REVIEW ARTICLE

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Systemic Management Strategies for Metastatic Soft Tissue Sarcoma

Sujana Movva[1] and *Claire Verschraegen*[2]

1 Emory University, Atlanta, GA, USA
2 University of New Mexico, Albuquerque, NM, USA

Contents

Abstract

Soft tissue sarcomas are rare tumours in adults and therefore require a multidisciplinary approach for optimal management. In the metastatic setting, chemotherapy is the primary modality of therapy. Doxorubicin alone or in combination with ifosfamide or dacarbazine has been the backbone of therapy since the 1970s. There is considerable activity for gemcitabine and docetaxel in leiomyosarcoma and for paclitaxel in angiosarcoma. Newer agents such as trabectedin and eribulin may have a role in certain sarcoma subtypes. Palifosfamide may offer a safer alternative to ifosfamide in the future. Many sarcomas have molecular aberrations that can be targeted. Agents that inhibit the insulin-like growth factor receptor-1, mammalian target of rapamycin and vascular endothelial growth factor are currently being investigated.

Soft tissue sarcomas (STS) represent less than 1% of adult malignancies.[1] In the advanced setting, doxorubicin either alone or in combination with other agents has remained the standard of care for several decades. Although most patients with metastatic disease remain incurable, some patients with limited disease can still achieve a long-term remission through a multidisciplinary

approach involving medical, surgical and radiation therapy. For these patients, the goals of care are to prolong life while maintaining or improving quality of life (QOL). In this scenario, stabilization of disease can be a meaningful endpoint. In that regard, Van Glabbeke et al.[2] have identified appropriate baseline criteria for future phase II sarcoma studies using absence of progression (or progression-free rate [PFR]) as a primary endpoint. References for drug activity were defined by this study as a 6-month PFR of 30–56% depending on histology for first-line treatment and a 3-month PFR of ≥40% in the second-line setting.

There are over 50 different types of STS, some more sensitive to chemotherapy than others. Traditionally, the activity of a new drug in STS was determined by studying it in all subtypes. However, as data accumulate for the sensitivity of certain subtypes to particular chemotherapies, there is a need for a histology-driven treatment approach. New therapies are also being identified based on the unique molecular signatures of the various sarcomas (table I). Safer ways to administer known active agents are also being developed.

The purpose of this review is to summarize current approaches to systemic therapy in metastatic STS as well as potential future therapeutic directions. Data from clinical trials including abstracts were reviewed using the PubMed Database as well as the American Society of Clinical Oncology Abstract Database and the Connective Tissue of Oncology Society Database.

Table I. Fusion transcripts in soft tissue sarcoma

Diagnosis	Chromosomal abnormality	Genes involved	Potential targeted therapy	References
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14) t(1;13)(p36;q14)	*PAX3-FKHR* *PAX7-FKHR*		
Alveolar soft part sarcoma	t(X;17)(p11.2;q25)	*TFE3-ASPL*	Sunitinib Cediranib	3,4
Angiomatoid fibrous histiocytoma	t(12;16)(q13;p11)	*FUS-ATF1*		
Clear cell sarcoma	t(12;22)(q13;q12)	*EWS-ATF1*	Tivantinib (ARQ197)	5
Congenital fibrosarcoma/congenital mesoblastic nephroma	t(12;15)(p13;q25)	*ETV6-NTRK3*		
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)	*PDFGB-COL1A1*	Imatinib	6
Desmoplastic small round cell tumour	t(11;22)(p13;q12)	*EWS-WT1*		
Endometrial stromal sarcoma	t(7;17)(p15;q21)	*JAZF1-JJAZ1*		
Ewing's sarcoma/peripheral primitive neuroectodermal tumour	t(11;22)(q24;q12) t(21;22)(q22;q12) t(7;22)(p22;q12) t(17;22)(q12;q12) t(2;22)(q33;q12) t(16;21)(p11;q22)	*EWS-FLI1* *EWS-ERG* *EWS-ETV1* *EWS-FEV* *EWS-E1AF* *FUS-ERG*	YK-4-279	7
Low-grade fibromyxoid sarcoma	t(7;16)(q33;p11)	*FUS-CREB3l2*		
Inflammatory myofibroblastic tumour	t(1;2)(q22;p23) t(2;19)(p23;p13) t(2;17)(p23;q23)	*TPM3-ALK* *TPM4-ALK* *CLTC-ALK*	Crizotinib	8
Myxoid liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q12)	*TLS-CHOP* *EWS-CHOP*		
Myxoid chondrosarcoma	t(9;22)(q22;q12) t(9;15)(q22;q21) t(9;17)q22;q11)	*EWS-CHN* *TFC12-CHN* *TAF2N-CHN*		
Synovial sarcoma	t(X;18)(p11;q11)	*SSX1-SYT* *SSX2-SYT* *SSX4-SYT*		

1. Standard Chemotherapy Drugs

1.1 Doxorubicin and Combinations

The sensitivity of STS to doxorubicin was first described in the 1970s.[9] Response rates for single-agent doxorubicin range from 9% to 27%.[10,11] There is a strong dose-response curve for doxorubicin, with higher response rates in patients who receive doses ≥60 mg/m^2.[12,13] A minority of patients may develop cardiotoxicity with anthracyclines.[14] Infusional rather than bolus administration or the use of dexrazoxane, a chelating agent that interferes with iron-mediated free radical generation, may decrease the risk of cardiomyopathy.[15] Pegylated liposomal doxorubicin is a formulation of doxorubicin in which a polyethylene glycol layer surrounds doxorubicin containing liposomes. Pegylation protects the liposomes from degradation by the reticuloendothelial system, thereby increasing the area under the plasma concentration-time curve and half-life of the drug. In contrast to doxorubicin, the agent is less likely to cause cardiac toxicity but does cause palmar plantar erythrodysesthesia (hand-foot syndrome) and significant infusion reactions. In a randomized trial of doxorubicin 75 mg/m^2 bolus every 3 weeks versus pegylated liposomal doxorubicin 50 mg/m^2 every 4 weeks, response rates to both agents by WHO criteria were equivalent.[11] In another study by the Italian Sarcoma Group, 25 patients with refractory or metastatic STS who had all previously been treated with doxorubicin were given pegylated liposomal doxorubicin at either 30 mg/m^2 or 50 mg/m^2 every 3 weeks.[16] There were three partial responses (PR), and treatment was well tolerated, with no patient experiencing cardiac toxicity. Responses were only seen in the group receiving the higher dose. Other phase II studies have also shown similar response rates.[17-19]

Historically, the addition of either ifosfamide, dacarbazine or both to doxorubicin increased the response rate, with no improvement in overall survival (OS).[13,20,21] Ifosfamide is an alkylating agent with similar single-agent activity to doxorubicin.[22,23] A dose-response curve also exists for this agent as patients who progress on ifosfamide at doses ≤10 g/m^2 show remissions when exposed to high-dose ifosfamide (doses >10 g/m^2).[24,25] Ifosfamide appears to be particularly active in synovial sarcoma, based on retrospective and small patient series data;[26,27] however, it has the potential to cause haemorrhagic cystitis, neurotoxicity and renal tubular acidosis.[28] Thus, most physicians are hesitant to use this drug in elderly patients and in those with pre-existing renal impairment. The single-agent activity of dacarbazine has been demonstrated in clinical trials and there appears to be enhanced sensitivity in patients with leiomyosarcoma (LMS).[29-31] Results from the prospective randomized European Organization for Research and Treatment of Cancer (EORTC) 62012[32] trial comparing single-agent doxorubicin with the combination of doxorubicin and ifosfamide may help determine the appropriate first-line therapy in advanced STS.

