Making the Best of Available Options for Optimal Sarcoma Treatment

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Keywords

Advanced soft tissue sarcoma · Next-generation sequencing · Trabectedin · Treatment optimization

Abstract

For 35 years options for treating advanced soft tissue sarcoma (STS) were limited to doxorubicin, dacarbazine and ifosfamide. In 2007, trabectedin was approved. Since then, several other agents have become available and many more are in development, ushering in a new era in disease management. Considerable scope exists for improving outcomes of advanced STS through better trial design and improved patient care in everyday practice. After anthracycline failure, there are a range of treatment options and, increasingly, the choice of therapy is histology driven. Introduction of newer agents and optimising use of established agents such as trabectedin has led to an increase in overall survival of advanced STS patients. Optimising treatment with trabectedin is being achieved through more extensive experience in drug management, mainly associated with use in earlier lines and uninterrupted use until disease progression. Identification by next-generation sequencing of a significant proportion of cases of actionable mutations among patients with advanced STS suggests a move towards matched ther-

apy in future. As the armamentarium of active agents in advanced sarcoma increases, so too will the challenge of selecting the right drug for the right patient at the right time, in accordance with the patient's lifestyle and wishes.

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Introduction

Until relatively recently, evolution in the treatment of advanced soft tissue sarcoma (STS) had been advancing somewhat glacially. Doxorubicin, which was introduced in the early 1970s, was and continues to be standard front-line therapy in palliative situations. Introduction of dacarbazine and ifosfamide in the early and late 1980s, respectively, was followed by a near 20-year gap before trabectedin was approved in 2007. Since then, pazopanib (2012) and eribulin (2015) have been approved and, in 2016, olaratumab (in combination with doxorubicin) received a positive opinion for marketing authorization from the European Medicine Agency's Committee for Medicinal Products for Human Use. The future looks dramatically different, however, as multiple agents are in early phase development for treatment of advanced STS. Ongoing phase I/II trials are investigating immune-on-

Table 1. Proof-of-concept first-line therapies in mesenchymal tumours

Histology	Target	Agent
Gastrointestinal stromal tumour	KIT/PDGFR	Imatinib
Dermatofibrosarcoma protuberans	t(17–22) PDGFR	Imatinib
Perivascular epithelioid cell tumour (PECcoma)	mTor/TSC1/2	Rapamycin inhibitors
Giant cell tumour of bone	Rank/RankL	Denosumab
Pigmented villonodular synovitis	t(1–2) CSF-1	Anti-CSF-1
Inflammatory myofibroblastic tumour	ALK alteration	Crizotinib
Alveolar soft tissue sarcoma	VEGFR?	Anti-VEGFR

cology therapies, vaccine therapy, tyrosine kinase inhibitors, targeted therapies, and new chemotherapeutic agents [1–11].

As the armamentarium of effective treatments expands, sarcoma oncologists can expect to face additional pressure to treat the “right patient in the right place at the right time with the right diagnosis, in molecular subsets of histological subgroups of rare STS, with the right treatment sequence using the right individually-adapted schedule, in accordance with the patient’s wishes.” In the research setting, investigators are being challenged to individualise reproducible biomarkers of efficacy/resistance. As evidenced by proof-of-concept therapies in certain STS subtypes (Table 1), individualising targets can provide clues to the provenance of mesenchymal tumours. Investigating agents with target-driven activity in specific STS histotypes increases the probability of a positive outcome in phase II trials.

Key Factors Affecting STS Treatment Outcomes

In the clinical trials framework in a disease as complex as STS, study outcomes can be influenced materially by aspects of study methodology.

Given the unique natural evolution of STS subtypes showing survival rates that vary by histotype (Fig. 1) [12], differences in the histological profiles of patient populations in phase II and subsequent confirmatory clinical trials can lead to inconclusive results. Indeed, histological variation is thought to explain in part the absence of efficacy confirmation in phase III studies of doxorubicin ± palifosfamide (an active metabolite of ifosfamide) [13], and doxorubicin ± evofosfamide (a hypoxia-activated prodrug of ifosfamide) [14], after positive results had been demonstrated in phase II studies.

