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CME Information

CME Released: 06/21/2010; Valid for credit through 06/21/2011

Target Audience

This activity is intended for oncologists and other physicians who care for patients with sarcomas.

Goal

The goal of this activity is to identify biomarkers and describe directed therapy for patients with sarcomas.

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Identify molecular markers of giant-cell tumors of bone
2. Describe the relevance of the p53 pathway in sarcoma
3. Specify tumors that may respond to inhibition of the vascular endothelial growth factor pathway
4. Identify the connective tissue tumor most associated with the insulin-like growth factor-1 receptor pathway

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Author(s)

David M. Thomas, FRACP, PhD

Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia

Disclosure: David M. Thomas, FRACP, PhD, has disclosed the following relevant financial relationships:
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Andrew J. Wagner, MD, PhD

Dana-Farber Cancer Institute, Boston, Massachusetts

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Editor(s)

Kerrin G. Robinson, MA

Assistant Managing Editor, *Journal of the National Comprehensive Cancer Network*

Disclosure: Kerrin G. Robinson, MA, has disclosed no relevant financial relationships.

CME Author(s)

Charles P. Vega, MD

Associate Professor; Residency Director, Department of Family Medicine, University of California, Irvine

Disclosure: Charles P. Vega, MD, has disclosed no relevant financial relationships.

CME Reviewer(s)

Sarah Fleischman

CME Program Manager, Medscape, LLC

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Laurie E. Scudder, DNP, NP

CME Accreditation Coordinator, Medscape, LLC

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Specific Targets in Sarcoma and Developmental Therapeutics CME

David M. Thomas, FRACP, PhD; Andrew J. Wagner, MD, PhD

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Abstract and Introduction

Abstract

Connective tissue tumors comprise a rich array of subtypes, many of which possess strong pathognomonic phenotypes and genotypes of therapeutic significance. This article describes recent applications of targeted and nontargeted therapeutic agents in connective tissue tumors that illustrate important themes in drug development. Targeted therapy has exploited the paradigms of oncogene and lineage addiction. In other cases, potential targets are more difficult to classify, such as the role of the insulin-like growth factor 1 pathway in Ewing's sarcoma. Understanding why these pathways seem critical in some cancers, and in some individuals but not others, is important in identifying novel therapeutic opportunities in an age of personalized medicine.

Introduction

The use of molecularly targeted therapies for the treatment of sarcomas began with the introduction of imatinib mesylate for treating gastrointestinal stromal tumor (GIST),[1] which was the result of a perfect storm: identification of common activating mutations in *KIT* in most GISTs; development of a drug that inhibits *KIT* activity and a few other kinases; validation of the role of *KIT* and the effects of imatinib in robust preclinical models; and markedly efficacious use of imatinib in the treatment of patients with GIST. The clinical development of imatinib became a paradigm for the creation of novel cancer therapies and has been used to treat other sarcomas, such unresectable or metastatic dermatofibrosarcoma protuberans (DFSP).[2–4] This disease is characterized by translocation and overexpression of platelet-derived growth factor (PDGF). Imatinib inhibits the PDGF receptor (PDGFR), blocking growth of DFSP. Again,

identification of a genetic lesion led to effective use of an agent specifically targeting the appropriate alteration.

The challenge, therefore, in rational cancer drug development is to identify appropriate targets against which an effective, specific, and nontoxic therapy can be directed. Sarcomas constitute a heterogeneous group of tumors that share a common mesenchymal origin. These diseases are often varied in histologic appearance, clinical behavior, and, importantly, genetic drivers. An increasingly detailed molecular understanding of many of these tumors is developing, and as candidate oncogenic pathways are identified, novel agents are being tested in laboratory and clinical settings. Conversely, the clinical application of approved or investigational targeted therapies for the treatment of sarcomas may inform laboratory studies of candidate pathways and define subsets of disease based on biochemical and clinical responses. This article discusses emerging targets for the treatment of sarcoma, identified through detailed laboratory analyses and clinical observations. The interplay of these approaches will lead to a more thorough understanding and classification of sarcomas and more effective, specifically targeted, less-toxic therapies.

