Histology-driven therapy for soft-tissue sarcomas

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Abstract
Soft-tissue sarcomas (STS) are a group of rare and heterogeneous mesenchymal tumours that can arise anywhere in the body. The aim of treatment in patients with advanced or metastatic STS is palliative and prognosis remains poor. Surgery remains the mainstay of treatment for localised disease, along with radiotherapy and chemotherapy has been traditionally reserved for metastatic disease, although it also has a role in the neoadjuvant and adjuvant setting. Several drugs have been investigated as second- or further-line therapy, with evidence of variable sensitivity across histological subtypes. As a result, the treatment scenario for STS is becoming more varied and the clinical decision on the best treatment options in the individual is usually driven by histology. In rare cancers such as STS, this tendency towards the use of histotype-tailored therapies will require further cooperation on a global scale as well as continuous research for methodological innovations in clinical research.

Key words: histologically directed treatment, histotype-tailored therapies, metastatic disease, soft-tissue sarcomas

Introduction

Soft-tissue sarcomas (STS) are a group of rare and heterogeneous mesenchymal tumours, including more than 50 different histological subtypes [1]. They recapitulate characteristics of muscle, fat, and fibrous supporting structures and can potentially arise everywhere in the body, although limbs and limb girdles are the most common primary sites [2]. Surgery remains the mainstay in the treatment of localised disease, along with radiotherapy which has been proven to be associated with a lower rate of local recurrence [3, 4]. Chemotherapy has been traditionally reserved for metastatic disease, although its role in the neoadjuvant and adjuvant setting has also been explored [5, 6]. As of today, the aim of treatment in patients with advanced or metastatic STS is palliative and prognosis remains poor (in old series, median survival has been in the order of 12 months [7]). In the last decade, several drugs have been tested as second- or further-line therapy, with evidence of a variable sensitivity to treatments across histological subtypes. On this basis, the treatment scenario for STS patients is becoming more and more varied and the clinical decision on the best sequence tends to be driven by histology.

Standard chemotherapy

Doxorubicin, alone or in combination with ifosfamide, has been widely used since 1970s in the treatment of advanced and metastatic STS. Doxorubicin as a single agent, administered at 75 mg/m^2 every 21 days, can produce an overall response rate of 20% with a median survival in the metastatic setting of one year [7, 8]. Unfortunately, doxorubicin use is limited by its well-known cardiotoxicity, which is mainly related to cumulative dose (>550 mg/m^2). An alternative is pegylated liposomal doxorubicin, which has a better tolerability profile, although convincing evidence of its efficacy compared with standard doxorubicin is lacking [9]. Ifosfamide is an alkylating agent which was introduced in the treatment of metastatic STS in the 1980s. As a single-agent, it is administered at doses of 6–9 g/m^2 and it is associated with an overall response rate of 20% [10]. Ifosfamide is highly effective in synovial sarcoma (SS) and has recently been reported as being effective in dedifferentiated liposarcoma when administered at high dose (14 g/sqm) as a continuous infusion (for 14 days every 4 weeks) [11, 12]. Ifosfamide is often used at high doses in second-line chemotherapy [13], mainly in synovial sar-

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comas and dedifferentiated liposarcomas, but also in patients already exposed to standard doses (~6–9 g/m^2). The toxicity profile is not negligible when administered over 4–5 days, but prolonged infusion over 14 days may make it more tolerable [14]. Conversely, ifosfamide showed poor activity in leiomyosarcoma, at least in retrospective series [6]. The role of the combination doxorubicin plus ifosfamide is still largely debated. In the metastatic setting, it has been proven to improve significantly progression free survival (PFS, 7.4 *vs* 4.6 months, p=0.0002) and response rate, but no significant impact on overall survival (OS) has been convincingly demonstrated [7]. On the basis of these data, the routine use of this combination for STS patients in the palliative setting cannot be regarded as standard. However, it can be considered in selected patients when tumour shrinkage is critical, for highly sensitive histotypes (i.e. synovial sarcoma) or in the adjuvant or neoadjuvant setting.