Investigator decisions can also be critical to the success of clinical trials. Aldoxorubicin (an albumin-binding pro-

drug of doxorubicin) showed promising activity versus doxorubicin in a phase II study in previously untreated patients with advanced STS [15]. However, rather than replicate this methodology to confirm activity, the phase III trial is comparing aldoxorubicin to treatment of investigator’s choice (dacarbazine, pazopanib, ifosfamide and doxorubicin) in pretreated patients with advanced STS [16], ultimately affecting the conclusions that can be drawn.

Selecting adequate primary endpoints also has a huge impact on the success of clinical trials. For example, the applicability of “tumour shrinkage” as an endpoint in studies of advanced STS is questionable. In the EORTC 62012 study of doxorubicin ± ifosfamide as first-line treatment of advanced STS, analysis of overall survival (OS) according to Response Evaluation Criteria In Solid Tumors (RECIST) showed no difference between patients with a complete response (CR)/partial response (PR) and those with stable disease (SD): 18.7 vs. 19.6 months [17]. It has since been established that, in advanced STS, the clinical benefit rate (CR + PR + SD) is of greater value than attempting to identify complete or partial responders. The absence of RECIST progression defines prognosis in advanced STS.

Questions also exist about the suitability of median OS as a primary endpoint in studies of advanced STS. In the phase III study of eribulin and dacarbazine in patients with advanced leiomyosarcoma and liposarcoma, the 2-month benefit in median OS in favour of eribulin was statistically significant (13.5 vs. 11.5 months; $p = 0.0169$), in the absence of differences between treatment arms in median progression-free survival (PFS; 2.6 months with both drugs; $p = 0.23$) or in response and disease control rates (RR 4%/SD 56% with eribulin and RR 5%/SD 53% with dacarbazine) [18]. In contrast, in 2 other large phase III randomized trials (STS-201 and PALETTE), the 2-month OS benefit observed in each study was not statistically significant, despite statistical differences between treatment arms in PFS [19, 20].

Fig. 1. Five-year survival rates in adult (≥ 20 years) patients with soft tissue sarcomas (all stages): 12 surveillance, epidemiology, and end results (SEER) geographical areas (US), 1988–2001 ($n = 28,758$). Data from [12]. * Excluding Kaposi's sarcoma.

Given that patients with advanced STS typically receive multiple consecutive lines of systemic treatment as well as loco-regional treatments (e.g., stereotactic radiation therapy, radiofrequency ablation, palliative surgery), selecting OS as an endpoint in clinical trials of first-line treatment may be somewhat ambitious considering that the final result could be “diluted” by additional active agents (e.g., approved drugs, broad-label drugs, off-label drugs, experimental drugs) used in the second line and later. In this context, results of the large randomized phase III ANNOUNCE trial of doxorubicin plus olaratumab versus doxorubicin monotherapy in patients with advanced or metastatic STS are eagerly awaited (ClinicalTrials.gov identifier: NCT02451943) [21]. Immunotherapy agents are also likely to interfere with OS outcomes in future. Although these agents have only a minimal effect on tumour shrinkage, they appear to stimulate the immune system and change the natural evolution of the disease course [22].

Considerable scope also exists for improving the management of advanced STS in daily practice. An analysis of 2,225 patients with advanced STS included in the French CONTICANET database indicated that a non-negligible 28% ($n = 625$) had not received any first-line treatment [23]. The fact that most non-treated patients were elderly underscores the need to develop a therapeutic program for this population. Of 1,600 patients who had received first-line therapy, only 950 received second-line therapy,

representing a 41% loss between the first and second lines. Although patient loss rates slowed between ensuing lines of therapy, they were still considerable (32% between second and third line, and 24% between third and fourth line).

Misclassification of sarcomas is another common problem in daily clinical practice. In the French Sarcoma Networks, for example, major discordance was found to be present in about 10% of cases [24]. This meant that each year, prior to implementing systematic review of pathological specimens, approximately 400 patients began treatment for a sarcoma that was not a sarcoma. Validating tumour histology prior to the start of treatment is essential for patient welfare and is also cost effective.

Importantly, decision making in advanced STS is highly complex and is dependent on diverse clinical presentations and tumour histologies [25]. Given the positive impact of clinical expertise on patient outcomes including improved survival [24], it is mandatory that systemic therapy be discussed in multidisciplinary tumour boards, especially in early lines of treatment in sarcoma patients [26].

Current STS Treatment Algorithm

The general treatment algorithm for STS is shown in Figure 2.

