The individual rarity of the many subtypes of soft tissue sarcomas has historically mandated an empiric approach to systemic therapy. Doxorubicin, first reported to have activity in sarcomas 40 years ago, remains the generalizable first-line treatment of choice for many subtypes, with no other drug or combination having shown an overall-survival advantage. Other cytotoxic agents, such as paclitaxel for angiosarcoma or gemcitabine with docetaxel for leiomyosarcoma, are commonly used for certain histologic subtypes based on relatively small studies. Trabectedin, particularly active against leiomyosarcoma and myxoid liposarcoma, is approved in many countries worldwide but not yet in the United States or Australia. Newer cytotoxic agents, including ifosfamide derivatives, are in current phase III testing. Although advances in systemic therapy of soft-tissue sarcomas have been hampered by their biologic heterogeneity, this diversity also serves as fertile ground for discovery and validation of targetable molecular drivers. The most notable success in this regard has been the development of small molecule therapies for gastrointestinal stromal tumors. Other targets of recent interest include mouse double minute 2 homolog (MDM2) in dedifferentiated liposarcoma and anaplastic lymphoma kinase (ALK) in inflammatory myofibroblastic tumor. Molecular therapies that have shown activity in diverse sarcoma populations include mammalian target of rapamycin (mTOR) inhibitors and vascular endothelial growth factor (VEGF-R) inhibitors. Among the latter, pazopanib demonstrated a progression-free survival over placebo in prior-treated patients with advanced sarcoma, and is now approved for use in the sarcomas in many countries. Efforts to understand the key molecular aberrations in any particular tumor continue towards a goal of individualized sarcoma therapy.

Sarcomas are a broad group of mesenchymal neoplasms, now subclassified into over 50 subtypes, representing approximately 2% of adult and 15% of pediatric cancers. These subtypes, many of which are quite distinct, are still generally classified using traditional morphological and immunohistochemical criteria. In the last 2 decades, the identification of translocations, many of which lead to the development of fusion proteins, have provided opportunities to further characterize them, at least for diagnostic and prognostic purposes. The argument of whether being a "lumper" or "splitter" really matters in determining patient care, particularly in advanced soft tissue sarcomas, has now been clearly overtaken by a desire to develop predictive molecular markers that may allow for a rational selection of targeted systemic agent.

The profound heterogeneity of sarcoma subtypes complicates the conduct and interpretation of clinical trials. Although therapeutic choices for many solid tumors have expanded over the last decade, systemic options for soft tissue sarcomas remain relatively limited. Select sarcomas, including gastrointestinal stromal tumors, Ewing’s Family of Tumors, and embryonal and alveolar rhabdomyosarcomas are exceptions that are effectively treated with specific therapies, with management strategies having evolved independently from other soft tissue sarcomas. For most soft tissue sarcomas the use of cytotoxic agents remains more or less empiric, some drugs having been in use for over 30 years despite lack of proven overall survival advantage. In some ways, the use of nonspecific cytotoxic agents seems appropriate for generalized treatment of soft tissue sarcomas, a histologically, genetically, and clinically diverse group of malignancies of profound individual rarity. Even in the case of so-called molecularly-targeted therapies, we remain limited in being able to prospectively predict a high likelihood of success with that agent. Until further progress is made toward identifying particular patient subsets based on a targetable molecular driver, we must rely on the arsenal of chemotherapies, and take a somewhat pragmatic approach to the use of these targeted agents in broader patient groups.

This review will focus on the progress that has been made in the development of systemic therapies, both cytotoxic and targeted, and the challenges we face in trying to optimize the use of these agents on an individualized basis.
**CYTOTOXIC CHEMOTHERAPY**

**Doxorubicin**

Doxorubicin remains the most active agent for the generalized treatment of soft tissue sarcomas. The first studies evaluating doxorubicin in cancer were published 40 years ago.\(^1\) Significant activity in soft tissue sarcomas were noted in these early studies, with reported response rates of up to 50%. In interpreting these results, it must be remembered that such studies predated modern imaging technology and did not employ current objective response criteria; interpretation is further complicated by the heterogeneity of sarcomas included in these early studies (e.g., both bone and soft tissue tumors, probable inclusion of unrecognized gastrointestinal stromal tumors). Modern studies of doxorubicin in unselected soft tissue sarcomas have reported response rates of less than 15%, and likely represent a more realistic measure of response activity in current practice.\(^2,3\) Although doxorubicin results in meaningful responses in some patients, its effect on overall survival is less clear, with median survival approximating 1 year in most studies. Despite its shortcomings, doxorubicin is generally accepted as standard first-line therapy for advanced soft tissue sarcomas.