1.2 Gemcitabine and Combinations

Gemcitabine is a nucleoside analogue with activity in STS as documented in phase II studies. Responses for single-agent gemcitabine, given weekly over 30 minutes, have generally been <10% in the first-line and refractory settings.[33,34] However, the activity of gemcitabine is dependent on the formation of its metabolite gemcitabine triphosphate. Data from the pancreatic cancer setting have suggested that patients who receive gemcitabine at a fixed dose rate of 10 mg/m^2/min have improved survival over those who receive gemcitabine as a standard 30-minute infusion.[35] In advanced STS, weekly gemcitabine at 1000 mg/m^2 for 7 of 8 weeks has been administered.[36] Patients who were responding to therapy were then given the same dose but for 3 of 4 weeks. Nine patients underwent cellular pharmacological studies of two different dose rates (1000 mg/m^2 over the standard 30-minute infusion on week 1 vs a pharmacologically based infusion of 150 minutes on week 2). There was a 1.4-fold increase in gemcitabine triphosphate cellularly with the 150-minute infusion.

Activity of the combination of gemcitabine and docetaxel was first reported in patients with advanced LMS.[37] Docetaxel is a microtubule

inhibitor of the taxane family. The activity of this drug in STS when administered as a single agent is conflicting, with some studies showing no responses.[38,39] However, in patients with angiosarcoma or Kaposi sarcoma, another microtubule inhibitor, paclitaxel, has shown clinical benefit.[40,41] Preclinical data have established the synergy of gemcitabine followed by docetaxel.[42] The combination of gemcitabine and docetaxel was therefore tested in 34 patients with unresectable LMS after failure of 0–2 prior chemotherapy regimens.[37] Gemcitabine was given at 900 mg/m^2 over 90 minutes on days 1 and 8 of a 21-day cycle. Docetaxel was given on day 8 only at a dose of 100 mg/m^2. Adjustments in dosing were made for patients who had previously received pelvic radiation. Remarkably, the objective response rate by the Response Evaluation Criteria in Solid Tumors (RECIST) was 53% with a progression-free survival (PFS) of 5.6 months. Although the majority of these patients had a uterine sarcoma, there were five patients with a non-uterine LMS, two of whom had an objective response. In a follow-up study by the Gynecology Oncology Group, the same combination was tested in patients with advanced uterine LMS in the first-line setting.[43] The objective response rate was 35.8% (RECIST), with a PFS of 4.4 months and OS of more than 16 months. These results were not confirmed in the French Sarcoma Group phase II study of gemcitabine alone (1000 mg/m^2 on days 1, 8 and 15 every 28 days) versus the combination of gemcitabine and docetaxel (900 mg/m^2 on days 1 and 8 and 100 mg/m^2 on day 8, respectively, every 21 days) as second-line therapy for metastatic uterine and non-uterine LMS.[44]

The high response rates for this combination in uterine sarcoma led investigators to study it in other STS. The Sarcoma Alliance for Research through Collaboration (SARC) enrolled STS patients in a phase II trial comparing fixed-dose rate gemcitabine and fixed-dose rate gemcitabine in combination with docetaxel.[45] A total of 122 patients were assessable for outcomes in the first- to fourth-line setting. Median PFS and OS were 6.2 and 17.9 months for the gemcitabine and docetaxel group and 3 and 11.5 months for the gemcitabine alone group, respectively, thus supporting the concept of synergy between these two drugs. Additional responses were seen in high-grade undifferentiated pleomorphic sarcomas, pleomorphic liposarcoma and rhabdomyosarcoma. In other retrospective data, additional responses were also seen in angiosarcomas, osteosarcomas, malignant peripheral nerve sheath tumours and Ewing's sarcoma.[42]

Vinorelbine, a vinca alkaloid, was combined with fixed-dose gemcitabine in a phase II study of advanced STS.[46] Patients were eligible if they had received ≤1 prior chemotherapy regimen. A total of 40 patients were given gemcitabine at 800 mg/m^2 over 90 minutes on days 1 and 8 after administration of vinorelbine 25 mg/m^2. The clinical benefit rate, defined as complete response (CR), PR or stable disease (SD) was 25%. There was one CR and four PRs by RECIST. Fifty percent of patients experienced grade 3 or 4 haematological toxicity, most commonly grade 3 neutropenia. Twenty-three percent had grade 3–4 nonhaematological toxicities, mostly of a gastrointestinal nature. It is unclear from this study if vinorelbine had any significant impact, but this combination offers an approach for patients who would not otherwise tolerate docetaxel, such as those who have pre-existing neuropathy.

1.3 Angiosarcoma and Paclitaxel

Angiosarcomas are rare vascular malignancies that represent 2% of all STS. They are extremely aggressive, with a 5-year OS of about 30% independent of stage.[47] Based on sarcoma cell-line data, single-agent paclitaxel has been studied in the advanced STS population. Unfortunately, the overall response rate was poor; however, one patient with a metastatic cutaneous angiosarcoma did have a CR of his scalp lesions and an improvement in the metastatic disease. In addition, two scalp angiosarcoma patients were treated off study and were described as having a dramatic response.[48] *In vitro* studies have shown that proangiogenic factors and receptors such as vascular endothelial growth factor (VEGF)-A, VEGF-C, VEGF receptor (VEGFR)-1, VEGFR-3,

vascular permeability factor (VPF), Flt-A, kinase insert domain receptor (KDR [FLK-1]) and Ets-1 are overexpressed in angiosarcoma.[49] Expression profiling has also shown distinct upregulation of vascular-specific receptor tyrosine kinases, including *TIE1*, *KDR*, *SNRK*, *TEK* and *FLT1* in angiosarcoma patient samples.[50] Paclitaxel has been shown to have potent antiangiogenic effects, thus providing an explanation for the activity seen in this sarcoma subtype.[51,52]

A subsequent phase II study of scalp- or face-only angiosarcoma utilized various dosing schedules of paclitaxel (250 mg/m^2 administered as a continuous infusion over 24 hours every 3 weeks, 175 mg/m^2 every 3 weeks administered as a 3-hour infusion, and 90 mg/m^2 administered weekly as a 1-hour infusion).[53] Eight of nine patients had either a PR or CR and results were seen in all treatment schedules used. Subsequent retrospective data by the EORTC showed activity of paclitaxel in soft-tissue angiosarcoma as well.[54] More recently, a prospective phase II study by the French Sarcoma Group investigated the use of paclitaxel on a weekly basis in patients with metastatic or advanced angiosarcoma (the ANGIOTAX study). The distribution of site was as follows: ten breast, six skin and scalp, six soft tissue and eight visceral. Patients were given paclitaxel 80 mg/m^2 weekly for 3 of 4 weeks with an objective response rate of 19% by RECIST after six cycles.[40] Median time to progression was 4 months with OS 8 months. The drug was well tolerated, with grade 3 and 4 toxicities related to cytopenias, nausea and vomiting, fatigue, CNS toxicity and mucositis. There was one death due to thrombocytopenia. The authors concluded that weekly paclitaxel was well tolerated and showed clinical benefit in patients with angiosarcoma.