Fig. 2. General treatment algorithm in soft tissue sarcoma [26]. CT, chemotherapy; LMS, leiomyosarcoma; LPS, liposarcoma; RT, radiotherapy; SS, synovial sarcoma; UPS, undifferentiated pleomorphic sarcoma.

Table 2. Systemic treatment for pretreated patients with advanced soft tissue sarcoma [26]

Histological subtype	Agent (year approved)
All sarcomas (Europe)	Trabectedin (2007)
All sarcomas (except liposarcomas, Europe)	Pazopanib (2012)
All sarcomas (US)	Gemcitabine ± docetaxel (2015)
Leiomyosarcoma; Liposarcoma (US)	Trabectedin (2015)
Translocation-related sarcoma (Japan)	Trabectedin (2015)
Liposarcoma (Europe and US)	Eribulin (2016)
Leiomyosarcoma (Europe)	Gemcitabine (option, ESMO 2018 guidelines) Gemcitabine + dacarbazine (option, ESMO 2018 guidelines)
Alveolar soft tissue sarcoma	Anti-angiogenic agents (option, ESMO 2018 guidelines)
Angiosarcoma	Paclitaxel/Gemcitabine (option, ESMO 2018 guidelines)
All sarcomas	High-dose ifosfamide for synovial sarcoma and undifferentiated pleomorphic sarcoma (ESMO 2018 guidelines) Dacarbazine, especially for leiomyosarcoma and solitary fibrous tumours (option, ESMO 2018 guidelines)

Anthracycline-Based Therapy

In patients with localised STS, first-line treatment is surgery ± radiotherapy ± chemotherapy. Recently, the

ISG-STs 1001 study demonstrated the added value of administering 3 cycles of anthracycline + ifosfamide neoadjuvant chemotherapy in patients with localised high-grade STS of the extremities or trunk wall [27]. Accord-

Fig. 3. Comparison of outcomes in the largest studies of trabectedin performed in Europe ($n = 1,361$) [30–34].

ingly, standard first-line systemic therapy in patients who relapse may need to change in future to account for previous exposure to anthracycline + ifosfamide.

In the advanced STS setting, single-agent doxorubicin remains the gold standard for chemotherapy, although multi-agent chemotherapy with adequate-dose anthracycline + ifosfamide may be an option in situations where a tumour response is considered potentially advantageous and the patient has a good performance status [26].

Patients with metastatic disease are candidates for palliation in cases where at least 2 different metastatic sites are involved (e.g., lung and liver, lung and bone) or for potentially curative therapy in cases of isolated (and resectable) lung metastases.

In the palliative setting of metastatic STS (80–90% of patients), first-line therapy is doxorubicin ± olaratumab (PDGFR α inhibitor). This new treatment paradigm is based on results of a phase II trial, which showed that median OS was significantly prolonged with the combination compared with doxorubicin alone (26.5 vs. 14.7 months; hazard ratio 0.46; 95% CI 0.30–0.71; $p = 0.0003$) [28]. Because tumour overexpression of PDGFR α had no effect on patient outcomes, mechanisms for the added value of this combination are not fully understood [26]. While results of the confirmatory phase III trial (ClinicalTrials.gov identifier: NCT02451943) [21] are awaited, olaratumab is cur-

rently available in some countries for use in combination with doxorubicin as first-line treatment of advanced STS.

In the potentially curative setting of metastatic STS (10–20% of patients), a more aggressive approach is required. First-line treatment is anthracycline-based multi-agent chemotherapy followed by surgery. Multi-agent chemotherapy with adequate-dose anthracyclines plus ifosfamide may be treatment of choice, particularly in subtypes sensitive to ifosfamide, when a tumour response is felt to be potentially advantageous. In advanced leiomyosarcomas, where the activity of ifosfamide is far less convincing based on available retrospective evidence, doxorubicin plus dacarbazine is the recommended option.

After Anthracycline Failure

At the time of anthracycline failure, several treatment options exist and, increasingly, the choice of therapy is histology driven (Table 2) [26]. Steady improvement in the median OS of patients with metastatic STS [29] can be attributed to the introduction of new agents administered consecutively along multiple treatment lines and to optimising the sequential use of currently available agents. More extensive clinical experience has identified ways in which established agents can be used to advantage.