Histology-driven chemotherapy

Dacarbazine and temozolomide

Temozolomide is an imidazotetrazine derivative of the alkylating agent dacarbazine. Both dacarbazine and temozolomide have been reported to be effective in pretreated STS patients, but their activity, alone or in combination, has been found to be promising in leiomyosarcoma [15]. In particular, the association between dacarbazine and gemcitabine was proven to be safe, thus representing a valuable treatment option in leiomyosarcoma [16]. Temozolomide in combination with bevacizumab, as well as dacarbazine as a single agent, have been found to be effective in the treatment of locally advanced/metastatic solitary fibrous tumour (SFT) [17]. In a recent paper from Stacchiotti et al., an SFT responding to dacarbazine harboured a methylation of the O6-methylguanine-DNA-methyltransferase (MGMT) gene, whose predictive value in this disease is a subject of research [18].

Taxanes and gemcitabine

Despite being poorly active in STS, taxanes have showed remarkable activity in angiosarcoma. Paclitaxel is a mitotic inhibitor with potent anti-angiogenic activity at low doses [19]. Weekly paclitaxel (80 mg/m^2 on days 1, 8, and 15 of a 4-week cycle) in patients affected by unresectable angiosarcoma achieved a response rate at 6 months of 19% and a median PFS of 4 months [20]. Its activity seems to be of interest when face and scalp are primarily involved, which might be due to either a more limited tumour bulk or to superior delivery of the drug [21]. Gemcitabine alone (1000 mg/m^2 i.v. per week for 3 weeks, every 4 weeks) was also shown to be active in advanced, progressive angiosarcoma, with overall high response rates and a favourable tolerability profile [22]. Docetaxel and gemcitabine, both with modest activity in STS, have been combined based on their synergism, and proved to be active in the treatment of leiomyosarcoma, especially uterine, and possibly pleomorphic sarcomas with myogenic differentiation. However, toxicity is substantial and there are conflicting results in comparison with gemcitabine alone, which is far better tolerated and could thus be preferred in the palliative setting [23, 24].

Trabectedin

In Europe, trabectedin was approved in 2007 as a second line in the treatment of advanced STS after the failure of anthracycline-based regimens. Despite a low overall response rate (4–8%), trabectedin provides durable control of disease in STS (6-month PFS 24–35.5%; median OS 9.2–13.9 months) [25–28]. Enhanced benefits as longer PFS (4.4 *vs* 2.6 months) and time to progression (TTP, 4.4 *vs* 3.0 months), higher ORR (6.4 *vs* 4.9%) and a favorable trend in survival (17.4 *vs* 13.3 months, p=0.0575) were consistently found in patients treated with trabectedin earlier as second-line chemotherapy with an OS rate at 12 months of 68.1% [29]. Furthermore it has been proven to be particularly effective in leiomyosarcomas and in some translocation-related sarcoma (TRS [30]), including synovial sarcoma (SS), endometrial stromal sarcoma (ESS), alveolar soft part sarcoma (ASPS) [31], clear cell sarcoma (CCS) and, above all, myxoid-round cell liposarcoma (MRC-L). MLS account for about 30–35% of liposarcomas and carry characteristic chromosomal translocations, t(12;16)(q13;p11), resulting in the DDIT3-TLS, and the rarer t(12;22)(q13;q12), resulting in DDIT3-EWS fusion protein. In metastatic MRC-L, trabectedin is associated with an overall response rate of 50% with a median PFS of 17 months [32]. Its value has also been proven in the neoadjuvant setting, where a 13% pathologic complete response has been reported [33]. Toxicity is manageable and mainly represented by an asymptomatic increase in liver enzymes and transient fatigue, while more significant toxicities, such as neutropenia and thrombocytopenia, can be markedly reduced through appropriate dosing, steroid premedication and careful patient selection [34]. The selective mechanism of action of trabectedin in MRC-L is specific and related to its ability to cause functional inactivation of the oncogenic chimera with consequent repression of adipocytic differentiation [35]. A substantial impact on the tumour microenvironment by reducing the production of key inflammatory media-

tors has also been described, though the clinical meaning is not yet elucidated [36].

Cisplatin and etoposide

Malignant peripheral nerve sheet tumours (MPNST) are an exceedingly uncommon biologically aggressive STS of neural differentiation, with a poor prognosis. Skotheim et al. identified topoisomerase IIa as a target gene in MPNST, suggesting a potential role for etoposide (a topoisomerase IIa inhibitor) in the treatment of this disease [37]. The combination of etoposide with carboplatin showed some activity in MPNST cases refractory to first-line therapy but, due to its rarity, only limited data are available [38]. However, this subtype could potentially benefit from the association of ifosfamide and etoposide, which is currently under evaluation.