2. New Chemotherapy Regimens

2.1 Pallfosfamide

Recently, palifosfamide was developed. Palifosfamide-tris (ZIO-201; Ziopharm Inc.) is a stabilized active metabolite of ifosfamide. It has broad activity against sarcoma cell lines, including those resistant to ifosfamide and cyclophosphamide therapy.[55] As an active metabolite, it does not degrade into acrolein (responsible for the bladder toxicity) or chloroacetaldehyde (responsible for the neurotoxicity), the toxic metabolites of ifosfamide. Animal models have shown synergy between doxorubicin and palifosfamide.[56] In a phase I study of the combination of palifosfamide and doxorubicin, the mean tolerated doses were 150 mg/m^2 for 3 consecutive days and 75 mg/m^2 administered on day 1, respectively. In that study, two of the eight sarcoma patients had a PR by RECIST.[57] This led to the randomized phase II trial of the combination of palifosfamide 150 mg/m^2 for 3 days and doxorubicin 75 mg/m^2 versus single-agent doxorubicin at the same dose.[58] Cycles were given every 3 weeks with response evaluation every 6 weeks. Patients were allowed to participate if they had a metastatic STS excluding alveolar soft part, gastrointestinal stromal tumour, Kaposi sarcoma, low-grade tumour, radiation-induced tumour or dermatofibrosarcoma protuberans. Patients had to be doxorubicin naïve, but could have been previously treated with ifosfamide. A total of 67 patients were enrolled, 66 patients were treated and 62 patients were eligible for primary endpoint analysis. Patients were allowed to continue with single-agent palifosfamide after the completion of six cycles of chemotherapy in either arm. Of note, one-third of the patients were over the age of 65 years. There was a response rate of 23% in the combination arm and 9% in the single-agent doxorubicin arm (RECIST). The hazard ratio for PFS was 0.427, favouring the combination arm ($p = 0.019$). Median PFS was 4.4 months for the doxorubicin arm and 7.8 months for the combination. This was also statistically significant. Haematological toxicity was slightly worse in the combination arm, but episodes of febrile neutropenia were similar. In addition, in the palifosfamide arm, there were no episodes of encephalopathy or haemorrhagic cystitis. The addition of mesna (an agent designed to reduce the incidence of haemorrhagic cystitis) was not necessary and the combination was given safely on an outpatient basis. To confirm these preliminary results, a randomized phase III trial with a

similar study design is currently recruiting patients worldwide.[59]

These data are important for many reasons. The combination of doxorubicin and palifosfamide was safely given on an outpatient basis and administered to 23 patients over the age of 65 years. Many sarcoma centres still require hospitalization of patients receiving doxorubicin and ifosfamide for hydration and close toxicity monitoring. Therefore, this new ifosfamide derivative may offer improved QOL outcomes. As such, the current phase III study also includes a QOL assessment. In addition, given the lack of significant renal toxicity, the combination of doxorubicin and palifosfamide may also be considered in elderly patients and those patients with retroperitoneal tumours in the future. However, further data from large randomized controlled studies need to be generated before such conclusions can be made. An interesting observation is that patients who had failed ifosfamide previously still responded to palifosfamide therapy. Although the explanation for this is not entirely clear, it may be related to the dosing of palifosfamide.

2.2 Trabectedin

Trabectedin (ET-743; Johnson and Johnson) is a marine-derived alkaloid that binds DNA through the minor groove. It is approved in Europe for patients for whom prior anthracycline therapy has failed. The response to single-agent therapy in the first-line setting parallels that of the combination of doxorubicin and ifosfamide.[60] In 36 patients with metastatic STS, trabectedin was given at a dose of 1.5 mg/m^2 as a 24-hour continuous infusion. The majority of these patients had never received chemotherapy before, and the predominant histologies were LMS and liposarcoma. Objective response rate was 17.1% by WHO criteria. Data from phase II and compassionate use trials show trabectedin to have a response rate of 4–8%, with a clinical benefit rate of 14–41% in pretreated patients.[60-63] Grade 3 and 4 toxicities were most commonly haematological or due to reversible elevated transaminase levels that usually occurred 3–4 days after drug administration. The elevated transaminases levels can be attenuated with the use of prophylactic dexamethasone.[64] Trabectedin is also a vesicant that can cause extravasation reactions and is best administered through a central catheter.

There is particular interest in this compound for use in patients with myxoid liposarcoma, LMS and other translocation-related sarcomas.[65,66] In 51 patients with myxoid liposarcoma treated with trabectedin on a compassionate use protocol there was a high response rate of 51% by RECIST with a PFS of 14 months.[67] In long-term follow-up of 32 of these patients treated since 2002, the overall response rate was 50%, with a PFS of 17 months and OS that has not been reached.[68] One proposed mechanism of action is to overcome the block in differentiation caused by the FUS-CHOP fusion protein that is found in myxoid liposarcoma.[69] Previous *in vitro* studies have also demonstrated that trabectedin sensitivity may depend on the status of the nucleotide excision repair (NER) DNA repair pathway and the homologous recombination repair (HRR) DNA repair pathway. For that reason, specific single nucleotide polymorphisms (SNPs) from NER and HRR DNA repair pathways were studied in 113 patients with advanced sarcomas who were enrolled in trabectedin studies. On univariate analysis, tumour histology, favourable NER status (high expression of common allele aspartic acid at codon 1104 of ERCC5 and/or high ERCC1 expression status), and favourable *BRCA1* haplotype (at least one triple-adenine plus guanine [AAAG] allele) were the sole variables significantly associated with PFS and OS. In addition, the proportion of translocation-related sarcoma subtypes (myxoid/round cell liposarcoma, synovial sarcoma, alveolar soft part sarcoma) was significantly higher in the 'favourable NER status' group ($p = 0.0001$).[70] Schoffski et al.[71] found that 32% of 245 retrospectively collected tumour samples of patients with advanced sarcomas treated with trabectedin had a molecular profile of low *BRCA*, high *ERCC1* or *XPG* (xeroderma pigmentosum group G gene) messenger RNA expression. This profile characterized by intact NER and deficient HRR identified a subgroup highly sensitive to trabectedin treatment. Therefore,

these signatures may represent a biomarker of trabectedin response independent of histology.

A randomized phase II study of two different schedules of trabectedin (1.5 mg/m^2 continuous infusion every 3 weeks vs 0.58 mg/m^2 over 3 hours weekly for 3 of 4 weeks) was carried out in patients with advanced LMS and liposarcoma. Time to tumour progression was 3.7 versus 2.3 months, favouring the every 24-hour arm every 3 weeks.[72] Phase I studies of the combination of trabectedin with agents such as doxorubicin, paclitaxel and platinum compounds have been conducted and show tolerability and potential activity in STS.[73-75]

2.3 Eribulin

Eribulin mesylate is a non-taxane inhibitor of microtubule growth. It is a synthetic analogue of halichondrin B, a marine sponge product, and is currently US FDA approved for refractory metastatic breast cancer.[76] *In vivo* cancer activity has been seen in sarcoma. Dose-limiting toxicities included neutropenia and fatigue in phase I studies.[77,78] EORTC 62052 investigated the use of eribulin 1.4 mg/m^2 on days 1 and 15 every 3 weeks in patients with LMS, adipocytic, synovial or other sarcomas.[79] Patients could have received up to two previous lines of therapy. Primary endpoint was PFR at 12 weeks according to RECIST. The PFR at 12 weeks was 32%, 45%, 21% and 19% in the LMS, adipocytic, synovial and other cohorts, respectively. The mean PFS and OS was 3 and 20 months in LMS and 3 and 10 months in adipocytic sarcoma, respectively. Grade 3 and 4 toxicities were mostly haematological.