Table 3. Clinical outcomes by histological subtype in the RetrospectYon study of trabectedin in patients with advanced soft tissue sarcoma ($n = 885$)

Histology	No. of patients	PFS, months			OS, months	
		median	95% CI	PFS rate at 3 months, %	median	95% CI
Solitary fibrous sarcoma	13	7.6	1.6–13.7	69	14.3	0.8–27.8
Liposarcoma	161	6.1	4.5–7.6	64	15.0	11.0–19.0
Leiomyosarcoma	321	5.5	4.5–6.5	69	15.1	13.4–17.0
Fibrosarcoma	10	5.4	2.5–8.3	70	13.7	7.2–20.2
Epithelioid sarcoma	10	4.6	2.5–6.8	70	12.0	8.3–15.7
Synovial sarcoma	101	3.9	2.1–5.8	53	9.9	6.7–13.0
DSCRT	5	3.4	0.0–9.1	60	14.0	0.0–34.8
Myxofibrosarcoma	20	2.8	1.5–4.2	47	8.1	4.8–11.4
Stromal sarcomas	14	2.8	1.7–3.9	43	12.8	8.2–17.3
Rhabdomyosarcoma	15	2.6	0.8–4.4	47	5.4	4.6–6.3
Sarcoma NOS	82	2.4	2.0–2.8	42	6.4	4.6–8.1
MPNST	19	2.4	1.0–3.7	42	7.8	3.3–12.2
Miscellaneous	89	2.3	1.0–3.7	46	8.0	6.7–9.3
Angiosarcoma	9	0.9	0.8–1.0	22	6.6	0.5–12.6

Adapted with permission from [33]. PFS, progression-free survival; OS, overall survival; DSCRT, desmoplastic small-round-cell tumour; MPNST, malignant peripheral nerve sheath tumour; NOS, not otherwise specified.

Increased experience with the use of a specific agent can have a positive impact on patient outcomes. This association became clear when examining outcomes of large European studies of trabectedin (Fig. 3) [30–34]. The studies were conducted over an approximate 20-year timeframe and involved 1,361 patients with sarcoma. Over time, improvements were observed in median PFS, 6-month PFS rate, and median OS. Indeed, the median OS of 21.3 months achieved with single-agent trabectedin in a recent phase IV study represents a valuable step forward, and one that is difficult to attain when treating patients with advanced STS [34].

Several studies have provided background evidence for optimising use of trabectedin through improved drug management.

Post hoc analyses of pivotal clinical trials revealed that about one-third of patients treated with trabectedin in any line were able to benefit from long-term tumour control, remaining on treatment for at least 6 cycles [19, 35]. Importantly, this proportion increased to more than half of patients (53%) when trabectedin was administered early in treatment (i.e., in the second line) [35]. No other systemic therapy for advanced STS has been shown to provide such prolonged treatment [36].

The phase II T-DIS study demonstrated that, in patients who were progression-free after 6 cycles of trabect-

edin, continuing treatment until disease progression produced better outcomes than interrupting treatment and restarting at the time of progressive disease (median PFS 7.2 vs. 4.0 months; $p = 0.02$) [37]. The authors concluded that interrupting trabectedin treatment is not recommended in patients without progressive disease if tolerance is acceptable, even though trabectedin retains its activity at rechallenge [38].

Flexible administration is also a key element in the successful management of sarcoma with trabectedin. In a large retrospective analysis of advanced STS ($n = 885$), 47% of patients had their trabectedin dose reduced for adverse effects or other reasons [33]. By managing patients in this manner, the number of treatment-associated deaths was limited to 4 patients (0.5%).

The varying sensitivity of histological subtypes to chemotherapy and their differential prognoses are well recognised. Several studies of trabectedin involving pretreated patients with advanced STS of multiple subtypes indicated that median OS was longer in the leiomyosarcoma and liposarcoma subgroups than in other histologies [33, 39, 40], although clinical benefit with trabectedin has been demonstrated in numerous other histological subtypes (Table 3) [26, 33]. The best results to date with trabectedin in advanced sarcoma were reported in a recent phase IV study performed in a heterogeneous population

Fig. 4. Treatment selection from the patient's perspective in advanced soft tissue sarcoma. CT, chemotherapy; IV, intravenous; TT, targeted therapy.

