Review

Soft Tissue Sarcomas of Adults: State of the Translational Science


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Abstract

Sarcomas—like leukemias, which are also mesodermal malignancies—carry biological significance disproportionate to their clinical frequency. Identification of mutations and translocations associated with these tumors has illuminated aberrant signaling pathways that cause these diseases, determine their behavior, and are therapeutic targets. Activated receptor-associated tyrosine kinase c-kit, mutated in most gastrointestinal stromal tumors, has proven to be a clinically effective target for enzyme inhibition. A translocation involving a single gene family, consisting of EWS and related genes, has been identified in five different sarcomas, and its chimeric protein products could prove similarly amenable to inhibitors. Resolution of the histopathological complexity is being aided by data from molecular and chromosomal characterization. Improvements in imaging, definition of prognostic factors, and surgical and radiotherapeutic treatment have resulted in improved local control. Continued progress will depend on further adapting the rapidly evolving technologies of genomics and proteomics. It will also depend on accurate histopathological diagnosis based on validated reagents and consistent methodologies applied to adequate tissue samples derived from patients with complete clinical data. Finally, multicenter, coordinated trials, such as those that occurred with assessment of imatinib mesylate in metastatic gastrointestinal stromal tumors, will assure the most rapid reductions in morbidity and mortality.

Introduction

The success of imatinib mesylate in treating GISTs has resulted in greater appreciation over the past 2 years of how studies of soft tissue sarcoma can enhance the understanding of cancer biology and development of targeted therapeutics. This realization has been long overdue. Sarcoma research over the last decade, particularly in the clinical arena, has languished. Chairs of cooperative groups and a few institutions of excellence have struggled to keep clinical and translational sarcoma research alive.

Variation in pathological definition has made it difficult to obtain exact numbers of patients with sarcomas. Based on the Surveillance, Epidemiology, and End Results (SEER) database, approximately 15,000 new cases of sarcoma, both bone and soft tissue, are diagnosed in the United States on an annual basis. This places sarcoma incidence within the same order of magnitude as myeloma, cervical carcinomas, gliomas, and carcinomas of the esophagus and makes it much more common than testicular carcinomas or Hodgkin’s disease.

Progress in treatment of adult soft tissue sarcomas from 1970–1990 included improvements in pathological definition, staging, use of radiotherapy as an adjunct to other modalities, definition of doxorubicin and ifosfamide as active drugs, and surgical advances in functional preservation. Parallel progress in treatment of pediatric sarcomas established a model for successful interinstitutional collaboration for multidisciplinary management of specific sarcoma types. During 1990 to 2000, progress included identification of translocations, further use of immunohistochemistry, introduction of new imaging modalities, and refinements in prognosis—advances made mostly through the

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3 The abbreviations used are: GIST, gastrointestinal stromal tumor; AJCC, American Joint Committee on Cancer; PNET, primitive neuroectodermal tumor; ALT, alternative lengthening of telomeres; FNA, fine needle aspiration; MFH, malignant fibrous histiocytoma; NCI, National Cancer Institute; EGF-R, epidermal growth factor receptor; PDGF-R, platelet-derived growth factor receptor; MRI, magnetic resonance imaging; PET, positron emission tomography; IMRT, intensity-modulated radiotherapy; EORTC, European Organization for Research and Treatment of Cancer; HR, hazard ratio; PI3K, phosphatidylinositol 3’-kinase.
work of individual institutions. This summary addresses three major areas critical to reduction in sarcoma morbidity and mortality in the 21st century: (a) molecular and pathological redefinitions of sarcomas; (b) improvement in primary management including new imaging modalities; and (c) identification and clinical development of targeted systemic therapies.

**Molecular and Pathological Redefinition**

**Current Prognostic Factors for Outcome in Soft Tissue Sarcoma**

Traditional staging for soft tissue sarcoma has been based predominantly on grade and presence of metastasis (1). Grade is a significant factor in outcome. In primary extremity lesions, 10-year disease-specific survival for high-grade lesions is 55% compared with 90% for low-grade lesions. Size was originally considered a subgroup of grade with small high-grade tumors (<5 cm) categorized as stage III, a category with poor 5-year survival of approximately 35%. Subsequently, it was found that patients with small high-grade tumors undergoing primary treatment at referral institutions had an overall metastasis-free survival of 90%, placing them in a lower risk group (2). Site is a major primary risk factor for outcome (Fig. 1A). In extremity/trunk sarcomas, local control is generally good, and systemic disease is the cause of demise. In retroperitoneal lesions, death is most often from local progression.

Less than 3% of adult sarcoma patients will have metastases to lymph nodes, although some epithelioid subtypes have a higher prevalence (3). Long-term survival associated with lymph node metastasis is equivalent to that associated with metastasis to any other site.

An analysis of 1000 consecutive patients identifying significant adverse factors for local recurrence, post-metastasis survival, distant recurrence, and disease-specific survival for extremity sarcoma resulted in the AJCC staging system (Table 1; Refs. 4 and 5). Large superficial lesions—both low-grade (1B) and high-grade (2C)—are rare. Excellent survival discrimination can be provided by an alternative system that incorporates low-grade tumors regardless of size and depth (1A, 1B, and 2A) into one category, combines small high-grade lesions (2B and 2C) into another, and divides large high-grade lesions into >5 cm (3A) and >10 cm (3B) categories (Fig. 1B; Ref. 6).

Recently, a nomogram for 12-year sarcoma subtype-specific death rate has been published based on the experience at Memorial Sloan-Kettering Cancer Center (7). This nomogram, which may prove more precise than the AJCC system, encompasses six of the more common histopathologies (fibrosarcoma, leiomyosarcoma, liposarcoma, MFH, malignant peripheral nerve sheath tumors, and synovial sarcoma), with all other histopathologies combined into one group.

**Molecular Pathogenesis of Soft Tissue Sarcomas**

In the past, the relative paucity of treatment options shaped a minimalist view of sarcoma classification, based on histological grade, size, depth, and location and not specific histopathological subtypes. This lumping approach may have hampered studies of biological prognostic markers, the roles of which may vary substantially among sarcoma subtypes. Likewise, low response rates to conventional or experimental therapies in studies combining multiple sarcoma subtypes may have obscured higher response rates in individual unrecognized subtypes.

