bridge J, Hogendoorn PC, Mertens F. *WHO classification of tumours of soft tissue and bone*. 4th ed. Lyon: IARC; 2013.

57. Bompas E, Le Cesne A, Tresch-Bruneel E, et al. Sorafenib in patients with locally advanced and metastatic chordomas: a phase II trial of the French Sarcoma Group (GSF/GETO). *Ann Oncol* 2015;26:2168–2173.

58. Stacchiotti S, Longhi A, Ferraresi V, et al. Phase II study of imatinib in advanced chordoma. *J Clin Oncol* 2012;30:914–920.

59. Hindi N, Casali PG, Morosi C, et al. Imatinib in advanced chordoma: A retrospective case series analysis. *Eur J Cancer* 2015;51:2609–2614.

60. Gronchi A, Stacchiotti S, Verderio P, et al. Short, full-dose adjuvant chemotherapy (CT) in high-risk adult soft tissue sarcomas (STS): long-term follow-up of a randomized clinical trial from the Italian Sarcoma Group and the Spanish Sarcoma Group. *Ann Oncol* 2016;27:2283–2288.

61. Posch F, Partl R, Döller C, et al. Benefit of adjuvant radiotherapy for local control, distant metastasis, and survival outcomes in patients with localized soft tissue sarcoma: comparative effectiveness analysis of an observational cohort study. *Ann Surg Oncol* 2018;25:776–783.

62. Italiano A, Mathoulin-Pelissier S, Cesne AL, et al. Trends in survival for patients with metastatic soft-tissue sarcoma. *Cancer* 2011;117:1049–1054.

63. Jiang C, Wang J, Wang Y, et al. Treatment outcome following transarterial chemoembolization in advanced bone and soft tissue sarcomas. *Cardiovasc Intervent Radiol* 2016;39:1420–1428.

64. Ni JY, Sun HL, Chen YT, et al. Drug-eluting bead transarterial chemoembolization in the treatment for unresectable soft tissue sarcoma refractory to systemic chemotherapy: a preliminary evaluation of efficacy and safety. *J Cancer Res Clin Oncol* 2018;144:157–163.

65. Smith KB, Indelicato DJ, Knapik JA, et al. Definitive radiotherapy for unresectable pediatric and young adult nonrhabdomyosarcoma soft tissue sarcoma. *Pediatr Blood Cancer* 2011;57:247–251.

66. Imai R, Kamada T, Araki N; Working group for carbon ion radiotherapy for bone and soft tissue sarcomas. Carbon ion radiotherapy for unresectable localized axial soft tissue sarcoma. *Cancer Med* 2018;7:4308–4314.

67. Wray CJ, Benjamin RS, Hunt KK, Cormier JN, Ross MI, Feig BW. Isolated limb perfusion for unresectable extremity sarcoma: results of 2 single-institution phase 2 trials. *Cancer* 2011;117:3235–3241.

68. Wong J, Chen YA, Fisher KJ, Zager JS. Isolated limb infusion in a series of over 100 infusions: a single-center experience. *Ann Surg Oncol* 2013;20:1121–1127.

69. Tap WD, Papai Z, Van Tine BA, et al. Doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARC021): an international, multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2017;18:1089–1103.

70. Seddon B, Strauss SJ, Whelan J, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. *Lancet Oncol* 2017;18:1397–1410.

71. 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;1:1272–1280.

72. Mir O, Domont J, Cioffi A, et al. Feasibility of metronomic oral cyclophosphamide plus prednisolone in elderly patients with inoperable or metastatic soft tissue sarcoma. *Eur J Cancer* 2011;47:515–519.

73. Angarita FA, Cannell AJ, Abdul Razak AR, Dickson BC, Blackstein ME. Trabectedin for inoperable or recurrent soft tissue sarcoma in adult patients: a retrospective cohort study. *BMC Cancer* 2016;16:30.

74. García-Del-Muro X, López-Pousa A, Maurel J, et al; Spanish Group for Research on Sarcomas. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. *J Clin Oncol* 2011;29:2528–2533.

75. Kratz F, Warnecke A, Scheuermann K, et al. Probing the cysteine-34 position of endogenous serum albumin with thiol-binding doxorubicin derivatives. Improved efficacy of an acid-sensitive doxorubicin derivative with specific albumin-binding properties compared to that of the parent compound. *J Med Chem* 2002;45:5523–5533.

76. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in trk fusion-positive cancers in adults and children. *N Engl J Med* 2018;378:731–739.

77. 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;388:488–497.