of patients ($n = 218$) with multiple subtypes of advanced STS, most commonly leiomyosarcoma (42%), liposarcoma (23%) and synovial sarcoma (10%) [34]. Most patients (90%) had received a median of 1 previous line of chemotherapy. Patients received a median of 6 trabectedin cycles, with 124 patients (56.9%) receiving 6 or more cycles and up to a maximum of 44 cycles. In the response assessment, 58 patients (26.6%) had an objective response (CR + PR) and 143 patients (65.5%) achieved disease control (CR + PR + SD). The 3-month PFS rate was 70%, and 70% of patients were still alive 1 year after treatment; median OS was 21.3 months. As the study was non-interventional, these patient outcomes reflect real-world experience with trabectedin.

Outcomes with other approved drugs for advanced STS can also be influenced by factors such as treatment line, administration flexibility, and histological subtype. A post hoc analysis of the treatment benefit of pazopanib across key subgroups in the PALETTE registration study indicated that median PFS was prolonged when pazopanib was administered in the second line versus third and later lines (24.7 vs. 18.9 weeks) [41]. Likewise, median OS was prolonged when pazopanib was administered in the second line compared with more advanced lines (13.7 vs. 11.3 months). Although the PALETTE trial ultimately failed to show a statistically significant difference in median OS between pazopanib and placebo

Table 4. Actionable mutations in pre-treated patients with soft tissue sarcoma

Targets in some STS	Agents
Intimal sarcomas (MDM2)	MDM2 inhibitors
DD LPS (MDM2-CDK4)	MDM2/CDK4 inhibitors
STS with CDKN2A/B deletion	CDK4/6 inhibitor
STS with BRAF V600E	Vemurafenib + trametinib
STS with KDR T771R	VEGFR inhibitor
STS with Notch alterations	Notch inhibitors
STST with PI3K/AKT alterations	M-TOR inhibitors
STS with NTRK alterations	Larotrectinib

DD LPS, dedifferentiated liposarcoma; STS, soft tissue sarcoma.

[20], it is thought that this may reflect a “rebound” effect accelerating progression after patients discontinue pazopanib therapy [42]. Adapting the pazopanib dose to manage toxicities was also beneficial in terms of improving outcomes: if ≥ 1 dose reduction, median PFS was prolonged versus no dose reduction (27.7 vs. 11.9 weeks); if ≥ 1 dose interruption, median PFS was prolonged versus no interruption (21.3 vs. 11.0 weeks) [41]. Interestingly, a retrospective review of phase II (EORTC 62043) and phase III (EORTC 62072) studies of pazopanib in advanced STS indicated that concomitant administration of

gastric acid suppression therapy (e.g., proton pump inhibitors) for at least 80% of the time was associated with significantly decreased median PFS (2.8 vs. 4.6 months; $p = 0.008$) and median OS (8.0 vs. 12.6 months; $p < 0.001$) compared with non-use of gastric acid suppression therapy [43]. Pazopanib and the newer tyrosine kinase inhibitor, regorafenib, have both shown activity versus placebo in advanced STS, except in liposarcoma subgroups [44, 45]. Patients with metastatic adipocytic tumours were thus excluded from participation in the PALETTE study [20].

Future Treatment of Advanced STS

The identification by next-generation sequencing of a significant proportion of cases of actionable mutations among populations of patients with advanced STS suggests a move towards more personalized medicine in future [46, 47]. Next-generation sequencing has an important role in assisting diagnosis and selecting matched therapies [46]. Several proof-of-concept therapies already exist (Table 4). A new trial (MultiSarc) to be undertaken in France is the first study to implement exome and RNA sequencing to assist decision making in patients with advanced STS. Patients are to be randomised to either use or no use of next-generation sequencing which, in practice, is randomising patients between standard and adap-

tive approaches to treatment. Patients are to receive up to 6 cycles of a doxorubicin-based regimen. In the event of no disease progression and target identification in the next-generation sequencing arm, maintenance therapy will be proposed according to the specific genetic alteration.

The approach to treatment selection for upcoming generations of sarcoma patients is likely to be increasingly from the patient's perspective (Fig. 4). Both now and in future, it is essential that the treatment plan be shared with the patient along with any additional information that he/she requires or requests and include accurate quality of life data that the patient can interpret and understand.