Receptor Activator of NF-κB Ligand

The regulation of bone homeostasis has been examined in considerable detail over the past decade, and has been exploited therapeutically for a range of diseases from osteoporosis to giant cell tumor (GCT) of bone and metastatic cancer. Two main cell types are involved in bone homeostasis: the osteoblast and the osteoclast.[5] The receptor activator of NF-κB (RANK) pathway is required for osteoclast differentiation, along with its ligand (RANKL) and a decoy receptor, osteoprotegerin.[6–9] Mice carrying loss-of-function alleles of rankl or RANK developed osteopetrosis, whereas those with mutant osteoprotegerin developed osteoporosis.[8,10] Moreover, osteoclast-like cells can now be generated in vitro in the absence of stromal cells by adding recombinant RANKL to primary cultures of monocytic cells.[11]

GCT of bone is a benign, locally destructive neoplasm, characterized by the presence of ”giant” osteoclast-like cells and a stromal mononuclear population.[12] The stromal population in GCT expresses high levels of RANKL, which probably recruits mononuclear precursor cells to the tumor site where they mediate the bony destruction associated with the tumor.[13,14] Unlike many targets discussed in this article, the overexpression of RANKL in GCT is not caused by known genetic or epigenetic events, and the molecular pathogenesis of GCT remains unclear.

GCT occurs in skeletally mature young people, and may cause pain, susceptibility to fracture, neurologic injury, and deformity.[12] GCT may be associated with benign pulmonary metastases, usually after surgical instrumentation. Finally, between 1% and 3% of GCTs may undergo true malignant degeneration, which is most frequently seen after prior radiotherapy.[15] Treatment of GCT has typically involved surgical curettage and sometimes excision.[16] Local recurrence rates vary from 10% to 50%, depending on the surgery performed and the disease site. The surgical morbidity associated with achieving clear margins in tumors affecting the axial skeleton in particular can cause patients to have serious sequelae. Radiotherapy has been shown to be effective in up to 80% of cases but is associated with late effects, including infertility and the risk for second malignancies. Systemic therapies have had limited success.

The development of denosumab, a monoclonal antibody to RANKL,[17] led to a prospective, phase II clinical trial of this agent in patients with unresectable or recurrent GCT.[18] This study enrolled 37 patients, with a high proportion having extensive prior treatment, tumors located in the axial skeleton, and, in some cases, metastatic disease. Based on the criteria for response in this study (progression-free survival at 25 weeks or histologic evidence of eradication of giant cells within the tumor on biopsy), 86% of patients experienced response to denosumab. All patients who underwent histologic assessment showed eradication of giant cells. Although it was not formally assessed, the investigators reported that 84% of patients experienced clinical benefit, including reduced pain and improved range of movement and functional status. Almost a third of patients showed bone repair on study. The drug, which was administered as a subcutaneous injection, was well tolerated and no treatment-related serious adverse events were reported during the study.

The precise role of denosumab in GCT remains the subject of clinical research. A current clinical trial is evaluating the adjuvant use of denosumab in patients with locally advanced but resectable disease, because whether treatment may reduce the risk for recurrence or facilitate less-morbid surgery is unknown. Another question relates to the use of denosumab in other giant cell–rich tumors, such as giant cell reparative granuloma, which appears to overexpress RANKL.[16]

Macrophage Colony–Stimulating Factor 1

Pigmented villonodular synovitis (PVNS) and tenosynovial GCT (TGCT) are closely related, benign, extraosseous neoplasms and, like GCT, are characterized by stromal cell proliferation accompanied by a giant cell infiltrate.[15] The proportion of giant cells is typically lower than that seen in GCT. The tumors are often seen around joints and involve tendon sheaths, particularly in the lower limb. Although these tumors typically do not metastasize, and rarely, if ever, have been reported to cause death, they are a source of recurrent morbidity and loss of function. Current standard of care, as for GCT of bone, is surgical extirpation. Although this procedure is usually effective, the infiltrating patterns of growth seen with PVNS/TGCT make complete excision difficult while preserving joint and tendinous structures, and local recurrences are common. Radiotherapy is occasionally used to control disease but may also be associated with long-term sequelae.