In recent years, it has become apparent that the genetics of sarcomas segregate into two major types, along the lines of broad distinctions originally noted by cancer cytogeneticists (8, 9): (a) sarcomas with specific genetic alterations and usually simple karyotypes, including fusion genes due to reciprocal translocations (e.g., PAX3-FKHR in alveolar rhabdomyosarcomas) and specific point mutations (e.g., KIT mutations in GISTs); and (b) sarcomas with nonspecific genetic alterations and complex unbalanced karyotypes, reflected by numerous genetic losses and gains. **Fig. 1** Primary soft tissue sarcoma survival by prognostic factors. A, survival by primary site based on 3677 patients evaluated at Memorial Sloan-Kettering Cancer Center, 1982–2001. B, distant relapse-free survival by stage based on grouped AJCC stages (excluding angiosarcoma, desmoid, dermatofibrosarcoma, protuberans, and malignant mesenchymoma) among 1326 patients with primary extremity soft tissue sarcoma, Memorial Sloan-Kettering Cancer Center, 1982–2001.
Most of the specific recurrent chromosomal translocations have been cloned, and most of the resulting fusion genes have been identified (Table 2). These include 11 different gene fusions involving the EWS gene or EWS family members (TLS, TAF2N, TLS-CHOP) found in five different sarcomas, and 10 other types of fusions in seven other sarcoma types (10). In aggregate, fusion gene-related sarcomas may account for a third of all sarcomas (8).

In addition to providing specific and powerful diagnostic markers, fusion genes resulting from these translocations encode chimeric proteins that are important to the biology of the tumors, acting as abnormal transcription factors that deregulate the transcription of multiple downstream genes and pathways (11). The key role of these chimeric proteins in pathogenesis is supported by their requirement for in vitro growth of corresponding sarcoma cell lines and the impact of relatively minor variability in the structure of these chimeric proteins (due to variant cytogenetic or molecular breakpoints) on tumor phenotype and clinical behavior (12–15).

Tumor-type specificity of these gene fusions may reflect a dynamic relationship with the cellular environment in which the gene fusion is oncogenic in a specific susceptible cell type at a particular developmental stage (16). The gene fusion may then modify the phenotype of the susceptible cell. Specificity for a particular mesenchymal cell type may account for the difficulty in developing transgenic mouse models of this class of sarcomas. Only one sarcoma translocation has been successfully modeled in mice, namely, a transgenic mouse model of myxoid liposarcoma using a TLS-CHOP transgene driven by the elongation factor-1 promoter (17). Attempts to model several other translocation-associated sarcomas have failed (18).

Separation of primary or early genetic lesions from secondary or late lesions has led to a relatively simple molecular pathological model in which the earliest known genetic event is a specific chromosomal translocation in a specific precursor cell or stem cell. In most cases, this is an apparently random event, but it could, in rare cases, be related to radiotherapy-induced DNA damage (19). The resulting aberrant transcription factors or tyrosine kinases deregulate multiple key cellular pathways. Thus, potential therapeutic targets include the resultant fusion proteins themselves as well as genes that are key downstream targets of these aberrant transcription factors (20–22). The aberrant transcriptional protein is important for the maintenance of the malignant phenotype and determines the behavior of the sarcoma after initiation. In some cases, secondary genetic lesions produce more aggressive tumor subsets as seen in sarcomas with complex karyotypes described in the next section.

### Sarcomas with Complex Karyotypes Lacking Specific Genetic Alterations

Sarcomas with complex unbalanced karyotypes lacking specific translocations include osteosarcoma, MFH, liposarcoma (other than myxoid type), angiosarcoma, MFH, liposarcoma (other than myxoid type), angio...
Sarcoma, leiomyosarcoma, adult fibrosarcoma, and skeletal chondrosarcoma.

Two possible pathways of karyotypic complexity have been suggested by mouse models. Both have been associated with abrogation of p53 checkpoint function. In the first, progressive telomere erosion resulted in associations between heterologous telomeres leading to chromosomal fusion-bridge-breakage cycles and nonreciprocal translocations (23). The unbalanced karyotype was then stabilized by the reactivation of telomerase or by the mechanism of ALT. In mice, this model has been associated with epithelial cancers, but similar cytogenetic processes have been observed in human sarcomas (24–26). In a second murine model of karyotypic complexity, impaired joining of nonhomologous ends promotes chromosomal translocations, amplifications, and deletions, due to an increase in unrepaired double-strand breaks. This mechanism has led to formation of soft tissue sarcomas in mice of the same histological types as human sarcomas lacking specific translocations (27). Although these sarcomas lack the convenient organizing principle provided by specific translocations, microarrays may help to identify meaningful patterns within the cytogenetic complexity of this group of soft tissue sarcomas (28).

Inactivation of the p53 pathway appears to be a key differentiating factor between sarcomas with simple genetic alterations and those with karyotypic complexity (Table 3). Common modes of p53 pathway inactivation in sarcomas include p53 point mutations, homozygous deletion of CDKN2A, which encodes both p14ARF and p16, and MDM2 amplification. In sarcomas with specific reciprocal translocations, p53 pathway alteration is a rare event, but when present, it has been a strong prognostic factor, associated with significantly decreased survival in synovial sarcoma (29), myxoid liposarcoma (30), and Ewing’s sarcoma/PNET (31, 32). Decreased survival in Ewing’s sarcoma/PNET was associated with deletion of CDKN2A representing a type of p53 pathway alteration through loss of the CDKN2A alternative product, p14ARF (33, 34). In these studies, the impact of secondary alterations in the p53 pathway on clinical behavior was statistically demonstrable despite their low prevalence. By contrast, among sarcomas with unbalanced karyotypes, p53 pathway alteration was more prevalent and had weaker prognostic value, often requiring large numbers of patients to achieve statistical significance (35, 36).

These observations are consistent with the p53 pathway being at least partially functional in most sarcomas with specific translocations, acting as an apoptotic or senescent brake on cellular effects of the fusion oncogene (37). In contrast, in sarcomas with nonspecific genetic alterations, p53 pathway inactivation may be a common early event needed to overcome checkpoints triggered by senescence, telomere erosion, or double-strand breaks in the progression of these sarcomas. Its more widespread role in this class of sarcomas may account for its limited ability to define distinct clinical subsets in these tumors.