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References

- 1 ClinicalTrials.gov. Activity and safety of regorafenib in patients with metastatic soft tissue sarcoma previously treated with anthracycline-based chemotherapy: a multinational, randomized, phase II, placebo-controlled trial. Available from: <https://clinicaltrials.gov/ct2/show/NCT01900743>.
- 2 Brodowicz T, Mir O, Wallet J, Italiano A, Blay JY, Bertucci F, et al. Efficacy and safety of regorafenib compared to placebo and to post-cross-over regorafenib in advanced non-adipocytic soft tissue sarcoma. *Eur J Cancer*. 2018 Aug;99:28–36.
- 3 Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetz SM, Hu J, 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 Nov;18(11):1493–501.
- 4 Attia S, Sankhala KK, Riedel RF, Robinson SI, Conry RM, Boland PM, et al. A phase 1B/phase 2A study of TRC105 (Endoglin Antibody) in combination with pazopanib (P) in patients (pts) with advanced soft tissue sarcoma (STS) [Abstract 11016]. *J Clin Oncol*. 2016;34(15 Suppl):11016.
- 5 ClinicalTrials.gov. A phase II study of mocetinostat administered with gemcitabine for patients with metastatic leiomyosarcoma with progression or relapse following prior treatment with gemcitabine-containing therapy. Available from: <https://clinicaltrials.gov/ct2/show/NCT02303262>.
- 6 ClinicalTrials.gov. A phase II multi-strata study of PM01183 as a single agent or in combination with conventional chemotherapy in metastatic and/or unresectable sarcomas. Available from: <https://clinicaltrials.gov/ct2/show/NCT02448537>.
- 7 D'Angelo SP, Shoushtari AN, Keohan ML, Dickson MA, Gounder MM, Chi P, et al. Combined KIT and CTLA-4 blockade in patients with refractory GIST and other advanced sarcomas: a phase Ib study of dasatinib plus ipilimumab. *Clin Cancer Res*. 2017 Jun;23(12):2972–80.
- 8 ClinicalTrials.gov. A phase 2 study of nivolumab and ipilimumab in advanced leiomyosarcoma of the uterus. Available from: <https://clinicaltrials.gov/ct2/show/NCT02428192>.
- 9 ClinicalTrials.gov. A pilot study of genetically engineered NY-ESO-1 specific NY-ESO-1^{259T} in HLA-A2+ patients with synovial sarcoma. Available from: <https://clinicaltrials.gov/ct2/show/NCT01343043>.