3. Targeted Therapies

3.1 Mammalian Target of Rapamycin Inhibitors

Activating mutations in growth factor receptors lead to activation of the phospatidylinositol 3-kinase (PI3k)/AKT/mammalian target of rapamycin (mTOR) pathway.[80] This pathway is involved in cell cycle progression, proliferation and angiogenesis.[81] The tuberous sclerosis complex (*TSC*) is a tumour suppressor gene. Cytoplasmic TSC1 and TSC2 proteins normally interact and inhibit mTOR activity. If these regulators are absent or abnormal, mTOR activity increases, leading to the development of various tumours, including perivascular epitheliod cell tumours (PEComas).[82] *PTEN*, which regulates PI3K activation, is the most frequently deleted tumour suppressor gene in various cancers. PI3K in turn activates AKT, which activates mTOR, leading to increased cell proliferation and reduction of apoptotic mechanisms.[83] *PTEN* can also be absent in STS. STS (160 LMS and various pleomorphic undifferentiated tumours) with complex genomics were studied by array comparative genomic hybridization and transcriptome analysis. Five groups were identified, corresponding to well differentiated LMS (group A) or to poorly differentiated LMS or undifferentiated pleomorphic sarcomas, groups (B–E). Genes of interest included loss of *PTEN*, especially in groups A, C and D.[84] However, PTEN expression by immunohistochemistry (IHC) in LMS has not been linked to outcome of treatment with mTOR inhibitors.[85]

Several mTOR inhibitors have been studied in the setting of advanced sarcoma. In a phase II study of ridaforolimus (AP23573; Ariad Pharmaceuticals and Merck & Company) in advanced refractory bone sarcoma and STS, 193 patients were evaluable.[86] The study drug was given at 12.5 mg/day intravenously for 5 days every 2 weeks. The most significant adverse effects were mucositis, rash, hyperlipidaemia, fatigue and thrombocytopenia. There were five PRs by RECIST with a clinical benefit rate (CR, PR or SD at 16 weeks) of 28%. Data from the SUCCEED (Sarcoma mUlti-Center Clinical Evaluation of the Efficacy of riDaforolimus) study, in which 711 patients were randomized to either maintenance oral ridaforlimus or placebo were recently reported. In order to participate, patients required SD or better on prior imaging, after completing at least first-line chemotherapy. There was a statistically significant improvement in PFS of 3.1 weeks (17.7 vs 14.6 weeks, favouring ridaforolimus) by central review. There was no significant improvement in OS for ridaforolimus,

and the adverse effect profile was similar to previous data.[87] Another mTOR inhibitor that has been studied, temsirolimus, was given at 25 mg/week for 3 of 4 weeks in advanced STS. Forty-one patients were evaluable, with one PR in a patient with fibrosarcoma that lasted 36 weeks.[88] The lack of significant objective responses seen in these studies may reflect two specific concepts: (i) RECIST criteria may not be an adequate tool for response evaluation when using targeted agents; and (ii) SD can be a valid endpoint in the management of metastatic sarcoma. On the other hand, identifying resistance mechanisms to mTOR inhibition may help improve therapeutic responses, as mTOR acts as an axis for sarcoma cell growth.

3.2 Insulin-Like Growth Factor Receptor Inhibitors

The insulin-like growth factor-1 receptor (IGF1R) pathway is a commonly activated pathway in many sarcomas. Insulin growth factor (IGF)-1 and IGF2 bind to IGF1R, activating the receptor, and stimulate intracellular signalling primarily through the Ras/Raf/mitogen-actived protein kinase (MAPK) and the PI3-K/ATK/mTOR pathways.[89] Overexpression of IGF2 by IHC has been seen in patients with solitary fibrous tumours, chondrosarcomas, undifferentiated pleomorphic sarcomas, Ewing's sarcomas, tenosynovial giant cell tumours, gastrointestinal stromal tumours, malignant peripheral nerve sheath tumours, myxoid liposarcomas and synovial sarcomas.[90]

Phase I studies of IGF1R monoclonal antibodies have shown these drugs to be well tolerated and to have anti-sarcoma activity. Objective responses were noted in Ewing's sarcoma patients and SD has been seen in patients with fibrosarcoma and synovial sarcoma.[91-93] Cixutumumab (IMC-A12) is a fully human IgG1 monoclonal antibody that selectively targets IGF-IR and therefore does not bind to the insulin receptor. A phase II study of cixutumumab in previously treated advanced STS and Ewing's sarcoma enrolled 113 patients. The Ewing family of tumours, rhabdomyosarcoma, leiomyosarcoma and synovial sarcoma cohorts were closed after the first stage due to inactivity. SD as best response was seen in 57% of adipocytic sarcoma patients with one PR. Another PR was also seen in the Ewing family of tumours cohort. The most common adverse events were nausea, diarrhoea, fatigue and hyperglycaemia.[94]

There is upregulation of the mTOR pathway when the IGF1R pathway is inhibited through feedback loops.[80] The combination of mTOR and IGF1R blockade may overcome this mechanism of resistance. Preclinical data support the combination of these drugs.[95-97] A phase I trial of the combination of everolimus, an mTOR inhibitor, and figitumumab (CP-751,871; Pfizer Inc.) was recently reported.[98] The study used the optimal phase I dose of each drug alone. Six patients were enrolled in the first cohort without any dose-limiting toxicities, thus this was determined to be the appropriate phase II dose. An additional 15 patients were treated at this dose level. Toxicities were mostly grade 1 or grade 2. The most common toxicity was mucositis. The majority of patients had SD for at least four cycles. One patient with malignant solitary fibrous tumour did have a PR by RECIST. There are other ongoing studies of IGF1R inhibition alone or in combination with other agents (table II).

3.3 Tyrosine Kinase Inhibitors and Antiangiogenic Agents

Clinical data have accumulated for the use of several tyrosine kinase inhibitors in the management of STS. Sorafenib, sunitinib, imatinib and pazopanib have all demonstrated activity in the phase II setting of advanced metastatic or recurrent STS (table III).[99-102] Although clinical responses were seen, most commonly in patients with LMS and angiosarcoma, the usual best clinical response was SD. In addition, data from these four phase II studies show these oral agents to be generally well tolerated. A double-blind, phase III trial of pazopanib 800 mg daily versus placebo in patients for whom at least one anthracycline-based regimen has failed was recently reported. Pazopanib is a multikinase angiogenesis inhibitor targeting VEGFR, PDGFR and

Table II. Tyrosine kinase therapy in soft tissue sarcoma

Study (year)	Agent	n	PFS rate at 3 mo (%)	Best response[a] (n)	PFS (mo)	OS (mo)
Maki et al.[99] (2009)	Sorafenib 400 mg bid	147	53 (entire population)	Angiosarcoma (5) LMS (1)	3.2	14.3
Sleijfer et al.[100] (2009)	Pazopanib 800 mg/day	142	26 (adipocytic) 44 (LMS) 49 (synovial) 39 (other)	LMS (1) Synovial (5) Other (3)	2.6 (adipocytic) 3.0 (LMS) 5.4 (synovial) 3 (other)	6.6 (adipocytic) 11.8 (LMS) 10.3 (synovial) 10.0 (other)
George et al.[101] (2009)	Sunitinib 37.5 mg/day	53	NA	DSRCT (1)	1.8	NA
Chugh et al.[102] (2009)	Imantinib 300 mg bid	190	NA	Angiosarcoma Fibrosarcoma LMS Liposarcoma MFH Osteosarcoma MPNST Synovial	2.8 (angiosarcoma) 1.9 (fibrosarcoma) 2.8 (LMS) 3.7 (liposarcoma) 1.9 (MFH) 1.9 (MPNST) 1.9 (synovial) 2.5 (rhabdomyosarcoma)	NA

a Tumour response measured by RESIST 1.0.

bid = twice daily; **DSRCT** = desmoplastic round cell tumour; **LMS** = leiomyosarcoma; **MFH** = malignant fibrous histiocytoma; **MPNST** = malignant peripheral nerve sheath tumour; **NA** = data not available; **OS** = overall survival; **PFS** = progression-free survival.

c-kit. Patients with adipocytic STS were excluded due to inactivity in the previous phase II trial. A total of 369 patients were randomized and the primary endpoint of PFS per independent review was significantly prolonged with pazopanib (4.6 vs 1.5 months). The interim analysis for OS did not show a statistically significant improvement of pazopanib versus placebo. Thromboembolic events, cardiotoxicity and pneumothorax ≥ grade 3 occurred at a frequency of <5%. Liver enzyme elevation was observed but was reversible in all cases.[103] Dasatinib is an orally administered kinase inhibitor of the Src family of kinases that shows preclinical anti-sarcoma activity.[104] The Sarcoma Alliance for Research through Collaboration (SARC) undertook a phase II study of dasatinib in advanced sarcoma. Dasatinib 100 mg twice daily was initially administered but was reduced to a starting dose of 70 mg twice daily because of toxicity. 114 patients with STS were evaluable, including patients with LMS, liposarcoma, undifferentiated pleomorphic sarcoma and malignant peripheral nerve sheath tumours. The primary endpoint was clinical benefit rate, defined as the objective response or SD at 6 months by Choi criteria. Unfortunately, only the population of undifferentiated pleomorphic sarcoma met the primary endpoint of ≥1% chance that the clinical benefit rate was >25%. Current studies are investigating the combination of tyrosine kinase inhibition with chemotherapy.