**Molecular Pathology of Adult Soft Tissue Sarcoma: New Directions.** Development of specific therapeutics for soft tissue sarcomas will benefit from framing their molecular pathogenesis in the context of the new understanding of cancer genetics, which has evolved from the “multiple hits” model to the “hallmarks of cancer” approach. As recently proposed, the hallmarks are six critical pathophysiological events required for cancer development including self-sufficiency of growth signals, insensitivity to anti-growth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis (38). These can occur in any order and by any number of mechanisms. Relating genetic alterations (whether specific translocations or complex, nonspecific alterations) in soft tissue sarcoma to these six hallmarks will provide a more rational foundation for identifying new targeting strategies.

Among tumors with complex karyotypes, the relative timing of common oncogenic events remains unclear and cannot readily be extrapolated from mouse models. Data from sarcomas that arise in patients with bilateral retinoblastoma or Li-Fraumeni syndrome may shed light on this issue because timing of one genetic event is known. For example, most sarcomas that arise in patients with bilateral retinoblastoma show p53 mutations (39). Equivalent data on the presence of Rb mutations or loss in sarcomas from patients with Li-Fraumeni syndrome (harboring constitutional p53 mutation) are not presently available (40). It remains to be determined whether functional differences arise in soft tissue sarcomas that inactivate the p53 pathway by 12q13 amplification causing MDM2 overexpression (e.g., atypical lipomatous tumors) compared with sarcomas with p53 mutations. The telomere phenotype of these sarcomas also remains unclear. Data from several studies suggest that telomere maintenance mechanisms may be substantially different in sarcomas compared with epithelial cancers. The ALT mechanism appears more common in sarcomas (25) but may occur preferentially in sarcomas lacking specific translocations (41). A subset of sarcomas with specific genetic alterations, usually complex, may represent a type of p53 pathway alteration through loss of p14ARF (33, 34). In these studies, the impact of secondary alterations in the p53 pathway on clinical behavior was statistically demonstrable despite their low prevalence.

### Table 3 Biological characteristics of sarcomas by type of associated genetic alterations

<table>
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<tr>
<th>Characteristic</th>
<th>Sarcomas with specific genetic alterations</th>
<th>Sarcomas with nonspecific genetic alterations</th>
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<tbody>
<tr>
<td>Karyotypes</td>
<td>Often simple</td>
<td>Usually complex</td>
</tr>
<tr>
<td>Translocations</td>
<td>Reciprocal &amp; specific</td>
<td>Nonreciprocal &amp; nonspecific</td>
</tr>
<tr>
<td>Average age at diagnosis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>27</td>
<td>57</td>
</tr>
<tr>
<td>Prevalence of p53 pathway alterations</td>
<td>Relatively low</td>
<td>High</td>
</tr>
<tr>
<td>Prognostic impact of p53 pathway alterations</td>
<td>Strong</td>
<td>Weak to moderate</td>
</tr>
<tr>
<td>Incidence in p53 mutant or knockout mouse models</td>
<td>Rare, if ever</td>
<td>Common</td>
</tr>
<tr>
<td>Incidence in bilateral retinoblastoma and Li-Fraumeni syndrome&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Incidence among radiation-induced sarcomas</td>
<td>Rare</td>
<td>Common</td>
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<sup>a</sup> Ref. 9. <sup>b</sup> Ref. 40.
comas may lack both telomerase activity and evidence of ALT (42), and there are recent data suggesting that such telomere maintenance mechanism-negative subsets may be associated with favorable prognosis (43). In contrast, another subset of sarcomas shows evidence of both telomerase activity and ALT (42, 43). However, many studies have only examined one aspect of the telomere phenotype at a time (telomerase activity, telomerase reverse transcriptase expression, or telomere length), and the study groups have been heterogeneous, complicating the interpretation of the observed correlations (44–46).

Among sarcomas with specific translocations, the interaction between fusion oncogenes and the p53 pathway, an area where interesting data have been emerging, also requires more study (47, 48). In addition, telomere phenotype—whether these tumors arise from telomerase-positive mesenchymal stem cells or reactivate telomerase in some other way—remains to be determined. Future studies will benefit from appropriate type-specific cell lines, still to be developed for some sarcomas.

Microarray Analysis

Because sarcomas comprise a heterogeneous group of tumors that are often difficult to classify, microarray analyses may prove particularly useful in sarcoma classification. Microarrays composed of either synthetic oligonucleotides or cDNAs allow determination of the parallel expression of thousands of genes in a given specimen (49), although difficulties remain in comparing results from these two methods. Statistical techniques applied to these data can be used to evaluate genes associated with various diagnostic groups and to discover classes of tumors not differentiated by conventional criteria. Such studies go beyond the problem of classification by elucidating mechanisms regulating tumor growth, identifying prognostic markers, and accelerating drug target discovery.

In microarray analysis, it is first necessary to profile as many tumor specimens as possible, covering the spectrum of conventionally determined diagnoses. For sarcomas, pathological review of the specimens is particularly important. Statistical tools are used to identify genes tracking with specific diagnoses. Parallel analysis looking for inherent subsets within the data are also carried out. These results can identify genes that discriminate subsets within a diagnostic entity and can reveal discordances between conventional diagnoses and gene expression patterns. If clinical data are available, genes that correlate with clinically relevant endpoints such as stage, therapeutic response, and metastasis can also be identified. From these analyses, the investigator compiles lists of genes that are relatively disease specific and may relate to diagnostic subset analysis or clinical correlates. These lists can then be mined to identify potentially useful diagnostic markers and genes that might participate in growth-regulatory pathways.

The heterogenous composition of tumors is a frequent concern in microarray analysis. Microdissection is labor intensive and requires amplification of the scant amount of RNA produced (50). As a result, most investigators use whole tissue samples that include inflammatory cells, endothelial cells, smooth muscle, and other normal elements. Gene expression signatures of normal elements can be recognized and subtracted by analysis software, but these cells may also be important to tumor biology. For example, high inflammatory cell content may affect tumor behavior. Follow-up studies using in situ techniques can resolve the cell type expressing any given gene.

Sample size for microarray analysis is critical. Samples that produce 1–10 μg of RNA are relatively easy to analyze. These amounts of tissue are readily obtained from core biopsies or surgical samples but are more than would usually be obtained from FNA used in sarcoma diagnosis. FNA material can be processed for microarray studies but requires high level RNA amplification, which may result in distortion of RNA abundance. Sample size requirements are critical in planning clinical studies because merging data from samples processed with amplification technologies with those processed without amplification is not practical. Obtaining samples from residual tumor after neoadjuvant therapy or from metastases and recurrences adds an important dimension to data analysis and should be sought whenever possible.