- 10 ClinicalTrials.gov. A phase 2 study of cabozantinib (XL184), a dual inhibitor of MET and VEGFR, in patients with metastatic refractory soft tissue sarcoma. Available from: <https://clinicaltrials.gov/ct2/show/NCT01755195>.
- 11 ClinicalTrials.gov. A clinicopathological phase II study of axitinib in patients with advanced angiosarcoma and other soft tissue sarcomas. Available from: <https://clinicaltrials.gov/ct2/show/NCT01140737>.
- 12 Gloeckler Ries LA, Ward KC, Young JL Jr. Sarcomas. In: Gloeckler Ries LA, Young JL, Keel GE, Eisner MP, Lin YD, Horner MJ, editors. SEER Survival Monograph: Cancer Survival Among Adults: US SEER Program, 1988–2001, Patient and Tumor Characteristics. National Cancer Institute, SEER Program, NIH. Pub. No. 07-6215, Bethesda, MD, 2007, pp 89–92.
- 13 Ryan CW, Merimsky O, Agulnik M, Blay JY, Schuetz SM, Van Tine BA, et al. PICASSO III: A phase III, placebo-controlled study of doxorubicin with or without palifosfamide in patients with metastatic soft tissue sarcoma. *J Clin Oncol*. 2016 Nov;34(32):3898–905.
- 14 Tap WD, Papai Z, Van Tine BA, Attia S, Ganjoo KN, Jones RL, 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 Aug;18(8):1089–103.
- 15 Chawla SP, Papai Z, Mukhametshina G, Sankhala K, Vasylyev L, Fedenko A, et al. First-line aldorubicin vs doxorubicin in metastatic or locally advanced unresectable soft-tissue sarcoma: a phase 2b randomized clinical trial. *JAMA Oncol*. 2015 Dec;1(9):1272–80.
- 16 Chawla SP, Ganjoo KN, Schuetz S, Papai Z, Van Tine BA, Choy E, et al. Phase III study of aldorubicin vs investigators' choice as treatment for relapsed/refractory soft tissue sarcomas [Abstract 11000]. *J Clin Oncol*. 2017;35(15 Suppl):11000.
- 17 Judson I, Verweij J, Gelderblom H, Hartmann JT, Schöffski P, Blay JY, 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 Apr;15(4):415–23.
- 18 Schöffski P, Chawla S, Maki RG, Italiano A, Gelderblom H, Choy E, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2016 Apr;387(10028):1629–37.
- 19 Demetri GD, Chawla SP, von Mehren M, Ritch P, Baker LH, Blay JY, 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 Sep;27(25):4188–96.
- 20 van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, 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 May;379(9829):1879–86.
- 21 ClinicalTrials.gov. A randomized, double-blind, placebo-controlled, phase 3 trial of doxorubicin plus olaratumab versus doxorubicin plus placebo in patients with advanced or metastatic soft tissue sarcoma. Available from: <https://clinicaltrials.gov/ct2/show/NCT02451943>.
- 22 Burgess MA, Bolejack V, Van Tine BA, Schuetz S, Hu J, D'Angelo SP, et al. Multi-center phase II study of pembrolizumab (P) in advanced soft tissue (STS) and bone sarcomas (BS): final results of SARC028 and biomarker analyses [Abstract 11008]. *J Clin Oncol*. 2017; 35(15 Suppl):11008.
- 23 Italiano A, Le Cesne A, Blay JY, Ray-Coquard IL, Mir O, Toulmonde M, et al. Patterns of care and outcome of patients (pts) with metastatic soft-tissue sarcoma (STS) according to histological subtype and treatment setting: the METASTAR study [Abstract 11014]. *J Clin Oncol*. 2016;34(15 Suppl):11014.
- 24 Blay JY, Soibinet P, Penel N, Bompas E, Duffaud F, Stoeckle E, et al.; NETSARC/RREPS and French Sarcoma Group–Groupe d'Etude des Tumeurs Osseuses (GSF-GETO) networks. Improved survival using specialized multidisciplinary board in sarcoma patients. *Ann Oncol*. 2017 Nov;28(11):2852–9.
- 25 Lurkin A, Ducimetière F, Vince DR, Decouvelaere AV, Cellier D, Gilly FN, et al. Epidemiological evaluation of concordance between initial diagnosis and central pathology review in a comprehensive and prospective series of sarcoma patients in the Rhone-Alpes region. *BMC Cancer*. 2010 Apr;10(1):150.
- 26 Casali PG, Abecassis N, Bauer S, Biagini R, Bielack S, Bonvalot S, et al.; ESMO Guidelines Committee and EURACAN. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018 Oct;29 Supplement_4:iv51–67.
- 27 Gronchi A, Ferrari S, Quagliuolo V, Broto JM, Pousa AL, Grignani G, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-ST5 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. *Lancet Oncol*. 2017 Jun;18(6):812–22.
- 28 Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D, 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 Jul;388(10043):488–97.
- 29 Italiano A, Mathoulin-Pelissier S, Cesne AL, Terrier P, Bonvalot S, Collin F, et al. Trends in survival for patients with metastatic soft-tissue sarcoma. *Cancer*. 2011 Mar;117(5):1049–54.
- 30 Yovine A, Riofrio M, Blay JY, Brain E, Alexandre J, Kahatt C, et al. Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. *J Clin Oncol*. 2004 Mar;22(5):890–9.
- 31 Le Cesne A, Blay JY, Judson I, Van Oosterom A, Verweij J, Radford J, et al. Phase II study of ET-743 in advanced soft tissue sarcomas: a European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial. *J Clin Oncol*. 2005 Jan;23(3):576–84.
- 32 Blay JY, Italiano A, Ray-Coquard I, Le Cesne A, Duffaud F, Rios M, et al. Long-term outcome and effect of maintenance therapy in patients with advanced sarcoma treated with trabectedin: an analysis of 181 patients of the French ATU compassionate use program. *BMC Cancer*. 2013 Feb;13(1):64.
- 33 Le Cesne A, Ray-Coquard I, Duffaud F, Chevreau C, Penel N, Bui Nguyen B, et al.; French Sarcoma Group. Trabectedin in patients with advanced soft tissue sarcoma: a retrospective national analysis of the French Sarcoma Group. *Eur J Cancer*. 2015 Apr; 51(6):742–50.
- 34 Buonadonna A, Benson C, Casanova J, Kasper B, López Pousa A, Mazzeo F, et al. A noninterventional, multicenter, prospective phase IV study of trabectedin in patients with advanced soft tissue sarcoma. *Anticancer Drugs*. 2017 Nov;28(10):1157–65.
- 35 Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetz SM, Staddon A, 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 Mar; 34(8):786–93.
- 36 Blay JY. Getting up-to-date in the management of soft tissue sarcoma. *Future Oncol*. 2018 May;14 10s:3–13.
- 37 Le Cesne A, Blay JY, Domont J, Tresch-Bruneel E, Chevreau C, Bertucci F, et al. Interruption versus continuation of trabectedin in patients with soft-tissue sarcoma (T-DIS): a randomised phase 2 trial. *Lancet Oncol*. 2015 Mar;16(3):312–9.
- 38 Kotecki N, Le Cesne A, Tresch-Bruneel E, Ray-Coquard I, Chevreau C, Bertucci F, et al. Impact of trabectedin interruption and subsequent rechallenge on progression in patients with advanced soft tissue sarcoma: long-term follow-up of the T-DIS trial. *Am J Clin Oncol*. 2018 Mar [Epub ahead of print].
- 39 Samuels BL, Chawla S, Patel S, von Mehren M, Hamm J, Kaiser PE, et al. Clinical outcomes and safety with trabectedin therapy in patients with advanced soft tissue sarcomas following failure of prior chemotherapy: results of a worldwide expanded access program study. *Ann Oncol*. 2013 Jun;24(6):1703–9.