Previous studies have shown a correlation between expression of tumour VEGF and grade, stage, disease-free survival and OS in STS.[105-107] Other mediators of angiogenesis have also been studied. STS have been shown to have higher levels of circulating angiopoietin 2 (Ang2) and basic fibroblastic growth factor when compared with healthy controls.[108] In addition, Ang2 is most elevated in patients with larger tumours and in those with tumours of the trunk. Microarray data have shown that STS have altered gene expression, with upregulation of platelet-derived growth factor receptor (PDGFR)α.

Bevacizumab, a monoclonal antibody to circulating VEGF, has been combined with various chemotherapy agents in the management of metastatic STS. However, when combined with doxorubicin, the response rate was lower than that of the historical response rate to single-agent

Table III. Active and pending studies of insulin-like growth factor-1 receptor (IGF1R) inhibition in soft tissue sarcoma (STS)

Sponsor	Agents	Study population	Clinicaltrials.gov identifier	Status
Cixutumumab (IMCA12)				
COG	Cixutumumab, temsirolimus (mTOR inhibitor)	Phase I, advanced solid tumours, ≤21 y	NCT00880282	Recruiting
COG	Cixutumumab, temozolomide, chemotherapy	Phase I, rhabdomyosarcoma, <49 y	NCT01055314	Recruiting
ImClone LLC	Cixutumumab	Phase I, solid tumours, ≥20 y	NCT01007032	Active but not recruiting
MDACC	Cixutumumab, temsirolimus (mTOR inhibitor)	Phase I, advanced cancer, ≥16 y	NCT00678769	Recruiting
University of Chicago	Cixutumumab, doxorubicin	Phase I/II, unresectable or metastatic STS, ≥16 y	NCT00720174	Recruiting
COG	Cixutumumab	Phase II, refractory solid tumours, <30 y	NCT00831844	Recruiting
MSKCC	Cixutumumab, temsirolimus	Phase II, STS, bone sarcoma, ≥18 y	NCT01016015	Recruiting
ImClone LLC	Cixutumumab	Phase II, advanced sarcoma (Ewing's, rhabdo, LMS, adipocytic, synovial), ≥12 y	NCT00668148	Active but not recruiting
Figitumumab (CP-751,871)				
Pfizer	Figitumumab, dacomitinib (PF-00299804; pan ERBB inhibitor)	Phase I, advanced solid tumours, ≥18 y	NCT00728390	Active but not recruiting
Pfizer	Figitumumab	Phase I, sarcoma, Ewing's, ≥9 y	NCT00474760	Active but not recruiting
Pfizer	Figitumumab, sunitinib	Phase I, advanced solid tumours, ≥18 y	NCT00729833	Active but not recruiting
Pfizer	Figitumumab	Phase I, advanced sarcomas and other malignant neoplasms, ≥18 y	NCT00927966	Active but not recruiting
Pfizer	Figitumumab	Phase I/II, Ewing's, ≥10 y	NCT00560235	Active but not recruiting
R1507				
Hoffman-La Roche	Figitumumab	Phase I, advanced solid tumours, ≥18 y	NCT00400361	Active but not recruiting
Hoffman-La Roche	Figitumumab, everolimus (mTOR inhibitor)	Phase I, advanced solid tumours, ≥18 y	NCT00985374	Active but not recruiting
Hoffman-La Roche	Figitumumab and standard chemotherapy	Phase I, advanced solid tumours, ≥18 y	NCT00811993	Active but not recruiting
Hoffman-La Roche	Figitumumab	Phase II, recurrent or refractory sarcoma, ≥2 y	NCT00642941	Active but not recruiting.
Ganitumab (AMG479)				
Duke University	Ganitumab, everolimus, panitumumab (EGFR antibody)	Phase I, advanced cancer, ≥18 y	NCT01061788	Recruiting
Indiana University School of Medicine	Ganitumab, everolimus	Phase I, advanced solid tumours, ≥18 y	NCT01122199	Recruiting
Amgen	Ganitumab, conatumumab (AMG655; TRAIL receptor 2 agonist)	Phase I/II, advanced solid tumours, ≥16 y	NCT00819169	Active but not recruiting
Amgen	Ganitumab	Phase II, Ewing's family, ≥16 y	NCT00563680	Active but not recruiting

COG = Children's Oncology Group; **EGFR** = epidermal growth factor receptor; **LMS** = leiomyosarcoma; **MSKCC** = Memorial Sloan-Kettering Cancer Center; **mTOR** = mammalian target of rapamycin; **TRAIL** = tumour-necrosis factor-related apoptosis-inducing ligand.

doxorubicin.[109] Sixty-five percent of patients did have SD. Of concern is that 35% of patients had a grade 2 or worse decline in left ventricular ejection fraction, despite receiving dexrazoxane once doxorubicin doses exceeded 300 mg/m^2. A phase I/II study of the combination of docetaxel, gemcitabine and bevacizumab in 35 assessable patients with chemotherapy-naïve STS was also recently reported.[110] Gemcitabine was given at three dose levels (1000, 1250 and 1500 mg/m^2) every 2 weeks. Docetaxel was given at 50 mg/m^2 and bevacizumab at 5 mg/kg also every 2 weeks. The overall response rate was 30.1% (RECIST), with an additional 47% achieving SD for a median of 6 months. Best responses were observed in patients with angiosarcoma with two confirmed complete pathological responses. Grade 3 and 4 adverse events were all attributed to bevacizumab, which was concerning, as the benefit of bevacizumab in this study is unclear. Bevacizumab and other antiangiogenic agents are currently being investigated in STS and more specifically in angiosarcoma.

4. Conclusion

STS comprises a heterogeneous group of diseases with unique molecular and clinical profiles, and therefore varying responses to treatments. Traditionally, doxorubicin-based regimens have been the standard of care. The identification of histological subtypes that may have heightened sensitivity to certain agents will likely cause a paradigm shift in the future. Angiosarcomas have marked sensitivity to paclitaxel and perhaps antiangiogenic agents. The combination of gemcitabine and docetaxel has significant activity in LMS. The role of trabectedin in the management of patients with metastatic myxoid liposarcoma and LMS is also continuing to evolve. In addition, potentially safer approaches to chemotherapy, such as palifosfamide, are being investigated. The OS of patients with advanced sarcomas has improved in the last 20 years,[111] partly due to identification of molecular signatures and targeting of signalling pathways. Collaborative studies of new agents will hopefully lead to more rapid determination of their efficacy.