Histology-driven target therapy

Imatinib

Dermatofibrosarcoma protuberans (DFSP) is a rare sarcoma of the skin of fibroblastic/myofibroblastic origin, which usually affects the dermis and underlying soft tissue. Nearly 90% of DFSPs are characterized by the presence of a rearrangement of chromosomes 17 and 22, which can be represented by both translocation t(17;22) (q22; q13) or by a supernumerary ring chromosome containing several copies of the t(17;22) breakpoint region. This genetic aberration results in the fusion of the COL1A1 and PDGFB genes, subsequent PDGFB upregulation under the control of the COL1A1 promoter and autocrine/paracrine stimulation through PDGFRα and PDGFRβ, which is thought to be a key point in DFSP pathogenesis. The identification of a specific pathway driving the development of DFSP, provided the background for testing imatinib activity in this disease; in 2005, McArthur et al. analysed the efficacy of imatinib, at the dose of 400 mg twice a day, in the treatment of six patients with locally advanced DFSP and two patients with metastatic disease. Interestingly, all the patients with t(11;22) translocation had a partial response [39]. These preliminary data were confirmed in a subsequent paper by Stacchiotti et al. [40]. Today, imatinib is approved in the US and Europe for the treatment of unresectable DFSP. Although wide surgical excision remains the standard of care, patients with locally advanced disease not suitable for surgical excision should be started on neoadjuvant imatinib, with the aim of achieving a response, followed by surgery.

Sirolimus

Perivascular epithelioid cell tumours (PEComas) belong to the STS family, and are marked by inactivating tumour suppressor complex (TSC) gene mutations. The loss of TSC, which normally acts as an inhibitor of the mammalian target of rapamycin (mTor), leads to a constitutive activation of the mTor pathway, which is thought to be crucial in the pathogenesis of this disease [41, 42]. Sirolimus acts by blocking mTor activation of downstream kinases and restoring balance in cells with defective TSC gene function. Evidence from the literature suggests that treatment with sirolimus induces radiological response in patients affected by PEComa and is associated with a clinical benefit, though response duration may be short-lasting [43–45].

Crizotinib

Half of all inflammatory myofibroblastic tumours (IMTs) carry rearrangements of the anaplastic lymphoma kinase (ALK) locus on chromosome 2p23, causing aberrant ALK expression [46]. Distant metastases occur primarily in ALK-negative IMTs, but local recurrence occurs regardless of ALK expression [46, 47]. In these patients crizotinib was proven to induce a long-term substantial partial response [48]. In addition, crizotinib showed good tolerability profile, also with long-term administration.

Pazopanib

Preclinical studies showed that VEGF is over-expressed and that circulating angiogenic factor levels correlate with extent of disease and risk of recurrence in patients with STS. Pazopanib, an oral angiogenesis inhibitor targeting VEGFR and PDGFR, was initially explored in a phase II study in patients with progressive STS stratified by histology (adipocytic STS *versus* leiomyosarcoma *versus* SS *versus* other eligible STS subtypes). The rate of PFS at 12 weeks, which was the primary endpoint, was 44% for leiomyosarcoma, 49% for SS and 39% for other types of sarcoma. The adipocytic stratum showed insufficient activity (26%) [49]. A subsequent randomised phase III study confirmed the activity of pazopanib in non-adipocytic progressive STS, showing a PFS of 4.6 months for pazopanib compared with 1.6 months for placebo ($p<0.0001$). A positive trend favouring pazopanib was also recorded in overall survival (12.5 months *versus* 10.7 months), without reaching statistical significance ($p=0.25$). No differences in efficacy were recorded among different histological subtypes [50].

Sorafenib

Sorafenib is an oral small molecule B-RAF and VEGFR inhibitor tested in many different subtypes of STS; several phase II studies are reported in the literature, and activity seems to be largely variable depending on histology.