Studies have suggested a dose-response relationship for doxorubicin.\(^4\) Modern dosing for sarcoma is typically up to 75 mg/m\(^2\). One drawback to doxorubicin is that cumulative dosing is limited by cardiotoxicity. Because of this, the treatment course of doxorubicin is necessarily curtailed, and those patients who benefit from treatment are without safe option for chronic therapy. Alternative agents have been looked at in hopes of circumventing the dose-limiting cardiotoxicity. Epirubicin was initially considered to have less cardiotoxicity, but with equimolar dosing, epirubicin has shown similar toxicity (and activity) as doxorubicin.\(^5-7\) Liposomal doxorubicin has been embraced by some as a lower-toxicity alternative to standard doxorubicin for treatment of soft tissue sarcomas. Although an initial study of liposomal doxorubicin in second line sarcoma treatment did not show activity, subsequent studies have reported activity similar to doxorubicin.\(^8-10\) Formal phase III testing has not been performed to test noninferiority to standard doxorubicin.

**Ifofosamide**

Ifofosamide is an alkylation agent that requires biotransformation in the liver for activation.\(^11\) Some of the metabolites of ifosfamide are associated with serious side effects including encephalopathy and hemorrhagic cystitis.\(^12\) Ifofosamide’s use in clinical practice was limited for many years because of the associated hemorrhagic cystitis until the availability of mesna in 1979. Numerous studies have been performed with ifosfamide in soft tissue sarcomas, with response rates comparable to those seen with doxorubicin.\(^13\) Although some reports suggested a dose-response relationship justifying high doses of ifosfamide of 12 to 18 g/m\(^2\), subsequent studies have not validated a benefit to such high doses and have confirmed excess toxicity with such dosing.\(^14,15\) A randomized trial exploring 2 different schedules of ifosfamide 9 g/m\(^2\) in comparison to doxorubicin did not demonstrate any advantage over doxorubicin.\(^2\) Along with doxorubicin, ifosfamide is currently considered one of the most active agents against soft tissue sarcomas.

**Dacarbazine**

The activity of dacarbazine in soft tissue sarcomas was first reported in the 1970s.\(^16\) Although its activity is generally considered less than that of doxorubicin or ifosfamide, dacarbazine has activity as second-line therapy.\(^17\) There has been resurgence in the use of dacarbazine for pretreated soft tissue sarcoma in recent years.\(^18\) Dacarbazine currently serves as the control arm in 2 large phase III trials in pretreated leiomyosarcoma and liposarcoma.\(^19,20\) The combination of dacarbazine and gemcitabine has shown improved overall survival (OS) and progression-free survival (PFS) over dacarbazine alone in a randomized phase II trial, and showed limited efficacy of single-agent dacarbazine with only a 2-month median PFS.\(^21\)

**Doxorubicin-Based Combination Therapies**

Numerous chemotherapies have been studied in combination with doxorubicin, including dacarbazine, cyclophosphamide, vincristine, and ifosfamide. Among these,
doxorubicin and ifosfamide containing regimens have been considered the most active. The combination of doxorubicin, ifosfamide, and dacarbazine (MAID) was reported to have a 47% response rate in a cooperative group phase II trial. Several studies of doxorubicin or epirubicin combined with ifosfamide reported response rates in excess of 50%, 23,24

The advent of growth factor support permitted dose intensity in combination regimens, and reports suggested that higher doses of doxorubicin and ifosfamide were associated with better outcome. However, subsequent studies have questioned the importance of dose-intensity in treatment of sarcomas and randomized trials have failed to show survival benefit to such strategies. 15,27,29