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References

1. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. CA Cancer J Clin 2011; 61 (2): 133-4
2. Van Glabbeke M, Verweij J, Judson I, et al. Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas. Eur J Cancer 2002; 38: 543-9
3. 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
4. Gardner K, Leahy M, Alvarez-Gutierrez M, et al. Activity of the VEGFR/KIT tyrosine kinase inhibitor cediranib (AZD2171) in alveolar soft part sarcoma [abstract]. London: Connective Tissue Oncology Society, 2008
5. Goldberg J, Demetri G, Choy E, et al. Preliminary results from a phase II study of ARQ 197 in patients with microphthalmia transcription factor family (MiT)-associated tumors [abstract]. J Clin Oncol 2009; 27 (15 Suppl.): 10502
6. Rutkowski P, Van Glabbeke M, Rankin CJ, et al. Imatinib mesylate in advanced dermatofibrosarcoma protuberans: pooled analysis of two phase II clinical trials. J Clin Oncol 2010; 28 (10): 1772-9
7. Erkizan HV, Kong Y, Merchant M, et al. A small molecule blocking oncogenic protein EWS-FLI1 interaction with RNA helicase A inhibits growth of Ewing's sarcoma. Nat Med 2009; 15: 750-6
8. 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
9. Benjamin RS, Wiernik PH, Bachur NR. Adriamycin: a new effective agent in the therapy of disseminated sarcomas. Med Pediatr Oncol 1975; 1: 63-76
10. Schoenfeld DA, Rosenbaum C, Horton J, et al. A comparison of adriamycin versus vincristine and adriamycin, and cyclophosphamide versus vincristine, actinomycin-D, and cyclophosphamide for advanced sarcoma. Cancer 1982; 50: 2757-62
11. Judson I, Radford JA, Harris M, et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOX-IL/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: 870-7
12. Patel SR, Vadhan-Raj S, Burgess MA, et al. Results of two consecutive trials of dose-intensive chemotherapy with doxorubicin and ifosfamide in patients with sarcomas. Am J Clin Oncol 1998; 21: 317-21
13. Borden EC, Amato DA, Rosenbaum C, et al. Randomized comparison of three adriamycin regimens for metastatic soft tissue sarcomas. J Clin Oncol 1987; 5: 840-50

14. Schein PS, Winokur SH. Immunosuppressive and cytotoxic chemotherapy: long-term complications. Ann Intern Med 1975; 82: 84-95
15. Seifert CF, Nesser ME, Thompson DF. Dexrazoxane in the prevention of doxorubicin-induced cardiotoxicity. Ann Pharmacother 1994; 28: 1063-72
16. Toma S, Tucci A, Villani G, et al. Liposomal doxorubicin (Caelyx) in advanced pretreated soft tissue sarcomas: a phase II study of the Italian Sarcoma Group (ISG). Anticancer Res 2000; 20: 485-91
17. Skubitz KM. Phase II trial of pegylated-liposomal doxorubicin (Doxil) in sarcoma. Cancer Invest 2003; 21: 167-76
18. Sutton G, Blessing J, Hanjani P, et al. Phase II evaluation of liposomal doxorubicin (Doxil) in recurrent or advanced leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. Gynecol Oncol 2005; 96: 749-52
19. Poveda A, Lopez-Pousa A, Martin J, et al. Phase II Clinical Trial With Pegylated Liposomal Doxorubicin (CAELYX®/Doxil®) and Quality of Life Evaluation (EORTC QLQ-C30) in adult patients with advanced soft tissue sarcomas: a study of the Spanish Group for Research in Sarcomas (GEIS). Sarcoma 2005; 9: 127-32
20. Edmonson JH, Ryan LM, Blum RH, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. J Clin Oncol 1993; 11: 1269-75
21. Antman K, Crowley J, Balcerzak SP, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. J Clin Oncol 1993; 11: 1276-85
22. Bramwell VH, Mouridsen HT, Santoro A, et al. Cyclophosphamide versus ifosfamide: a randomized phase II trial in adult soft-tissue sarcomas. The European Organization for Research and Treatment of Cancer [EORTC], Soft Tissue and Bone Sarcoma Group. Cancer Chemother Pharmacol 1993; 31 Suppl. 2: S180-4
23. Antman KH, Ryan L, Elias A, et al. Response to ifosfamide and mesna: 124 previously treated patients with metastatic or unresectable sarcoma. J Clin Oncol 1989; 7: 126-31
24. Patel SR, Vadhan-Raj S, Papadopolous N, et al. High-dose ifosfamide in bone and soft tissue sarcomas: results of phase II and pilot studies – dose-response and schedule dependence. J Clin Oncol 1997; 15: 2378-84
25. Buesa JM, Lopez-Pousa A, Martin J, et al. Phase II trial of first-line high-dose ifosfamide in advanced soft tissue sarcomas of the adult: a study of the Spanish Group for Research on Sarcomas (GEIS). Ann Oncol 1998; 9: 871-6
26. Rosen G, Forscher C, Lowenbraun S, et al. Synovial sarcoma: uniform response of metastases to high dose ifosfamide. Cancer 1994; 73: 2506-11
27. Sleijfer S, Ouali M, van Glabbeke M, et al. Prognostic and predictive factors for outcome to first-line ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas: an exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG). Eur J Cancer 2010; 46 (1): 72-83
28. Cohen MH, Creaven PJ, Tejada F, et al. Phase I clinical trial of isophosphamide (NSC-109724). Cancer Chemother Rep 1975; 59: 751-5
29. Buesa JM, Mouridsen HT, van Oosterom AT, et al. High-dose DTIC in advanced soft-tissue sarcomas in the adult: a phase II study of the E.O.R.T.C. Soft Tissue and Bone Sarcoma Group. Ann Oncol 1991; 2: 307-9
30. Zucali PA, Bertuzzi A, Parra HJ, et al. The 'old drug' dacarbazine as a second/third line chemotherapy in advanced soft tissue sarcomas. Invest N Drugs 2008; 26: 175-81
31. Gottlieb JA, Benjamin RS, Baker LH, et al. Role of DTIC (NSC-45388) in the chemotherapy of sarcomas. Cancer Treat Rep 1976; 60: 199-203
32. European Organization for Research and Treatment of Cancer. Doxorubicin with or without ifosfamide and pegfilgrastim in treating patients with locally advanced or metastatic soft tissue sarcoma [ClinicalTrials.gov identifier NCT00061984]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://clinicaltrials.gov [Accessed 2011 Sep 29]
33. Von Burton G, Rankin C, Zalupski MM, et al. Phase II trial of gemcitabine as first line chemotherapy in patients with metastatic or unresectable soft tissue sarcoma. Am J Clin Oncol 2006; 29: 59-61
34. Svancarova L, Blay JY, Judson IR, et al. Gemcitabine in advanced adult soft-tissue sarcomas: a phase II study of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer 2002; 38: 556-9
35. Tempero M, Plunkett W, Ruiz Van Haperen V, et al. Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 2003; 21: 3402-8
36. Patel SR, Gandhi V, Jenkins J, et al. Phase II clinical investigation of gemcitabine in advanced soft tissue sarcomas and window evaluation of dose rate on gemcitabine triphosphate accumulation. J Clin Oncol 2001; 19: 3483-9
37. Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J Clin Oncol 2002; 20: 2824-31
38. van Hoesel QG, Verweij J, Catimel G, et al. Phase II study with docetaxel (taxotere) in advanced soft tissue sarcomas of the adult. EORTC Soft Tissue and Bone Sarcoma Group. Ann Oncol 1994; 5: 539-42
39. Verweij J, Catimel G, Sulkes A, et al. Phase II studies of docetaxel in the treatment of various solid tumours. EORTC Early Clinical Trials Group and the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer 1995; 31A Suppl. 4: S21-4
40. 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: 5269-74
41. Cianfrocca M, Lee S, Von Roenn J, et al. Randomized trial of paclitaxel versus pegylated liposomal doxorubicin for advanced human immunodeficiency virus-associated Kaposi sarcoma: evidence of symptom palliation from chemotherapy. Cancer 2010; 116 (16): 3969-77