Preliminary data from a phase II study on recurrent metastatic sarcoma suggested a potential activity of sorafenib (800 mg/day) in angiosarcoma and leiomyosarcoma [51]. A subsequent study from Ray-Coquard et al. [52] showed only limited activity of the drug in angiosarcoma (no response in chemotherapy naive patients, 23% response rate in the pretreated population) and short duration of tumour control. Conversely, its potential activity in metastatic leiomyosarcoma has been recently confirmed in a phase II study from Santoro et al. [53]. Preliminary results have also been reported from the French Sarcoma Group in progressive epithelioid hemangioendothelioma [54] in which the 9-month progression-free survival rate was 30.7%, and in SFT [55], in which two out of the five treated patients achieved 9 months' disease control, but sorafenib needs to be validated in larger cohort of patients. Gounder et al. retrospectively evaluated data from 26 patients with desmoid-type fibromatosis treated with sorafenib (400 mg/day), and reported 25% partial response rate and 70% stable disease rate at 6 months [56]. Interestingly, 70% of the patients reported a rapid improvement in symptoms during treatment, suggesting that response was more a function of disease biology (APC mutation for intra-abdominal desmoids *versus* b-catenin mutation commonly observed in others) than due to sorafenib's anti-angiogenic effect.

Sunitinib

Alveolar soft part sarcoma (ASPS) is a rare chemoresistant subtype of STS. The upstream target analysis showed a consistent activation of PDGFR, as well as EGFR, MET and RET pathways. VEGFR axis has also been proven to be occasionally activated. The downstream target analysis showed a strong activation of phosphatidylinositol 3-kinase/AKT, extracellular signal-regulated kinases1/2, mTOR and its targets, without any upstream mTOR effector deregulation. These preclinical findings provided a rationale for the use of sunitinib malate, an oral receptor tyrosine kinase inhibitor targeting PDGFR, VEGFR and RET receptors [57]. Sunitinib, at the dose of 37.5 mg once daily, was tested in nine patients with progressive, advanced ASPS, reporting partial response as best response in five cases, stable disease in three, and progression in one [58]. Encouraging results were also reported for SFT. In a case series analysis, Stacchiotti et al. reported the use of sunitinib malate in 11 patients with progressive metastatic SFT resistant to chemotherapy, with six non-dimensional responses (all with Response Evaluation Criteria in Solid Tumors [RECIST] "stable disease"), one patient with stable disease, and three with progressive disease, according to Choi criteria [59]. The same group reported activity of sunitinib malate in a clear cell sarcoma, a rare STS variant expressing the melanocyte-specific form of the microphthalmia transcription factor (MITF) and showing PDGFRB activation [60].

Ongoing studies

Several ongoing clinical trials aim to explore the value of histotype-tailored treatment. An example is the ongoing phase III study from the Italian Sarcoma Group, which is comparing standard neoadjuvant chemotherapy of epirubicin plus ifosfamide *versus* histology-driven chemotherapy, in localized high-risk STS. Five histological groups (80% STS) are included in the study: leiomyosarcoma, MRC-L, SS, MPNST and undifferentiated pleomorphic sarcoma. The histology-driven chemotherapy for these groups are, respectively, gemcitabine plus dacarbazine, trabectedin, high-dose ifosfamide, ifosfamide plus etoposide and gemcitabine plus docetaxel. The primary end point will be disease-free survival (DFS) and, secondarily, OS [61]. The ANGIO-TAX-PLUS is a phase II randomised study from the French Sarcoma Group exploring the value of adding bevacizumab to weekly paclitaxel [62] in metastatic and locally advanced angiosarcoma, while the LMS03 from UNICANCER is a phase II study exploring the efficacy of gemcitabine with pazopanib as second-line treatment in patients with metastatic leiomyosarcoma. Cediranib is a new anti-angiogenic drug whose activity in the treatment of ASPS is under evaluation in an ongoing phase II study [63]. Conversely, other studies aim to explore the activity of a new compound in different histological subtypes of STS sharing the same genetic abnormality: this is the case in the CREATE study, which is assessing anti-tumour activity of crizotinib in patients with a variety of STS (IMT, ASPS, CCS and alveolar rhabdomyosarcoma), harbouring alterations leading to ALK and/or MET activation [64].

Conclusions

During the last decade, the number of treatment options available for STS patients has increased substantially, although most new agents have anti-tumour activity confined to specific histological subtypes. In a rare group of cancers such as STS, this tendency toward the use of histotype-tailored therapies will require further cooperation on a global scale, as well as continuous research for methodological innovations in clinical research.