Diagnostic gene expression profiles have been described for rhabdomyosarcoma and Ewing’s sarcoma (51). The Ewing’s profile includes some genes that appear to be downstream of the pathogenic EWS-FLI1 fusion oncogene (48). Characteristic gene expression profiles have also been described for GIST and synovial sarcoma (52, 53). Interestingly, MFH has exhibited considerable heterogeneity, but this may resolve into distinct patterns with larger sample numbers. Of importance, KIT emerged as one of the prominent discriminator genes for MFH on microarray analysis (53).

Microarray analyses of sarcomas will also allow identification of expressed genes that are inhibited by targeted therapeutics developed for treatment of other, more common cancers. Expression of erb-B2 by the epithelial component of biphasic synovial sarcoma has recently been demonstrated by expression microarray and tissue microarray analysis, raising the possibility that Herceptin may be of value in this disease (54).

Pathology of Soft Tissue Sarcomas

Pathological assessment of soft tissue sarcomas has advanced considerably in the past 10–15 years. More accurate diagnostic subclassification has been aided by characterization of previously unrecognized morphological entities and centralization of pathology review for major clinical trials. Further refinement has resulted from use of validated histological grading systems, particularly those of the French Cancer Centers and the United States NCI, of which the French system is now widely recognized as the most useful (55, 56). New cytogenetic and molecular genetic techniques have demonstrated diagnostic and prognostic utility (11, 57).

These advances have lead to greater appreciation of the distinct clinicopathological and biological features and natural histories that characterize the approximately 50 histological subtypes of soft tissue sarcoma. Use of the term “MFH” has also decreased; rather than being the most common adult sarcoma, MFH is now regarded as a diagnosis of exclusion, essentially synonymous with undifferentiated pleomorphic sarcoma (58). The clinical and prognostic heterogeneity formerly subsumed within MFH is now better recognized (59, 60), and this is reflected in the new 2002 WHO Classification (58). The most common constituents of the group formerly classified as MFH include myxofibrosarcoma, liposarcoma (both dedifferentiated and pleomorphic types), and leiomyosarcoma. Sarcomatoid ex-
amples of nonmesenchymal neoplasms have also often been mislabeled as MFH. As a result, retrospective reclassification of existing large case registries dominated by the diagnostic category “MFH” will likely be needed.

Despite these advances, pathological studies in soft tissue sarcoma continue to be plagued by small numbers (particularly of single histological types), inconsistent or poorly defined diagnostic criteria, and limited follow-up data. In addition, cytogenetic and molecular genetic techniques are used routinely in a small minority of centers. Even in specialized centers, little use is made of the potential prognostic information provided by differences in fusion genes or breakpoints in tumors such as Ewing’s sarcoma/PNET, synovial sarcoma, and alveolar rhabdomyosarcoma. Validation studies, as well as comparative analyses of different techniques such as reverse transcription-PCR and fluorescent in situ hybridization, are needed. Given the small numbers of these tumors seen by most laboratories, results are likely to be unreliable, and centralized evaluation may be needed (61).

Guidelines are also needed concerning optimal provision of sarcoma tissue for pathological analysis. Whereas diagnoses based on FNA or narrow gauge core needle biopsies are increasingly popular, limited sample volumes can make grading and subclassifying sarcomas difficult. Alterations due to preoperative radiation or chemotherapy often make meaningful pathological assessment of resected specimens impossible. Greater use of initial open biopsies should thus be considered not only to optimize diagnostic/grading accuracy but also to allow acquisition of untreated tissue for cytogenetics and essential, immediate snap freezing.

In assessing the effect of preoperative therapy, pathologists cannot readily distinguish between spontaneous and therapy-induced changes including necrosis and hyalinization. These factors appear to have considerable prognostic significance in osteosarcoma or Ewing’s sarcoma of bone, but their significance requires further study in soft tissue sarcoma.

The prognostic importance of accurate histotyping, histological grading, molecular prognostication (e.g., by fusion gene analysis), and newly developed prognostic nomograms (7) still needs to be tested in large-scale studies. Histological grading has not been improved to date by more objective measures of cell proliferation, DNA flow cytometry, or tumor suppressor gene analysis. Given the recognized shortcomings of current grading systems in some tumor types (e.g., most of the sarcoma types in young adults), histotype-specific grading schemes must be considered. Improvements in predicting treatment response may result from more accurate histotyping [for example, distinguishing monophasic synovial sarcoma, which is particularly chemosensitive, from other fascicular spindle cell sarcomas, which are not as chemosensitive (62)] and genetic testing (for example, c-kit mutational analysis in GIST that correlates well with response to imatinib mesylate). Pathological studies are critical to identifying new therapeutic targets. Much interest is currently focused on agents that bind receptor tyrosine kinases such as c-kit, EGF-R, and PDGF-R. Determination of treatment sensitivity will require testing for protein expression by immunohistochemistry or Western blot that is validated, at least initially, by molecular genetic analysis. Large-scale “shotgun” immunohistochemical approaches to identify therapeutic targets using suboptimal antibodies and techniques should be avoided, and technical standardization, or even centralization, needs to be considered (63).

Tissue microarrays may be of particular value in this regard.

**Recommendations**

There is an urgent need for common, complete, and uniform reporting of sarcoma pathology (Ref. 64; Table 4). This includes reporting histological type, grade, size, depth, margins, and availability of snap-frozen tissue and ancillary studies to evaluate clinically important molecular markers of soft tissue sarcoma with a set of minimum quality assurance requirements for consistency and validation.

Accurate pathological diagnosis and classification of different subtypes of soft tissue sarcomas are critical to the molecular characterization and evaluation of targeted therapeutics in histology-specific clinical trials. Consideration should be given to evaluation by a reference panel of experienced sarcoma pathologists, and for patients with these rare diseases to be referred to sarcoma centers of excellence for second opinions regarding optimal therapy and an opportunity to participate in clinical trials.

**Management of Soft Tissue Sarcomas**

**Imaging**

Advances in primary management have been aided by improved diagnostic imaging. Because of its pluridirectional imaging capabilities and superior contrast resolution, MRI is the
primary modality used for lesion detection and local staging of soft tissue sarcomas (65, 66). Considerable overlap in morphological and signal features of most masses (long T1 and long T2) limits the ability of MRI to identify types and subtypes of soft tissue sarcoma and to discriminate benign from malignant masses. Correct histological diagnosis can be made in 25–40% of soft tissue masses (67, 68).