- 40 Le Cesne A, Blay JY, Cupissol D, Italiano A, Delcambre C, Penel N, Isambert N, Chevreau C, Bompas E, Bertucci F, Chaigneau L, Piperno-Neumann S, Salas S, Rios M, Guillemet C, Bay J, Ray-Coquard IL, Mir O, Haddag L, Foulon S. 1396O – Results of a prospective randomized phase III T-SAR trial comparing trabectedin vs best supportive care (BSC) in patients with pretreated advanced soft tissue sarcoma (ASTS). *Ann Oncol* 2016;27(Suppl 6):Abstract 1396O.
- 41 Le Cesne A, Bauer S, Demetri GDS, van der Graaf WTA, Han G, Dezzani L, Ahmad Q, Gelderblom H. 1501P – Safety and efficacy of pazopanib (PAZ) in advanced soft tissue carcinoma (aSTS) by prior lines of therapy, age, and dose modifications: PALETTE subgroup analyses. *Ann Oncol* 2017;28(Suppl 5):Abstract 1501P.
- 42 Votrient-H-C-1141-II-07. EPAR – Assessment Report – 24 May 2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/001141/WC500131044.pdf.
- 43 Mir O, Touati N, Lia M, Litière S, Le Cesne A, Sleijfer S, et al. Impact on outcome of concomitant administration of gastric acid suppression (GAS) therapy and pazopanib in soft tissue sarcoma (STS) patients treated within EORTC 62043/62072 trials. P2-Poster 113. Presented at: [Connective Tissue Oncology Society \(CTOS\) Annual Meeting](#), 9–12 November 2016, Lisbon, Portugal.
- 44 Sleijfer S, Ray-Coquard I, Papai Z, Le Cesne A, Scurr M, Schöffski P, 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 Jul;27(19):3126–32.
- 45 Mir O, Brodowicz T, Italiano A, Wallet J, Blay JY, Bertucci F, 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 Dec;17(12):1732–42.
- 46 Gounder MM, Ali SM, Robinson V, Bailey M, Ferraro R, Patel NM, et al. Impact of next-generation sequencing (NGS) on diagnostic and therapeutic options in soft-tissue and bone sarcoma. *J Clin Oncol*. 2017;35(15 Suppl):11001.
- 47 Italiano A, Khalifa E, Laizet Y, Toulmonde M, Cousin S, Lucchesi C. Genetic landscape of soft-tissue sarcomas: moving toward personalized medicine. *J Clin Oncol*. 2017;35(15 Suppl):11002.