References

1. Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F, WHO Classification of Tumours of Soft Tissue and Bone. Fourth ed 2013.
2. Clark MA, Fisher C, Judson I, Thomas JM. Soft-tissue sarcomas in adults. N Engl J Med. 2005;353(7):701-11.
3. Pisters PW, O'Sullivan B, Maki RG. Evidence-based recommendations for local therapy for soft tissue sarcomas. J Clin Oncol. 2007;25(8):1003-8.
4. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol. 1998;16(1):197-203.
5. Gronchi A, Casali PG. Adjuvant therapy for high-risk soft tissue sarcoma in the adult. Curr Treat Options Oncol. 2013;14(3):415-24.
6. Lorigan P, Verweij J, Papai Z, et al. Phase III trial of two investigational schedules of ifosfamide compared with standard-dose doxorubicin in advanced or metastatic soft tissue sarcoma: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol. 2007;25(21):3144-50.
7. Van der Graaf WTA, Judson I, Verweij J, et al. Results of a randomised phase III trial (EORTC 62012) of single agent doxorubicin *versus* doxorubicin plus ifosfamide as first line chemotherapy for patients with advanced, soft tissue sarcoma: a survival study by the EORTC Soft Tissue and Bone Sarcoma Group [abstract]. 2012.
8. Scurr M, Judson I. Neoadjuvant and adjuvant therapy for extremity soft tissue sarcomas. Hematol Oncol Clin North Am. 2005;19(3):489-500, vi.
9. Judson I, Radford JA, Harris M, et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) *versus* doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer. 2001;37(7):870-7.
10. Tascilar M, Loos WJ, Seynaeve C, et al. The pharmacologic basis of ifosfamide use in adult patients with advanced soft tissue sarcomas. Oncologist. 2007;12(11):1351-60.
11. Martin-Liberal J, Alam S, Constantinidou A, et al. Clinical activity and tolerability of a 14-day infusional ifosfamide schedule in soft-tissue sarcoma. Sarcoma. 2013;2013:868973.
12. Sanfilippo R, Constantinidou A, Bertulli R, et al. Sensitivity of well-differentiated/dedifferentiated liposarcoma (WD/DD) and myxoid round cell/liposarcoma (MRCL) to high-dose ifosfamide: combined analysis from two European referral institutions [abstract 10023]. J Clin Oncol. 2011;29(suppl).
13. Le Cesne A, Antoine E, Spielmann M, et al. High-dose ifosfamide: circumvention of resistance to standard-dose ifosfamide in advanced soft tissue sarcomas. J Clin Oncol. 1995;13(7):1600-8.
14. Meazza C, Casanova M, Luksch R, et al. Prolonged 14-day continuous infusion of high-dose ifosfamide with an external portable pump: feasibility and efficacy in refractory pediatric sarcoma. Pediatr Blood Cancer. 2010;55(4):617-20.
15. Penel N, Van Glabbeke M, Marreaud S, et al. Testing new regimens in patients with advanced soft tissue sarcoma: analysis of publications from the last 10 years. Ann Oncol. 2011;22(6):1266-72.
16. Losa R, Fra J, Lopez-Pousa A, et al. Phase II study with the combination of gemcitabine and DTIC in patients with advanced soft tissue sarcomas. Cancer Chemother Pharmacol. 2007;59(2):251-9.
17. Park MS, Patel SR, Ludwig JA, et al. Combination therapy with temozolamide and bevacizumab in the treatment of hemangiopericytoma/solitary fibrous tumor [abstract 10512]. J Clin Oncol. 2008;26(15 Suppl).
18. Stacchiotti S, Tortoreto M, Bozzi F, et al. Dacarbazine in solitary fibrous tumor: a case series analysis and preclinical evidence vis-a-vis temozolomide and antiangiogenics. Clin Cancer Res. 2013;19(18):5192-201.
19. Pasquier E, Honore S, Pourroy B, et al. Antiangiogenic concentrations of paclitaxel induce an increase in microtubule dynamics in endothelial cells but not in cancer cells. Cancer Res. 2005;65(6):2433-40.
20. Penel N, Bui BN, Bay JO, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. J Clin Oncol. 2008;26(32):5269-74.
21. Schlemmer M, Reichardt P, Verweij J, et al. Paclitaxel in patients with advanced angiosarcomas of soft tissue: a retrospective study of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer. 2008;44(16):2433-6.
22. 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(2):501-8.
23. Duffaud F, Pautier P, Nguyen BB, et al. A pooled analysis of the final results of the two randomized phase II studies comparing gemcitabine (G) vs gemcitabine 1 docetaxel (G+D) in patients (pts) with metastatic/relapsed leiomyosarcoma (LMS) [abstract 13450]. Ann Oncol. 2010;21(Suppl 8):viii 408.
24. Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. J Clin Oncol. 2007;25(19):2755-63.
25. Garcia-Carbonero R, Supko JG, Manola J, et al. Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy. J Clin Oncol. 2004;22(8):1480-90.
26. Le Cesne A, Blay JY, Judson I, et al. Phase II study of ET-743 in advanced soft tissue sarcomas: a European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial. J Clin Oncol. 2005;23(3):576-84.
27. Yovine A, Riofrio M, Blay JY, et al. Phase II study of ectein-