42. Leu KM, Ostruszka LJ, Shewach D, et al. Laboratory and clinical evidence of synergistic cytotoxicity of sequential treatment with gemcitabine followed by docetaxel in the treatment of sarcoma. J Clin Oncol 2004; 22: 1706-12
43. Hensley ML, Blessing JA, Mannel R, et al. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. Gynecol Oncol 2008; 109: 329-34
44. Pautier P, Bui Nguyen B, Penel N, et al. Final results of a FNCLCC French Sarcoma Group multicenter randomized phase II study of gemcitabine (G) versus gemcitabine and docetaxel (G+D) in patients with metastatic or relapse leiomyosarcoma (LMS) [abstract]. J Clin Oncol 2009; 27 (15 Suppl.): 10527
45. 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. J Clin Oncol 2007; 25: 2755-63
46. Dileo P, Morgan JA, Zahrieh D, et al. Gemcitabine and vinorelbine combination chemotherapy for patients with advanced soft tissue sarcomas: results of a phase II trial. Cancer 2007; 109: 1863-9
47. Fury MG, Antonescu CR, Van Zee KJ, et al. A 14-year retrospective review of angiosarcoma: clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy. Cancer J 2005; 11: 241-7
48. Casper ES, Waltzman RJ, Schwartz GK, et al. Phase II trial of paclitaxel in patients with soft-tissue sarcoma. Cancer Invest 1998; 16: 442-6
49. Penel N, Marréaud S, Robin YM, et al. Angiosarcoma: state of the art and perspectives. Crit Rev Oncol Hematol. Epub 2010 Nov 3
50. Antonescu CR, Yoshida A, Guo T, et al. KDR activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors. Cancer Res 2009; 69: 7175-9
51. Belotti D, Vergani V, Drudis T, et al. The microtubule-affecting drug paclitaxel has antiangiogenic activity. Clin Cancer Res 1996; 2: 1843-9
52. Schwartz EL. Antivascular actions of microtubule-binding drugs. Clin Cancer Res 2009; 15: 2594-601
53. Fata F, O'Reilly E, Ilson D, et al. Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. Cancer 1999; 86: 2034-7
54. 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: 2433-6
55. Kolb EA, Gidwani P, Gale RP, et al. A preclinical evaluation of ZIO-201 (isophosphoramide mustard [IPM]-lysine) in sarcoma [abstract no. 610]. CTOS; 2006 Nov 2-4; Venice
56. Waud WR, Miller G. Antitumor efficay of ifosfamide and palifosfamide-tris in combination with doxorubicin in MX-1 xenograft model in mice (Study ZP-29) [abstract]. Birmingham (AL): Southern Research Institute, 2008
57. Chawla SP, Camacho L, Chua VS, et al. A study of palifosfamide in combination with doxorubicin: safety and preliminary efficacy [abstract no. 35011]. CTOS 14th Annual Meeting; 2008 Nov 13-15; London
58. Verschraegen CF, Chawla SP, Mita MM, et al. A phase II, randomized, controlled trial of palifosfamide plus doxorubicin versus doxorubicin in patients with soft tissue sarcoma (PICASSO) [abstract]. 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition). J Clin Oncol 2010; 28 (15 Suppl.): 10004
59. ZIOPHARM. Study of palifosfamide-tris in combination with doxorubicin in patients with front-line metastatic soft tissue sarcoma (PICASSO III) [ClinicalTrials.gov identifier NCT01168791]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://clinicaltrials.gov [Accessed 2011 Sep 29]
60. 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: 1480-90
61. Yovine A, Riofrio M, Blay JY, et al. Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. J Clin Oncol 2004; 22: 890-9
62. Samuels BL, Tap WD, Patel S, et al. Trabectedin (Tr) as single agent for advanced soft tissue sarcomas (STS) failing standard of care: interim analysis of 1400 patients (pts) in an expanded access program study [abstract]. J Clin Oncol 2010; 28 (15 Suppl.): 10027
63. 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: 576-84
64. Paz-Ares L, Lopez-Pousa A, Poveda A, et al. Trabectedin in pre-treated patients with advanced or metastatic soft tissue sarcoma: a phase II study evaluating co-treatment with dexamethasone. Invest New Drugs. Epub 2010 Oct 20
65. Dileo P, Grosso F, Casanova M, et al. Trabectedin (T) in metastatic Ewing's family tumors (EFT) patients (pts) progressing after standard chemotherapy [abstract]. 2007 ASCO Annual Meeting Proceedings (Post-Meeting Edition). J Clin Oncol 2007; 25 (18 Suppl.): 10040
66. Dileo P, Sanfilippo R, Grosso F, et al. Trabectedin (T) in advanced, pretreated synovial sarcomas (SS): a retrospective analysis of 39 patients (pts) from three European institutions [abstract]. 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition). J Clin Oncol 2010; 28 (15 Suppl.): 10030
67. Grosso F, Jones RL, Demetri GD, et al. Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas: a retrospective study. Lancet Oncol 2007; 8: 595-602
68. 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: 1439-44
69. Forni C, Minuzzo M, Virdis E, et al. Trabectedin (ET-743) promotes differentiation in myxoid liposarcoma tumors. Mol Cancer Ther 2009; 8: 449-57
70. Italiano A, Laurand A, Laroche A, et al. ERCC5/XPG, ERCC1, and BRCA1 gene status and clinical benefit of trabectedin in patients with soft tissue sarcoma. Cancer 2011 Aug 1; 117 (15): 3445-56
71. Schoffski P, Taron M, Jimeno J, et al. Predictive impact of DNA repair functionality on clinical outcome of

advanced sarcoma patients treated with trabectedin: a retrospective multicentric study. Eur J Cancer 2011 May; 47 (7): 1006-12