The high response rates of combined doxorubicin and ifosfamide eventually led to evaluation in clinical trials compared to single-agent doxorubicin (Table 1). Although doxorubicin and ifosfamide regimens were often found to have higher response rates, no significant difference in overall survival compared with single-agent doxorubicin has been observed. Based on these data, single-agent doxorubicin has been the accepted standard in Europe for a number of years. In the United States, many centers have continued to view combined doxorubicin and ifosfamide as standard treatment for advanced soft tissue sarcomas. In 2012, results from EORTC 62012 were reported, a large phase III trial comparing doxorubicin and ifosfamide with single-agent doxorubicin, and using growth factor support to promote modern dose intensity in the combination arm.3 This trial, long awaited as the definitive answer to the question of single-agent or combination therapy, showed improved response rate and progression-free survival with doxorubicin and ifosfamide, but no significant overall survival advantage compared to doxorubicin alone. However, given the PFS and response advantage reported in the EORTC 62012 trial, it remains unknown whether the potentially more “active” combination regimen might have meaningful benefit to any individual patient with soft-tissue sarcoma.

It seems that in 2013, we have come full circle to the recognition of single-agent doxorubicin as the standard therapy for advanced soft tissue sarcomas. Doxorubicin is the recognized first-line chemotherapy for general soft tissue sarcoma use, with no other single-agent or combination showing significant overall survival superiority.2 The use of doublet therapy in patients whom aggressive downsizing or subsequent metastasectomy is of clinical relevancy remains a valid consideration.

**Other Chemotherapy Strategies**

The nucleoside analog gemcitabine has shown modest activity against soft tissue sarcomas in a number of phase II studies. 30–34 Subsequently, the combination of gemcitabine plus docetaxel was found to have activity that suggested possible synergy between the agents, despite the general lack of activity of single-agent docetaxel in soft tissue sarcomas. 35–39

The activity of gemcitabine and docetaxel is considered to be most pertinent to leiomyosarcoma, in particular uterine leiomyosarcoma. A randomized trial including a variety of histologies showed an advantage of the combination over single-agent gemcitabine, while another randomized trial specifically in leiomyosarcoma did not show a difference in response rates, questioning the utility of the combination. 40

Despite a lack of comparative efficacy data with doxorubicin, the gemcitabine and docetaxel combination is sometimes used as a first-line regimen in the United States. The toxicity of this regimen is often underestimated, and it should not be assumed to have a better tolerability than single-agent doxorubicin. A phase III trial comparing gemcitabine and docetaxel with doxorubicin in the first-line setting is currently ongoing in the United Kingdom. 41

In recent years, we have seen an increased trend of selecting chemotherapy based on histologic subtype. Included among the types of sarcoma for which alternate chemotherapy choices are often considered are synovial sarcoma (high-dose ifosfamide42), angiosarcoma (taxanes, 43 liposomal doxorubicin44), leiomyosarcoma (gemcitabine and docetaxel, 38 trabectedin45), and myxoid liposarcoma (trabectedin45). Most of these associations are based on small series or phase II trials, and randomized trials validating such choices are either lacking or ongoing.

**New Cytotoxics**

Trabectedin is a marine alkaloid initially isolated from an invertebrate sea squirt, *Ecteinascidin turbinate*. Its cytotoxic mechanism of action is not fully defined, but is thought to exhibit its activity through binding to the minor groove of DNA. 46 Based on many phase II data demonstrating activity in pretreated soft tissues sarcomas, especially leiomyosarcoma and liposarcomas, trabectedin has been approved in numerous countries worldwide, with notable exceptions being the United States and Australia. 45,47 Trabectedin is currently in phase III testing versus dacarbazine in leiomyosarcoma and liposarcoma, the results of which may serve to support registration in other countries. 20

Eribulin is a synthetic analog of halichondrin B, derived from marine sponges, that works through inhibition of microtubule function in a mechanism of action distinct from those of other antitubulin drugs. A phase II study by the EORTC showed favorable progression-free survival, most notably in liposarcoma and leiomyosarcoma, and a phase III trial versus dacarbazine is currently accruing in pretreated patients with these histologies. 19,48