ascidin-743 in advanced pretreated soft tissue sarcoma patients. J Clin Oncol. 2004;22(5):890-9.
28. Demetri GD, Chawla SP, von Mehren M, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. J Clin Oncol. 2009;27:4188-96.
29. Blay JY, Casali P, Nieto A, et al. Efficacy and safety of trabectedin as treatment for advanced or metastatic liposarcoma or leiomyosarcoma. Future Oncol. 2014;10:59-68.
30. Le Cesne A, Cresta S, Maki RG, et al. A retrospective analysis of antitumour activity with trabectedin in translocation-related sarcomas. Eur J Cancer. 2012;48(16):3036-44.
31. Pink D, Bertz-Lepel J, Busemann C, et al. Efficacy of trabectedin in patients with advanced or metastatic alveolar soft-part sarcoma. Onkologie. 2012;35:249-52.
32. Grosso F, Sanfilippo R, Virdis E, et al. Trabectedin in myxoid liposarcomas (MLS): a long-term analysis of a single-institution series. Ann Oncol. 2009;20(8):1439-44.
33. Gronchi A, Bui BN, Bonvalot S, et al. Phase II clinical trial of neoadjuvant trabectedin in patients with advanced localized myxoid liposarcoma. Ann Oncol. 2012;23(3):771-6.
34. Grosso F, Dileo P, Sanfilippo R, et al. Steroid premedication markedly reduces liver and bone marrow toxicity of trabectedin in advanced sarcoma. Eur J Cancer. 2006;42(10):1484-90.
35. Di Giandomenico S, Frapolli R, Bello E, et al. Mode of action of trabectedin in myxoid liposarcomas. Oncogene. 2013 Nov 11. doi: 10.1038/onc.2013.462.
36. Germano G, Frapolli R, Simone M, et al. Antitumor and anti-inflammatory effects of trabectedin on human myxoid liposarcoma cells. Cancer Res. 2010;70(6):2235-44.
37. Skotheim RI, Kallioniemi A, Bjerkhagen B, et al. Topoisomerase-II alpha is upregulated in malignant peripheral nerve sheath tumors and associated with clinical outcome. J Clin Oncol. 2003;21(24):4586-91.
38. Steins MB, Serve H, Zuhlsdorf M, et al. Carboplatin/etoposide induces remission of metastasised malignant peripheral nerve tumours (malignant schwannoma) refractory to first-line therapy. Oncol Rep. 2002;9(3):627-30.
39. McArthur GA, Demetri GD, van Oosterom A, et al. Molecular and clinical analysis of locally advanced dermatofibrosarcoma protuberans treated with imatinib: Imatinib Target Exploration Consortium Study B2225. J Clin Oncol. 2005;23(4):866-73.
40. Stacchiotti S, Pedeutour F, Negri T, et al. Dermatofibrosarcoma protuberans-derived fibrosarcoma: clinical history, biological profile and sensitivity to imatinib. Int J Cancer. 2011;129(7):1761-72.
41. Kenerson H, Folpe AL, Takayama TK, Yeung RS. Activation of the mTOR pathway in sporadic angiomyolipomas and other perivascular epithelioid cell neoplasms. Hum Pathol. 2007;38(9):1361-71.
42. Pan CC, Chung MY, Ng KF, et al. Constant allelic alteration on chromosome 16p (TSC2 gene) in perivascular epithelioid cell tumour (PEComa): genetic evidence for the relationship of PEComa with angiomyolipoma. J Pathol. 2008;214(3):387-93.
43. Italiano A, Delcambre C, Hostein I, et al. Treatment with the mTOR inhibitor temsirolimus in patients with malignant PEComa. Ann Oncol. 2010;21(5):1135-7.
44. McCormack FX, Inoue Y, Moss J, et al. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med. 2011;364(17):1595-606.
45. Wagner AJ, Malinowska-Kolodziej I, Morgan JA, et al. Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. J Clin Oncol. 2010;28(5):835-40.
46. Coffin CM, Patel A, Perkins S, et al. ALK1 and p80 expression and chromosomal rearrangements involving 2p23 in inflammatory myofibroblastic tumor. Mod Pathol. 2001;14(6):569-76.
47. Coffin CM, Hornick JL, Fletcher CD. Inflammatory myofibroblastic tumor: comparison of clinicopathologic, histologic, and immunohistochemical features including ALK expression in atypical and aggressive cases. Am J Surg Pathol. 2007;31(4):509-20.
48. Butrynski JE, D'Adamo DR, Hornick JL, et al. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. N Engl J Med. 2010;363(18):1727-33.
49. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol. 2009;27(19):3126-32.
50. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012;379(9829):1879-86.
51. Maki RG, D'Adamo DR, Keohan ML, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. J Clin Oncol. 2009;27(19):3133-40.
52. Ray-Coquard I, Italiano A, Bompas E, et al. Sorafenib for patients with advanced angiosarcoma: a phase II trial from the French Sarcoma Group (GSF/GETO). Oncologist. 2012;17(2):260-6.
53. Santoro A, Comandone A, Basso U, et al. Phase II prospective study with sorafenib in advanced soft tissue sarcomas after anthracycline-based therapy. Ann Oncol. 2013;24(4):1093-8.
54. Chevreau C, Le Cesne A, Ray-Coquard I, et al. Sorafenib in patients with progressive epithelioid hemangioendothelioma: a phase 2 study by the French Sarcoma Group (GSF/GETO). Cancer. 2013;119(14):2639-44.
55. 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(6):1626-7.
56. Gounder MM, Lefkowitz RA, Keohan ML, et al. Activity