Conventional MRI is the modality of choice for depicting morphological changes in the tumor and surrounding tissue after neoadjuvant therapy but is limited in its ability to determine tumor necrosis. Dynamic enhanced MRI techniques can reliably predict degree of tumor necrosis and identify tumor recurrence after surgery (69). Because of postprocessing subtraction techniques that are required with its use and its uncertain impact on influencing management, dynamic MRI is not routinely used in clinical practice. The regional nature of MRI precludes identification of lymph nodes outside of the imaging plane and of pulmonary metastases; computerized tomography is the current mainstay for staging of disease in the lungs.

PET can overcome limitations in MRI in quantifying biological activity and for whole body staging. Studies suggest that PET is reliable for separating high- from low-grade tumors, in determining biological activity of a tumor, and in predicting tumor necrosis after neoadjuvant therapy (70–75). In addition, PET allows detection of abnormal lymph nodes away from the site of the tumor as well as lung metastases (74). PET imaging does not allow prediction of the histology of a mass.

Few studies have examined the reliability of MRI for detecting tumor recurrence after surgery (69, 76–79) or compared PET and MRI in pre- or postoperative settings (80). Ultrasound may be useful for following patients for postoperative recurrence in the extremities (81).

**Extremity Sarcomas**

The surgical approach to soft tissue sarcoma has evolved over several decades. In the 1970s, amputation was considered standard treatment for limb sarcoma. This changed in 1982, after a randomized trial from NCI that found a local recurrence rate after function-sparing surgery and radiotherapy of only 15%, with no difference in survival compared with amputation (82). With the introduction of multimodality therapy in the 1980s, amputation rates dropped to less than 10%, and local recurrence rates in patients undergoing limb preservation were reduced to 5–15%.

In the 1990s, improved selection of patients for adjuvant therapy has resulted from data from randomized radiotherapy and brachytherapy trials. Advances in reconstructive procedures have permitted closure of large soft tissue defects with pedicle or free tissue transfers and repair of bone defects with cadaver allografts or vascularized autogenous bone grafts using microvascular techniques to optimize wound healing. These advances have helped correct functional deficits in patients who might otherwise require amputation.

Randomized radiotherapy trials have begun to define the optimal application of external beam radiotherapy and brachytherapy in the treatment of soft tissue sarcoma. Brachytherapy, the direct application of radioactive seeds into the tissue at risk of disease, enables a high radiation dose to be delivered a short distance (typically about 5 mm), with rapid fall-off of dose delivered to surrounding structures. In a randomized trial, 164 patients with completely resected extremity and truncal sarcomas underwent intraoperative randomization to adjuvant brachytherapy (42–45 Gy) or surgery alone (83). Updated follow-up for this trial, which completed accrual in 1992, revealed that local disease-free survival at 10 years for the brachytherapy arm was 83% compared with 67% for patients treated with surgery alone ($P = 0.39$). Patients with high-grade tumors had a 10-year local disease-free survival of 90% with brachytherapy compared with 63% with surgery alone ($P = 0.002$), with no difference in overall survival. Results from this trial also suggested that focused targeting of radiotherapy to no more than 2 cm from the gross tumor volume was associated with excellent local control and less long-term tissue fibrosis and edema than is typically seen with external beam radiotherapy.

Use of postoperative external beam radiotherapy in extremity sarcoma has been best defined by a NCI trial comparing limb-sparing surgery alone with limb-sparing surgery plus postoperative external beam radiotherapy (84). Patients with high-grade sarcomas also received chemotherapy postoperatively. The study showed external beam radiotherapy reduced the 10-year local recurrence rate in both high-grade extremity sarcoma (0% with surgery plus radiotherapy versus 22% with surgery alone) and low-grade extremity sarcoma (5% with surgery plus radiotherapy versus 36% with surgery alone) without a significant effect on overall survival.

The relatively low local recurrence rate even in those receiving surgery alone in this trial—with no local recurrences if margins of >1 cm were achieved—suggested that select patients could safely be treated with surgery only and avoid long-term morbidity from radiotherapy. In a series of 77 patients treated with limb-sparing surgery without radiotherapy at Brigham and Women’s Hospital, 10-year local recurrence rate was 7% with a median follow-up of 126 months (85). Margin had a significant influence on local recurrence; 10-year local recurrence rate was 13% if <1 cm margins were achieved compared with 0% when ≥1 cm margins were achieved. The results suggest that it is important to find clinical, pathological, and molecular criteria for selection of patients for limb-sparing surgery without radiotherapy. Patients to target for this strategy are those with primary presentation and closest margin of 1 cm or greater in whom local recurrence would not preclude subsequent limb salvage.

External beam radiotherapy for soft tissue sarcoma may be administered preoperatively or postoperatively. Each has advantages and disadvantages, including significant differences in radiotherapy planning volumes. In a recent randomized controlled Phase III trial, wound complications were more common with preoperative compared with postoperative radiotherapy (35% versus 17%; $P = 0.01$), with the risk exclusively confined to lower extremity lesions (86). Tumor size and anatomical site were also significant factors. At 3.3 years median follow-up, local control (93%) was identical, and progression-free survival was not significantly different in the two treatment arms. A small improvement in overall survival ($P = 0.0481$) with preoperative radiotherapy was partially explained by increased deaths unrelated to sarcoma in the postoperative group. Limb function and general health status were the same for both groups 12 months after surgery, but after 2 years, rates of grade 2 or
greater fibrosis (56% versus 28%; \( P = 0.003 \)) and edema (24% versus 7%; \( P = 0.01 \)) were higher in the postoperative arm because of larger irradiation volumes and higher doses of radiotherapy with this approach (87). Additional data of up to 16 years prospective functional assessment show significantly greater risk of bone fracture with postoperative radiotherapy related primarily to the higher doses used (88).

Thus, increased risk of wound complications with preoperative radiotherapy must be balanced against greater risk of late complications with postoperative radiotherapy. The survival advantage noted after 3.3 years of median follow-up in the preoperative group warrants longer follow-up (86).