Several compounds related to ifosfamide metabolites are in current phase III testing and hold promise to circumvent some of the toxicities of ifosfamide while maintaining activity. Palifosfamide, the DNA-alkylating metabolite of ifosfamide, does not generate acrolein and chloracetaldehyde as toxic byproducts of metabolism and bypasses potential resistance mechanisms mediated by aldehyde dehydrogenase enzymes. 49 A randomized phase II trial showed improved progression-free survival of doxorubicin with palifosfamide compared with doxorubicin alone. 50 TH-302 is a hypoxia-activated prodrug composed of 2-nitroimidazole conjugated to a bromo-substituted analog of isophosphoramide mustard, an active metabolite of ifosfamide. 51 A phase I trial of
doxorubicin + TH-302 in patients with soft tissue sarcoma showed promising activity with modest side effects. Two current phase III trials are comparing single-agent doxorubicin to doxorubicin with TH-302 or palifosfamide, respectively. If positive, these trials will force examination of the role of ifosfamide in sarcoma treatment, warranting careful consideration of issues such as quality of life and cost.

**Future Directions**

Although select chemotherapy agents have activity against soft tissue sarcoma, their overall effect against these diseases remains minimal. In the clinic, it is clear that select patients benefit from these drugs, with occasional profound responses seen, and therefore cytotoxics are still the primary treatment of choice for most patients with metastatic disease. Single-agent doxorubicin, 40 years after its first reports of activity, remains the standard to which new agents should be compared in randomized trials.

**MOLECULARLY TARGETED AGENTS**

Sarcomas such as GIST and DFSP have helped pave the way for direct bench to bedside translation and have provided important insights into treating other solid tumors with molecularly-directed therapies. In the case of GIST, a confluence of key events have enabled a dramatic improvement in outcomes for patients including the discovery of activating mutations in KIT, the development of a reliable and broadly applicable diagnostic test (CD117 expression), and the availability of a reasonably selective and potent kinase inhibitor (imatinib) that targets the most common driver mutations in GIST. Following on from these initial proof of principle studies, progress has continued at a steady rate, and we now have three approved agents for the treatment of metastatic GIST, an approved adjuvant systemic therapy, and continued refinements of treatment algorithms focused on personalizing treatments for each patient’s unique disease characteristics. These advancements have largely come about because of ongoing efforts to develop and share GIST laboratory models that have allowed for rapid and reasonably robust translation of new agents into the clinic, proof of concept trials with a strong translational focus, and outstanding international collaborative efforts focused on conducting adequately powered definitive clinical trials.

**mTOR Inhibitors**

The phosphotidylinositol 3-kinase (PI3K)/Akt/mTOR pathway is a cell signaling pathway which plays a central role in the control of cell proliferation, survival, mobility and angiogenesis. The mTOR pathway is abnormally activated in a number of sarcomas, providing a rationale for the formal evaluation of mTOR inhibitors as therapeutic agents. The largest trials of mTOR inhibition in sarcomas conducted to date have been with the mTOR inhibitor ridaforolimus. In a phase I dose escalation trial of ridaforolimus administered to patients with advanced malignancies, seven patients with sarcoma were enrolled; with all of these patients noted to have a partial response (two patients), minor response or stable disease for more than three months. This led to the conduct of a phase II study of ridaforolimus in patients with advanced soft tissue or bone sarcoma, with a primary endpoint of clinical benefit response, defined as complete or partial response or stable disease for ≥16 weeks. Of the 212 patients enrolled on this trial, 61 patients (29%) had a clinical benefit response, including five partial responses.