of Sorafenib against desmoid tumor/deep fibromatosis. Clin Cancer Res. 2011;17(12):4082-90.

57. Mendel DB, Laird AD, Xin X, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res. 2003;9(1):327-37.
58. Stacchiotti S, Negri T, Zaffaroni N, et al. Sunitinib in advanced alveolar soft part sarcoma: evidence of a direct antitumor effect. Ann Oncol. 2011;22(7):1682-90.
59. Stacchiotti S, Negri T, Palassini E, et al. Sunitinib malate and figitumumab in solitary fibrous tumor: patterns and molecular bases of tumor response. Mol Cancer Ther. 2010;9(5):1286-97.
60. Stacchiotti S, Grosso F, Negri T, et al. Tumor response to sunitinib malate observed in clear-cell sarcoma. Ann Oncol. 2010;21(5):1130-1.
61. ClinicalTrials.gov. Localized High-Risk Soft Tissue Sarcomas Of The Extremities And Trunk Wall In Adults: An Integrating Approach Comprising Standard Vs Histotype-Tailored Neoadjuvant Chemotherapy [NCT01710176]. 2012 October 12 [cited 2014 March 26]; Available from: http://clinicaltrials.gov/ct2/show/NCT01710176?term=NCT01710176&rank=1.
62. ClinicalTrials.gov. Efficacity of Weekly Paclitaxel in Association or Not With Bevacizumab in Metastatic or Locally Advanced Angiosarcomas (ANGIO-TAX-PLUS) [NCT01303497]. 2014 March 6 [cited 2014 March 26]; Available from: http://clinicaltrials.gov/ct2/show/NCT01303497?term=NCT01303497&rank=1.
63. ClinicalTrials.gov. Phase II Study of Cediranib (AZD2171) in Patients With Alveolar Soft Part Sarcoma [NCT00942877]. 2014 March 14 [cited 2014 March 26]; Available from: http://clinicaltrials.gov/ct2/show/NCT00942877?term=NCT00942877&rank=1.
64. ClinicalTrials.gov. CREATE: Cross-tumoral Phase 2 With Crizotinib [NCT01524926]. 2013 November 14 [cited 2014 March 26]; Available from: http://clinicaltrials.gov/show/NCT01524926.