**Retroperitoneal Sarcomas**

Retroperitoneal sarcomas represent approximately 15% of all soft tissue sarcomas and are generally liposarcomas or leiomyosarcomas. Because of their large size (average, 17 cm) and locally advanced presentation (60% high grade), these malignancies are often difficult to manage. The majority are insidious in terms of growth, lack of early symptoms, and involvement of contiguous structures such as major blood vessels, nerves, and viscera.

Standard therapy for retroperitoneal sarcoma is surgical resection. Most series report overall resectability rates of approximately 50%, dependent on factors including whether the tumor is primary or recurrent, anatomical location, and the necessity of en-bloc resection including surrounding viscera, as well as surgical evaluation and referral patterns (89–91). Unlike extremity sarcoma, the majority of deaths from retroperitoneal sarcoma result from local disease progression. Therefore, the most important factor contributing to long-term disease-free survival is complete primary tumor resection (92). Approximately 75% of patients with retroperitoneal sarcoma require en-bloc surgical resection containing contiguous organs and vascular structures. Even with aggressive surgical management, local recurrence rates are 40–70%, with local failures and attrition occurring beyond 5 years, particularly for low-grade liposarcoma (93, 94).

The inability to obtain negative margins and the resulting high local failure rates favor use of multiple modalities in the treatment of retroperitoneal sarcomas. Although adjuvantive radiation therapy is of proven benefit in extremity sarcoma, there is no consensus regarding its routine use in retroperitoneal sarcoma. Trials of adjuvant radiation therapy suggesting benefit for local disease control are difficult to interpret due to small patient numbers, nonrandomized trial design, and use of different sequences (preoperative versus postoperative) and various boost techniques [intraoperative radiotherapy versus brachytherapy (95–98)]. Large field sizes contribute to toxicity, generally favoring the use of preoperative radiation therapy with a coned down intraoperative boost dose (either electron beam, intraoperative radiotherapy, or brachytherapy).

Despite these problems, the usual approach to retroperitoneal sarcoma is to use adjuvant radiotherapy with definitive surgical resection. Chemotherapy may also be considered in higher grade lesions, and in some centers preoperative radiotherapy is used with postoperative or intraoperative boost treatment (95, 99). Doses must be restricted because of sensitive normal structures within the target volume, particularly small bowel, which is frequently relocated and can become tethered or fixed at the original location of the tumor.

In a clinical trial of postoperative radiotherapy for retroperitoneal sarcoma, a delay in time to recurrence was observed, although an effect on overall survival was not evident (89). More recently, in a trial using preoperative radiotherapy, displacement of small bowel from the target area almost completely eliminated bowel toxicity (96). A further advantage of this approach is that the entire tumor, including peritoneal coverage, can be encompassed in the radiotherapy volume before potential seeding of tumor cells within the abdomen during surgery. Based on these results, a randomized trial of preoperative radiotherapy for low-grade retroperitoneal sarcoma is being considered in Europe and North America (100).

IMRT is an advanced form of three-dimensional conformal radiotherapy with the potential to improve outcomes in the treatment of sarcomas. With IMRT, radiation beams are not only shaped at their perimeters but also have variable intensity across their profiles (101–103). IMRT permits conformation of dose to targets of unusual shape by combining inverse treatment planning (where dose to normal tissues and target regions is specified in advance) with computer-controlled dynamic beam shaping and filtration, usually with computer-controlled multileaf collimation. Full exploitation of IMRT will be dependent on highly accurate imaging techniques (104). Accurate description of disease tissue (e.g., hypoxic versus proliferative components) as well as normal tissue is also necessary for inverse planning.

Opportunities for clinical benefit with IMRT include conformal avoidance of normal tissue targets that could result in improved wound healing (in preoperative radiotherapy); avoidance of skin and s.c. tissues (with chemoradiation in multimodality adjuvant protocols); avoidance of lymphatic tissues to minimize edema; avoidance of weight-bearing bone, possibly reducing late onset bone fracture; reduced fibrosis by selective dose targeting; protection of intra-abdominal structures; and improved delivery of radiotherapy to “critical sites” such as the base of the skull and the spine.

**Chemotherapy for Soft Tissue Sarcomas**

**Metastatic Disease.** Anthracyclines and ifosfamide have been established as the most active chemotherapeutic agents for metastatic adult soft tissue sarcomas with single-agent response rates of 16–36% (105). Other agents have had response rates of 10–20%, but only dacarbazine has been used extensively in combination chemotherapy studies (105).

Combination regimens have response rates of 35–60% but have increased toxicity compared with single agents. In general, combinations not containing an anthracycline had poor activity (105). In a meta-analysis of eight randomized controlled trials (2281 patients) comparing doxorubicin-based combinations versus doxorubicin as a single agent, no differences in response rates (odds ratio, 0.79; \( P = 0.10 \)) or survival (odds ratio, 0.84; \( P = 0.13 \)) were seen (106). A cooperative group study of doxorubicin/ifosfamide combination had improved response rate (\( P = 0.03 \)), with a trend for improved survival, whereas another study using the same combination showed no benefit (107, 108). An ifosfamide-based regimen had a significantly higher response rate (\( P < 0.002 \)) and a longer time to progres-
Corresponding absolute benefits for adjuvant chemotherapy for ease-free (the chemotherapy group had significantly longer median disease-free survival compared with none in the standard arm (P = 0.06). In a study of 75 mg/m² versus 50 mg/m² doxorubicin, each combined with ifosfamide, the response rates were similar, and there was no survival benefit (113). Data on high-dose chemotherapy with autologous bone marrow/stem cell support are often contaminated by the inclusion of patients with pediatric sarcomas and are thus difficult to interpret.

Adjuvant Chemotherapy. A meta-analysis of 14 randomized controlled trials (1568 patients) of adjuvant doxorubicin-based chemotherapy versus control showed improvements in local relapse-free survival (HR, 0.73; P = 0.16), distant relapse-free interval (HR, 0.70; P = 0.0003), and overall recurrence-free survival (HR, 0.75; P = 0.0001), but no difference was seen in overall survival (HR, 0.89; P = 0.12; Ref. 114). Corresponding absolute benefits for adjuvant chemotherapy for these end points were 6%, 10%, 10%, and 4%, respectively, at 10 years. Greatest benefit in terms of overall survival was in 886 patients with sarcoma of the extremities (HR, 0.8; P = 0.29), corresponding to a 7% absolute benefit at 10 years.