72. 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
73. Sessa C, Perotti A, Noberasco C, et al. Phase I clinical and pharmacokinetic study of trabectedin and doxorubicin in advanced soft tissue sarcoma and breast cancer. Eur J Cancer 2009 May; 45 (7): 1153-61
74. Chu Q, Mita A, Forouzesh B, et al. Phase I and pharmacokinetic study of sequential paclitaxel and trabectedin every 2 weeks in patients with advanced solid tumors. Clin Cancer Res 2010 May 1; 16 (9): 2656-65
75. Sessa C, Cresta S, Noberasco C, et al. Phase I clinical and pharmacokinetic study of trabectedin and cisplatin in solid tumours. Eur J Cancer 2009 Aug; 45 (12): 2116-22
76. Kuznetsov G, Towle MJ, Cheng H, et al. Induction of morphological and biochemical apoptosis following prolonged mitotic blockage by halichondrin B macrocyclic ketone analog E7389. Cancer Res 2004; 64: 5760-6
77. Goel S, Mita AC, Mita M, et al. A phase I study of eribulin mesylate (E7389), a mechanistically novel inhibitor of microtubule dynamics, in patients with advanced solid malignancies. Clin Cancer Res 2009; 15: 4207-12
78. Tan AR, Rubin EH, Walton DC, et al. Phase I study of eribulin mesylate administered once every 21 days in patients with advanced solid tumors. Clin Cancer Res 2009; 15: 4213-9
79. Schoffski P, Ray-Coquard IL, Cioffi A, et al. Activity of eribulin mesylate (E7389) in patients with soft tissue sarcoma (STS): phase II studies of the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC 62052) [abstract]. 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition). J Clin Oncol 2010; 28 (15 Suppl.): 10031
80. Wan X, Helman LJ. The biology behind mTOR inhibition in sarcoma. Oncologist 2007; 12: 1007-18
81. Wullschleger S, Loewith R, Hall MN. TOR signaling in growth and metabolism. Cell 2006; 124: 471-84
82. Martignoni G, Pea M, Reghellin D, et al. Molecular pathology of lymphangioleiomyomatosis and other perivascular epithelioid cell tumors. Arch Pathol Lab Med 2010; 134 (1): 33-40
83. Hernando E, Charytonowicz E, Dudas ME, et al. The AKT-mTOR pathway plays a critical role in the development of leiomyosarcomas. Nat Med 2007; 13: 748-53
84. Gibault L, Perot G, Chibon F, et al. New insights in sarcoma oncogenesis: a comprehensive analysis of a large series of 160 soft tissue sarcomas with complex genomics. J Pathol 2011; 223 (1): 64-71
85. Italiano A, Kind M, Stoeckle E, et al. Temsirolimus in advanced leiomyosarcomas: patterns of response and correlation with the activation of the mammalian target of rapamycin pathway. Anticancer Drugs 2011 Jun; 22 (5): 463-7
86. Chawla SP, Sankhala KK, Chua V, et al. A phase II study of AP23573 (an mTOR inhibitor) in patients (pts) with advanced sarcomas [abstract]. 2005 ASCO Annual Meeting Proceedings (Post-Meeting Edition). J Clin Oncol 2005; 23 (16 Suppl.): 9068
87. Chawla SP, Blay J, Ray-Coquard IL, et al. Results of the phase III, placebo-controlled trial (SUCCEED) evaluating the mTOR inhibitor ridaforolimus (R) as maintenance therapy in advanced sarcoma patients (pts) following clinical benefit from prior standard cytotoxic chemotherapy (CT). 2011 ASCO Annual Meeting Proceedings (Post-Meeting Edition). J Clin Oncol 2011; 28 (15 Suppl.): 10005
88. Okuno SH, Mahoney MR, Bailey HH, et al. A multicenter phase 2 consortium (P2C) study of the mTOR inhibitor CCI-779 in advanced soft tissue sarcomas (STS) [abstract]. J Clin Oncol 2006; 24 (18 Suppl.): 9504
89. Rikhof B, de Jong S, Suurmeijer AJ, et al. The insulin-like growth factor system and sarcomas. J Pathol 2009; 217: 469-82
90. Steigen SE, Schaeffer DF, West RB, et al. Expression of insulin-like growth factor 2 in mesenchymal neoplasms. Mod Pathol 2009; 22: 914-21
91. Tolcher AW, Sarantopoulos J, Patnaik A, et al. Phase I, pharmacokinetic, and pharmacodynamic study of AMG 479, a fully human monoclonal antibody to insulin-like growth factor receptor 1. J Clin Oncol 2009; 27: 5800-7
92. Olmos D, Postel-Vinay S, Molife LR, et al. Safety, pharmacokinetics, and preliminary activity of the anti-IGF-1R antibody figitumumab (CP-751,871) in patients with sarcoma and Ewing's sarcoma: a phase 1 expansion cohort study. Lancet Oncol 2010; 11 (2): 129-35
93. Kurzrock R, Patnaik A, Aisner J, et al. A phase I study of weekly R1507, a human monoclonal antibody insulin-like growth factor-I receptor antagonist, in patients with advanced solid tumors. Clin Cancer Res; 16: 2458-65
94. Schoffski P, Adkins D, Blay J, et al. Phase II trial of anti-IGF-1R antibody cixutumumab in patients with advanced or metastatic soft-tissue sarcoma and Ewing family of tumors [abstract]. 2011 ASCO Annual Meeting Proceedings (Post-Meeting Edition). J Clin Oncol 2011; 29 (15 Suppl.): 10004
95. Beltran PJ, Chung YA, Moody G, et al. Efficacy of ganitumab (AMG 479), alone and in combination with rapamycin, in ewing's and osteogenic sarcoma models. J Pharmacol Exp Ther 2011 Jun; 337 (3): 644-54
96. Kolb EA, Kamara D, Zhang W, et al. R1507, a fully human monoclonal antibody targeting IGF-1R, is effective alone and in combination with rapamycin in inhibiting growth of osteosarcoma xenografts. Pediatr Blood Cancer 2010; 55 (1): 67-75
97. Kurmasheva RT, Dudkin L, Billups C, et al. The insulin-like growth factor-1 receptor-targeting antibody, CP-751,871, suppresses tumor-derived VEGF and synergizes with rapamycin in models of childhood sarcoma. Cancer Res 2009; 69: 7662-71
98. Quek RH, Wang Q, Morgan JA, et al. Combination mTOR+IGF-1R inhibition: phase I trial of everolimus and figitumumab in patients with advanced sarcomas and other solid tumors. Clin Cancer Res 2011 Feb 15; 17 (4): 871-9

99. 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: 3133-40
100. 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: 3126-32
101. George S, Merriam P, Maki RG, et al. Multicenter phase II trial of sunitinib in the treatment of nongastrointestinal stromal tumor sarcomas. J Clin Oncol 2009; 27: 3154-60
102. Chugh R, Wathen JK, Maki RG, et al. Phase II multicenter trial of imatinib in 10 histologic subtypes of sarcoma using a bayesian hierarchical statistical model. J Clin Oncol 2009; 27: 3148-53
103. Van Der Graaf WT, Blay J, Chawla SP, et al. PALETTE: a randomized, double-blind, phase III trial of pazopanib versus placebo in patients (pts) with soft-tissue sarcoma (STS) whose disease has progressed during or following prior chemotherapy – an EORTC STBSG Global Network Study (EORTC 62072) [abstract]. 2011 ASCO Annual Meeting. J Clin Oncol 2011; 29 (18 Suppl.): LBA10002
104. Schuetze S, Wathen K, Choy E, et al. Results of a Sarcoma Alliance for Research through Collaboration (SARC) phase II trial of dasatinib in previously treated, high-grade advanced sarcoma [abstract]. 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition). J Clin Oncol 2010; 28 (15 Suppl.): 10009
105. Pakos EE, Goussia AC, Tsekeris PG, et al. Expression of vascular endothelial growth factor and its receptor, KDR/Flk-1, in soft tissue sarcomas. Anticancer Res 2005; 25: 3591-6
106. Chao C, Al-Saleem T, Brooks JJ, et al. Vascular endothelial growth factor and soft tissue sarcomas: tumor expression correlates with grade. Ann Surg Oncol 2001; 8: 260-7
107. Yudoh K, Kanamori M, Ohmori K, et al. Concentration of vascular endothelial growth factor in the tumour tissue as a prognostic factor of soft tissue sarcomas. Br J Cancer 2001; 84: 1610-5
108. Yoon SS, Segal NH, Olshen AB, et al. Circulating angiogenic factor levels correlate with extent of disease and risk of recurrence in patients with soft tissue sarcoma. Ann Oncol 2004; 15: 1261-6
109. D'Adamo DR, Anderson SE, Albritton K, et al. Phase II study of doxorubicin and bevacizumab for patients with metastatic soft-tissue sarcomas. J Clin Oncol 2005; 23: 7135-42
110. Verschraegen CF, Arias-Pulido H, Lee SJ, et al. Phase I/II study of the combination of docetaxel, gemcitabine, and bevacizumab in patients with advanced or recurrent soft tissue sarcoma.[abstract no. 876705]. CTOS; 2010 Nov 12; Paris
111. Italiano A, Mathoulin-Pelissier S, Cesne AL, et al. Trends in survival for patients with metastatic soft-tissue sarcoma. Cancer 2011; 117 (5): 1049-54

Correspondence: *Sujana Movva*, MD, Emory University School of Medicine, Department of Hematology and Medical Oncology, 550 Peachtree Street, Glenn Building Lobby, Atlanta, GA 30308, USA.
E-mail: sujana.movva@emory.edu