78. Mir O, Brodowicz T, Italiano A, 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;17:1732–1742.

79. van der Graaf WT, Blay JY, Chawla SP, et al; EORTC Soft Tissue and Bone Sarcoma Group; PALETTE study group. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012;379:1879–1886.

80. Wagner AJ, Chugh R, Rosen LS, et al. A phase I study of the HSP90 inhibitor retaspimycin hydrochloride (IPI-504) in patients with gastrointestinal stromal tumors or soft-tissue sarcomas. *Clin Cancer Res* 2013;19:6020–6029.

81. 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;27:3126–3132.

82. Wilky BA, Trucco MM, Subhawong TK, et al. Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial. *Lancet Oncol* 2019;20:837–848.

83. Van Glabbeke M, Verweij J, Judson I, Nielsen OS, EORTC Soft Tissue and Bone Sarcoma Group. Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas. *Eur J Cancer* 2002;38:543–549.

84. Demetri GD, Le Cesne A, Chawla SP, et al. First-line treatment of metastatic or locally advanced unresectable soft tissue sarcomas with conatumumab in combination with doxorubicin or doxorubicin alone: a phase I/II open-label and double-blind study. *Eur J Cancer* 2012;48:547–563.

85. Tap WD, Wagner AJ, Papai Z, et al. ANNOUNCE: A randomized, placebo (PBO)-controlled, double-blind, phase (Ph) III trial of doxorubicin (dox) + olaratumab versus dox + PBO in patients (pts) with advanced soft tissue sarcomas (STS). *J Clin Oncol* 2019;37:LBA3. –LBA.

86. Neckers L. Heat shock protein 90: the cancer chaperone. *J Biosci* 2007;32:517–530.

87. Demetri GD, Chawla SP, Ray-Coquard I, et al. Results of an international randomized phase III trial of the mammalian target of rapamycin inhibitor ridaforolimus versus placebo to control metastatic sarcomas in patients after benefit from prior chemotherapy. *J Clin Oncol* 2013;31:2485–2492.

88. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol* 2018;15:731–747.

89. Amatu A, Sartore-Bianchi A, Siena S. *NTRK* gene fusions as novel targets of cancer therapy across multiple tumour types. *ESMO Open* 2016;1:e000023.

90. Garbay D, Maki RG, Blay JY, et al. Advanced soft-tissue sarcoma in elderly patients: patterns of care and survival. *Ann Oncol* 2013;24:1924–1930.

91. Pautier P, Floquet A, Penel N, et al. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcomas: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). *Oncologist* 2012;17:1213–1220.

92. Nakamura T, Tsukushi S, Asanuma K, et al. The clinical outcome of eribulin treatment in Japanese patients with advanced soft tissue sarcoma: a Tokai Musculoskeletal Oncology Consortium study. *Clin Exp Metastasis* 2019;36:343–350.

93. 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;387:1629–1637.

94. Demetri GD, von Mehren M, Jones RL, 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;34:786–793.

95. Mahmood ST, Agresta S, Vigil CE, et al. Phase II study of sunitinib malate, a multitargeted tyrosine kinase inhibitor in patients with relapsed or refractory soft tissue sarcomas. Focus on three prevalent histologies: leiomyosarcoma, liposarcoma and malignant fibrous histiocytoma. *Int J Cancer* 2011;129:1963–1969.

96. Ray-Coquard IL, Domont J, Tresch-Bruneel E, et al. Paclitaxel given once per week with or without bevacizumab in patients with advanced angiosarcoma: a randomized phase ii trial. *J Clin Oncol* 2015;33:2797–2802.

97. Italiano A, Toulmonde M, Cioffi A, et al. Advanced well-differentiated/dedifferentiated liposarcomas: role of chemotherapy and survival. *Ann Oncol* 2012;23:1601–1607.

98. Gupta S, Gouw L, Wright J, et al. Phase II study of amrubicin (SM-5887), a synthetic 9-aminoanthracycline, as first line treatment in patients with metastatic or unresectable soft tissue sarcoma: durable response in myxoid liposarcoma with TLS-CHOP translocation. *Invest New Drugs* 2016;34:243–252.

99. Samuels BL, Chawla SP, Somaiah N, et al. Results of a prospective phase 2 study of pazopanib in patients with advanced intermediate-grade or high-grade liposarcoma. *Cancer* 2017;123:4640–4647.