A small Italian study (n = 104) published after the meta-analysis has suggested benefit for high-dose epirubicin and ifosfamide in high-grade extremity sarcomas (115). Although the chemotherapy group had significantly longer median disease-free survival (P = 0.04) and overall survival times (P = 0.03) compared with control, there was no difference in distant relapse rates at 4 years. A study of the EORTC is examining this combination in a larger cohort of patients randomized after definitive surgery to combination chemotherapy or observation. Outside the trial setting, an anthracycline/ifosfamide combination is commonly used for younger patients with large high-grade extremity sarcomas (116). However, the long-term benefits have yet to be established.

In summary, the current approach to primary extremity and truncal sarcoma is largely dependent on the size, grade, and location of the lesion. For s.c. or i.m. small (≤5 cm) high-grade sarcomas or low-grade sarcomas of any size, surgery alone should be considered if >1-cm margins can be achieved. Postoperative radiotherapy should be considered in cases of margins of <1 cm, deep extra muscular involvement, or previous excisional biopsy. Although size is clearly a continuum in predicting risk from distant metastasis, various cutoff points such as >5 cm, >8 cm, or >10 cm have been used to target patients at high risk for distant metastasis for chemotherapy. Optimal approach to large high-grade extremity and retroperitoneal sarcomas awaits further refinement of biological and clinical end points for selecting patients most likely to benefit from systemic chemotherapy.

### Recommendations

Expanded studies of PET would be beneficial in identifying its role in primary management and assessing response to therapy (Table 5). IMRT is a promising technique for the delivery of radiation therapy that should be actively studied in well-controlled trials of patients with soft tissue sarcomas. In patients with retroperitoneal soft tissue sarcomas, local recurrence is the main cause of mortality. A national trial evaluating the role of radiotherapy to enhance control and survival is warranted and should be planned and carried out. Newer targeted therapeutic molecules need to be evaluated in neoadjuvant and adjuvant trials.

### Targeted Therapies

**GIST as a Model.** Diseases driven by a single genetic mutation provide highly informative proof-of-concept models. Thus, sarcomas, particularly those with simple and few genetic abnormalities, may provide the best targets to advance development of targeted therapeutics. The success of imatinib mesylate in treatment of GIST provides important lessons for development of targeted therapeutics.
development of new therapeutics from targets identified in other sarcomas. Imatinib mesylate was originally identified through a search for specific inhibitors of tyrosine kinases known to be active in human proliferative disorders. Imatinib mesylate was found to be a potent protein-tyrosine kinase inhibitor of the 2-phenylaminopyrimidine class with the ability to inhibit these kinases in cell lines at low dose (117–119).

Clinical trials showed the effectiveness of imatinib mesylate in treating chronic myelogenous leukemia; these provided proof of concept (120). Because imatinib also demonstrated activity in inhibiting c-kit, GIST, which is known to express mutated KIT, was a logical second target tumor in which to investigate its clinical activity. Demonstration of a rapid and sustained partial response in a Finnish patient prompted initiation of two clinical trials (121). In a Phase I EORTC trial involving 35 patients with GIST, a response rate of 63% was achieved, and after 18 months of follow-up, 17 patients have sustained partial responses (122). Side effects most commonly seen were nausea, vomiting, and edema. Incidental and very late leukopenia, severe skin rash, or intratumoral/intra-abdominal bleeding were also observed.

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Phase II studies have confirmed activity of imatinib in GIST. In a United States/Finnish trial of 147 GIST patients, 73% remain on the drug with a median follow-up of 15 months (123). In an EORTC trial involving 27 patients with c-kit-positive GISTS, a response rate of approximately 70% was achieved (124). At 12 months, 19 patients were progression free. The value of PET scans has also been demonstrated in these trials. In patients with 18F-fluorodeoxyglucose-avid tumors, PET scans became normal within 8 days, with response detected much later by computed tomography scan and MRI.

Two large Phase III studies were started in early 2001 in the United States, Canada, and Europe to assess survival, progression-free survival, and toxicity in locally advanced or metastatic GIST among patients randomized to receive 400 mg of imatinib once or twice a day (125, 126). The EORTC study accrued 946 patients in 11 months, and the United States study accrued 746 patients in just over 9 months. Preliminary results from both trials suggest that the drug is tolerable and extends progression-free survival compared with historical controls.

Identifying New Targets in Sarcomas. Identification of new molecular targets for treatment of sarcomas can be conceptualized as occurring by two major routes: (a) targets discovered through investigating the action of drugs identified empirically as clinically effective, as with all-trans-retinoic acid in the treatment of acute promyelocytic leukemia; and (b) drugs designed specifically for targets identified as critical to a tumor’s biology, as with development of imatinib mesylate for chronic myelogenous leukemia and GIST. Even with sarcomas of rela-
tively simple karyotypes, numerous potential targets for rational drug design—the second approach—exist (Fig. 2).

The challenge in identifying targets in sarcomas is to find specific targets important to cellular function. More precise pathological definition of sarcoma subtypes through supporting array and karyotyping data will be essential. Ideal targets will be (a) those in which a single validated molecule is critical to the pathogenesis in humans, (b) expressed and active, (3) a target for which there are no alternative pathways to bypass the blockade, and (4) necessary and sufficient for sarcoma cell survival. Sarcomas, such as those that bear a translocation or an identified single mutation, will be highly relevant for informative proof of concept. However, even for these, a number of factors must be considered in profiling the target and making a decision regarding its relevance (Table 6).

Translocations identified in sarcomas may represent highly relevant targets because their protein products may have many of these characteristics. However, only if the tumor has 100% target incidence, the target is 100% necessary and sufficient, and the target is active in 100% of cells, will all patients respond. If the target is 100% sufficient, but only half the cells or tumors of a specific histopathological entity have the target (i.e., a 50% target incidence), the observed outcome will only be a 50% response rate (Table 7). If cell or disease target incidence drops to 25% with only 75% dependence on the target, the response rate will be 19% (Table 7). For an infrequent target (for example, one occurring only 5% of patients), even if the drug is 100% sufficient in those tumors, the observed outcome will only be a 5% response rate (Table 7). Applying this sensitivity analysis to GISTs, nearly 100% of the GISTs most likely have activated c-kit, but only 75% may be dependent on activation of c-kit, so overall response would be predicted to be 75%. This prediction corresponds well to what has been observed clinically: approximately 60–65% of GIST patients treated with imatinib mesylate have partial response, with an additional 20% having nonprogressive disease. Such analyses underscore the facts that expression alone does not equate with activation or relevance of a putative target and that if patients are selected poorly, opportunities for proof of concept or identifying a new target may be missed.