In light of what was considered to be promising clinical activity and an acceptable safety profile in this phase II trial, this agent was evaluated in a large, international randomized phase III double-blind placebo-controlled trial: ‘Ridaforolimus in Treatment of Sarcoma–SUCCEED (Sarcoma Multi-Center Clinical Evaluation of the Efficacy of Ridaforolimus)’. Results of the SUCCEED trial were initially presented at the ASCO Annual Meeting in Chicago 2011, and have recently been published. 711 patients with bone or soft tissue sarcoma who had achieved a favorable response to chemotherapy (objective response or stable disease) were randomized to receive ridaforolimus or placebo on a 1:1 basis as a maintenance therapy. The study’s primary endpoint PFS was met, with a statistically significant difference between the two arms; median PFS: 17.7 versus 14.6 weeks for ridaforolimus versus placebo (hazard ratio = 0.72; 95% confidence interval: 0.61, 0.85; p = 0.0001). Median OS was not significantly different: ridaforolimus 90.6 versus 85.3 weeks with placebo (HR = 0.93; 95% CI: 0.78, 1.12; p = 0.46). There were other clear signals of biologic activity of ridaforolimus in these patients, as evidenced by a significantly higher clinical benefit rate, 40% compared with 29%; and a mean decrease of 1.3% as the best response in target lesions in the ridaforolimus group compared to a 10.3% increase in the placebo group.

The key issue relates to whether the magnitude of the benefit seen would be considered large enough to transform clinical practice. Early indications, at least as far as regulatory approval goes, suggests this may not be the case with a rejection by the United States Food and Drug Administration (FDA) and other agencies, as has been discussed in the accompanying manuscript by Blay et al. Given clear hints of biologic activity, the challenge is to be able to better define subpopulations of patients with tumors that are more (or less) dependent on signaling through mTOR. The investigators from this study have collected tumor samples from treated patients, with analyses ongoing to identify potential predictive markers of mTOR inhibition. These results will be eagerly awaited, but it remains to be seen whether the molecular tools available to us at this stage are sophisticated enough to allow us to determine this with any confidence.

**ANGIOGENESIS INHIBITORS**

A number of angiogenesis inhibitors have been trialed in sarcomas, initially based on a rationale that increased VEGF expression correlates with higher-grade soft tissue sarcomas (STS) and a poorer outcome. The best studied of these is pazopanib, the agent now approved by several regulatory
authorities for the treatment of refractory soft tissue sarcoma. Pazopanib is an oral kinase inhibitor targeting VEGF-R, PDGFR and c-KIT that showed promising activity in a large multiarm phase II trial of soft tissue sarcomas conducted by the EORTC. In an effort to differentiate activity across a spectrum of STSs, and take a pragmatic approach in being able to predict what tumor types would not benefit from pazopanib, this trial stratified patients into four different arms based on traditional anatomic pathology criteria. Activity, defined as progression free rate at 12 weeks (PFR12 weeks) was seen in three (synovial sarcoma, leiomyosarcoma and other STS subtypes) of the groups; but not in the adipocytic group, although the limited number of patients studied did not fully explore potential activity of pazopanib in this subgroup. These results provided the rationale for the conduct of an international randomized phase III (the PALLETTE, or Pazopanib Explored in Soft Tissue Sarcoma) trial in patients with STS refractory to conventional chemotherapy. In this trial, 369 patients who had received up to 4 lines of prior chemotherapy were randomized to pazopanib (800 mg/d) or placebo. Although the primary endpoint of the study, OS was not found to be statistically significant on an interim analysis (p = 0.18, 11.9 versus 10.4 months); there was a significant improvement in PFS seen (p < 0.0001, HR: 0.31; 4.6 versus 1.5 months). The lack of translation of translation from a PFS to an OS benefit was surprising, given that cross-over from placebo to pazopanib was not allowed; and that this trial was really designed to enrol patients who were refractory to chemotherapy, i.e., for whom this would be the last treatment. However, there was a high rate of use post-trial systemic therapy with other agents, potentially impacting on the ultimate effect of pazopanib.