100. Sultan I, Rodriguez-Galindo C, Saab R, Yasir S, Casanova M, Ferrari A. Comparing children and adults with synovial sarcoma in the Surveillance, Epidemiology, and End Results program, 1983 to 2005: an analysis of 1268 patients. *Cancer* 2009;115:3537–3547.

101. Vlenterie M, Litière S, Rizzo E, et al. Outcome of chemotherapy in advanced synovial sarcoma patients: Review of 15 clinical trials from the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group; setting a new landmark for studies in this entity. *Eur J Cancer* 2016;58:62–72.

102. Pender A, Davis EJ, Chauhan D, et al. Poor treatment outcomes with palliative gemcitabine and docetaxel chemotherapy in advanced and metastatic synovial sarcoma. *Med Oncol* 2018;35:131.

103. Li T, Wang L, Wang H, et al. A retrospective analysis of 14 consecutive Chinese patients with unresectable or metastatic alveolar soft part sarcoma treated with sunitinib. *Invest New Drugs* 2016;34:701–706.

104. Kummar S, Allen D, Monks A, et al. Cediranib for metastatic alveolar soft part sarcoma. *J Clin Oncol* 2013;31:2296–2302.

105. Cohen JW, Widemann BC, Derdak J, et al. Cediranib phase-II study in children with metastatic alveolar soft-part sarcoma (ASPS). *Pediatr Blood Cancer*. 2019;66:e27987.

106. Schöffski P, Wozniak A, Kasper B, et al. Activity and safety of crizotinib in patients with alveolar soft part sarcoma with rearrangement of TFE3: European Organization for Research and Treatment of Cancer (EORTC) phase II trial 90101 'CREATE'. *Ann Oncol* 2018;29:758–765.

107. Weiss SW, Enzinger FM. Malignant fibrous histiocytoma: an analysis of 200 cases. *Cancer* 1978;41:2250–2266.

108. Fletcher CD, Gustafson P, Rydholm A, Willén H, Akerman M. Clinicopathologic re-evaluation of 100 malignant fibrous histiocytomas: prognostic relevance of subclassification. *J Clin Oncol* 2001;19:3045–3050.

109. Penel N, Marréaud S, Robin YM, Hohenberger P. Angiosarcoma: state of the art and perspectives. *Crit Rev Oncol Hematol* 2011;80:257–263.

110. Stacchiotti S, Palassini E, Sanfilippo R, et al. Gemcitabine in advanced angiosarcoma: a retrospective case series analysis from the Italian Rare Cancer Network. *Ann Oncol* 2012;23:501–508.

111. Bui N, Kamat N, Ravi V, Chawla S, Lohman M, Ganjoo KN. A multicenter phase II study of Q3 week or weekly paclitaxel in combination with bevacizumab for the treatment of metastatic or unresectable angiosarcoma. *Rare Tumors* 2018;10:2036361318771771.

112. Ogata D, Yanagisawa H, Suzuki K, Oashi K, Yamazaki N, Tsuchida T. Pazopanib treatment slows progression and stabilizes disease in patients with taxane-resistant cutaneous angiosarcoma. *Med Oncol* 2016;33:116.

113. Valentin T, Fournier C, Penel N, et al. Sorafenib in patients with progressive malignant solitary fibrous tumors: a subgroup analysis from a phase II study of the French Sarcoma Group (GSF/GETO). *Invest New Drugs* 2013;31:1626–1627.

114. Martin-Broto J, Stacchiotti S, Lopez-Pousa A, et al. Pazopanib for treatment of advanced malignant and dedifferentiated solitary fibrous tumour: a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2019;20:134–144.

115. Chase DR, Enzinger FM. Epithelioid sarcoma. Diagnosis, prognostic indicators, and treatment. *Am J Surg Pathol* 1985;9:241–263.

116. Armah HB, Parwani AV. Epithelioid sarcoma. *Arch Pathol Lab Med* 2009;133:814–819.

117. Pink D, Richter S, Gerdes S, et al. Gemcitabine and docetaxel for epithelioid sarcoma: results from a retrospective, multi-institutional analysis. *Oncology* 2014;87:95–103.

118. Monga V, Swami U, Tanas M, et al. A phase I/II study targeting angiogenesis using bevacizumab combined with chemotherapy and a histone deacetylase inhibitor (valproic acid) in advanced sarcomas. *Cancers (Basel)* 2018;10:E53.

119. Mavrogenis AF, Rossi G, Rimondi E, Calabrò T, Papagelopoulos PJ, Ruggieri P. Palliative embolization for osteosarcoma. *Eur J Orthop Surg Traumatol* 2014;24:1351–1356.