Consistent and reliable diagnostics are critical for preclinical development as well as optimizing clinical outcome through proper patient selection. Both Western blotting and immunohistochemistry techniques require extensive experience with the reagents. Quality control and revalidation of procedures should be conducted in an ongoing manner. Unfortunately, variability in the application of immunohistochemical and other tissue analyses can prevent achievement of the required sensitivity, specificity, and reliability outside of specialized reference or research laboratories.

Careful study of empiric responders may yield information on pathways relevant to a subset of cases. Future screening can then be directed to detect such cases and enrich them for targeted studies. For example, although c-kit mutations have been found in 87% of GIST patients, response to imatinib therapy has been shown to be highly dependent on the site of the c-kit mutation (127). In patients with tumors having c-kit mutations in exon 11, the response rate was 90% compared with a response rate of <20% in patients with tumors with wild-type c-kit (127). To date, the molecular mechanisms responsible for differences in the effect of c-kit mutations remain only partially understood. Unstable genomes may lead to the evolution of resistance mechanisms. Definition of such resistance mechanisms may yield identification of other targets. Careful analyses of GISTs resistant to imatinib mesylate will likely uncover new cellular control pathways. For example, imatinib-resistant GIST cell cultures feature activation of the downstream signaling intermediate PI3K. These GIST cell cultures undergo apoptosis after treatment with the PI3K inhibitor, LY29004 (Fig. 3). If this finding can be extended to other resistant GISTs, PI3K becomes a potential therapeutic target not only in GIST but in other malignancies as well.

Although simple models are instructive, complex sarcomas with more diverse karyotypes (such as those of high-grade sarcomas) or sarcomas expressing resistance mutations (such as those beginning to be identified in GIST) will likely require combination therapies. Patient populations will need to be defined according to the presence or absence of targets. Use of targeted therapies for undefined “sarcomas” (without further molecular characterization) with an infrequent oncogenic cellular or disease mutation will likely result in disappointingly low response rates (Table 7). For example, certain preclinical lines of evidence suggest that EGF-R inhibitors may be beneficial in malignant peripheral nerve sheath tu-

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**Fig. 3** Apoptosis of imatinib-resistant GIST cells in culture after treatment with the PI3K inhibitor, LY29004. Terminal deoxynucleotidyl transferase-mediated nick end labeling apoptosis assay in imatinib-resistant GIST882 cells cultured with (B and D) and without (A and C) PI3K inhibitor. The cell counterstain is 4’6-diamidino-2-phenylindole (blue), and apoptotic cells are indicated by FITC labeling (green) in A and B. Gray-scale representation of the 4’6-diamidino-2-phenylindole stain in C and D reveals nuclear fragmentation in apoptotic cells (courtesy of J. Fletcher, 2002).
Because aberrant expression may be infrequent, these factors will need to be kept in mind as histopathological and therapeutic outcomes are correlated, and consideration will need to be given to potential combination therapies. Nevertheless, the promise of the much greater benefit for a smaller patient population, when compared with less specific anticancer therapies used for larger patient populations, justify the effort for these and other targeted therapeutics (Fig. 4).

**Recommendations.** Characterization and targeting of c-kit with imatinib mesylate for GIST is a model for successful molecular therapeutic intervention in patients with soft tissue sarcomas (Table 8). Lessons learned from the GIST/imatinib mesylate experience should continue to guide the development of targeted systemic interventions, not only in other histological subtypes of sarcoma but in other solid tumors as well. Both appropriately chosen new targeted agents and combinations of targeted therapies should be explored in well-designed clinical trials for patients with these diseases. New models for interinstitutional collaborations and for partnership with pharmaceutical companies should be considered.

**Conclusion**

Sarcomas carry significance disproportionate to their clinical frequency because of mechanistic understandings that have emerged from their study. Specific translocations with relatively simple genotypes that are susceptible to analysis have illuminated aberrant signaling and transcriptional control in these diseases and determine their behavior. Further characterizing these changes will result in identification of additional therapeutic targets.

Continued progress will depend upon further adapting the rapidly evolving technologies of genomics and proteomics. It will also result in resolution of the daunting complexity of sarcomas with development of improved classification and specific therapeutic inhibitors. As with the genome effort, centralizing molecular and pathological definition and clinical management in a few organized centers of excellence and institutional consortia through cooperative oncology groups will lead to the most rapid reductions in morbidity and mortality. The overarching goal of the recommendations made herein, when coupled with similar approaches to bone and pediatric sarcomas, is to lead to a plan that will result in significant reduction of sarcomas as a cause of cancer mortality by 2025.

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**Table 8** Recommendations regarding development of targeted therapies for soft tissue sarcomas

- Facilitate development of an “encyclopedia” of soft tissue sarcomas with access to tissue samples and sera
  - International registry
  - Addressing differences in ethics of tissue collection
  - Screening for tyrosine kinase libraries
  - Developing reference sarcoma cell lines
- Improve sarcoma clinical trials mechanisms
  - Strengthen cooperative group sarcoma committees
  - Consider new institutional collaborations
  - Facilitate the hybrid of targeted drug development and parallel clinical observation-guided initiatives
  - Redefine clinical benefit (measurement of treatment outcomes)
- Targets
  - Ensure assay validation
  - Validate diagnostics concomitant with therapeutic trials
  - Consider combination therapy
  - Potential targets:
    - EGF-R/Her-2 neu
    - PDGFR-R/pAKT
    - Cyclins
    - Pgp
    - FTI (PNET, MPNST)
    - PPAR-γ
    - MAP-k
    - Bcl-2 (antisense)
    - IFN-AR

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*PgP, P glycoprotein; FTI, farnesyl transferase inhibitor; MPNST, malignant peripheral nerve sheath tumor; PPAR, peroxisome proliferation-activated receptor; MAP-k, mitogen-activated protein kinase; IFN-AR, IFN-α/β receptor.*
with a wide range of expertise in sarcomas including surgeons, radiation oncologists, medical oncologists, pathologists, cancer biologists, and patient advocates. The names of these individuals, together with a transcript of the complete presentations and proceedings, is available online.4

References


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