Many other angiogenesis inhibitors have also shown some level of activity in specific subtypes of soft tissue sarcomas, particularly in angiosarcomas and alveolar soft part sarcomas (ASPS). With angiosarcomas, activity has been noted with a number of agents including sorafenib (5 of 37 patients with a partial response); and bevacizumab (17% objective response rate with 50% stable disease from 30 evaluable patients). ASPS is an essentially chemoresistant disease. In a case series of 10 patients with unresectable progressive ASPS, treated with sunitinib 37.5 mg daily continuously via a compassionate access scheme, five of eight (63%) assessable patients demonstrated a partial response with a further patient exhibiting stable disease for >6 months. Cediranib, a multitargeted kinase inhibitor with potent VEGF-inhibition is currently being tested in international collaborative efforts in two phase II trials; a single-arm and a randomized, placebo-controlled study. Initial results of the single-arm study, based on data from the first 28 of a total of 60 planned patients treated showed 12 (43%) PRs and a further 10 (36%) patients with stable disease.

Considerable efforts are underway to explore potential underlying mechanisms of response to cediranib in these trials. However, it still remain unclear on how we can potentially identify what the molecular drivers are in these individual tumors that confers such a high degree of sensitivity to these particular kinase inhibitors. The dynamic interplay between tumor cells, and their surrounding stroma has made it difficult to determine what angiogenic pathways are activated at the time of treatment. The approach to developing angiogenesis inhibitors in sarcomas has therefore needed to be pragmatic, relying on clinical observations in patient populations defined by traditional anatomic pathology criteria rather than being (predictive) biomarker driven, as is the current desire for drug development in many solid tumors.

**Other Pathway-Directed Agents**

Several other pathways are being actively investigated as new agents become available for clinical evaluation. Some of these are pathways that have been well described for years, but thought to be too difficult to target in vivo. For example, dysregulation of the p53 pathway via mutation of p53 is commonly seen in pleomorphic sarcomas. In the case of well-differentiated/dedifferentiated liposarcoma, p53 is dysregulated via amplification of MDM2, a key modulator of p53; along with amplification of CDK4.

A number of first and second-generation p53/MDM2 inhibitors along with inhibitors of CDK4 are now in early clinical development. A key focus for the development of these molecules, both at the proof of concept stage and beyond, will be on understanding how complex the modulation of p53 really is in an in vivo setting, and therefore not only how “drugable” it is but also on whether a single target such as p53/MDM2 can act as a critical gateway to a protein such as p53.

An alternate approach that has been adopted with success on a number of occasions has involved taking a proactive role in rapidly translating emerging data on newly identified molecular drivers into small proof of concept trials. These have often been in rare sarcomas, that interestingly have also been resistant to conventional cytotoxics; perhaps adding further weight to the argument that these tumors were dependent on a single molecular pathway. An early example of this approach was with the development of imatinib in dermatofibrosarcoma protubersans (DFSP). In DFSP, a characteristic translocation (t17:22) results in the creating of a fusion oncogene between COL1A1 and PDGFB, which functionally switches on PDGFB resulting in a constitutively activated pathway. Imatinib’s PDGF inhibition has been exploited successfully with confirmed clinical activity in this disease, leading to its expanded regulatory approval for this indication.

Other successes have been noted through taking similar opportunistic approaches. These might be through the use of an existing drug to rationally treat a newly discovered target, such as with DFSP; or by efforts to identify patients for participation in a trial of a new therapeutic targeting a previously identified pathway. A recent example of this has been with the recruitment of two patients with Inflammatory myofibroblastic tumor (IMTs) on the phase I trial of the MET and ALK inhibitor crizotinib. Dysregulation of ALK can occur in approximately half of patients with IMT. One of these two patients treated on the crizotinib trial, who had an ALK-translocated IMT had a sustained response, while the other patient who did not have an ALK translocation did not
respond. As was seen with crizotinib’s development in non-small cell lung cancer, the high rates of response in ALK-translocated tumors may suggest similar results in the subset of translocated-IMT.

CONCLUSION
The systemic management of sarcomas continues to evolve. With regards to cytotoxic chemotherapy, doxorubicin remains at the core of conventional management of patients with most sarcoma subsets. As is now the case with most solid tumors, much of the current focus on improving outcomes in sarcoma revolves around the ability to better understand what the key molecular drivers are in an individual’s tumor, thus enabling a more tailored treatment approach. Parallel to this, efforts will continue to improve clinical outcomes using a more empiric approach, by either combining cytotoxic agents with targeted therapeutics or by combining cytotoxics.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

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