Recent progress has been made in understanding the pathogenesis of PVNS/TGCT. In 2006, a group from Stanford reported a recurrent translocation involving macrophage colony–stimulating factor 1 (*CSF1*, also known as M-CSF) in PVNS/TGCT.[19] Chromosome 1p13 is fused to 2q35, linking the *CSF1* gene to the *COL6A3* promoter and leading to overexpression of CSF1. The authors postulate that overexpression of CSF1 leads to recruitment of monocytes to the tumor site, because CSF1 is required for monocyte lineage differentiation. The translocation is found in a minority of tumor cells, and most cells within a tumor express the CSF1 receptor (CSF1R). Imatinib mesylate has submicromolar activity against the ABL, KIT, PDGFR, and CSF1R kinases and clinically important activity in several sarcomas, including GIST[1] and DFSP.[2] A case report suggests that imatinib may have activity in PVNS/TGCT, presumably through targeting CSF1R.[20] As a result of this observation, a clinical trial using a related compound (nilotinib) is under development for patients with otherwise refractory PVNS/TGCT.

p53 Pathway

The *p53* gene, located at 17p13, is mutated in almost half of all cancers, and the pathway in which it plays a central role is dysregulated in almost all cancers.[21] One of the gene's transcriptional targets, MDM2, physically binds and inhibits p53.[21,22] *MDM2* is amplified in up to 10% of all cancers, and is especially frequently affected in some sarcomas (see later discussion).

A related gene, *MDM4*, may act in a similar fashion to *MDM2*. *MDM2* is inhibited by *p14ARF*, located at 9p21. *p14ARF* sequesters *MDM2* away from *p53*, thereby liberating *p53* to act as a tumor suppressor. Good evidence suggests that this pathway is linear and nonredundant, because mutations in either *p14ARF*, *MDM2*, or *p53* seem mutually exclusive, consistent with mutual interdependence of each component,[22] whereas preclinical studies indicate that *p53* is required for the biologic effects of *MDM2*.[23]

Different tumors target specific individual components of the *p53* pathway.[21] *MDM2* is clearly frequently amplified in soft tissue and bone sarcomas (20%–30%), and almost universally amplified in certain sarcoma types, such as well- and de-differentiated liposarcoma (WDLPS/DDLPS).[15] Amplification of *MDM2* has also been reported in 20% to 60% of malignant peripheral nerve sheath tumors and a high proportion of osteosarcomas.[21,24] Mechanistically, the near-universal amplification of *MDM2* in WDLPS/DDLPS is from the incorporation of regions of chromosome 12 into a cancer-associated neochromosome.[12] Ring or accessory neochromosomes are a near-pathognomonic feature of WDLPS/DDLPS and other sarcomas, including DFSP and parosteal osteosarcoma. Amplification of *MDM2* and mutations in *p53* are rarely reported in the same sarcoma.[24]

Over the past 5 years a series of small molecule antagonists of *MDM2* have been developed, including nutlin 3a.[25] Nutlin sterically interferes with binding between *MDM2* and *p53*. Treatment of cancer cell lines carrying amplified *MDM2* in vitro and in vivo results in activation of *p53*, leading to growth arrest and apoptosis. Importantly, nutlin 3a seems to be ineffective in cell lines carrying mutations in *p53* but may be overcome by cotreatment with DNA-damaging agents.[26] Significant interest has been shown regarding the activity of *MDM2* antagonists in diseases in which *MDM2* amplification is extremely common, such as WDLPS/DDLPS and malignant peripheral nerve sheath tumors. The clinical role of *MDM2* antagonists is an area of active investigation, with early-phase clinical trials underway.

Retinoblastoma Pathway

Like p53, the Rb pathway is almost universally dysregulated in cancer, although (unlike p53) it has important developmental as well as tumor suppressor roles.[27] The Rb pathway controls the cell cycle at the G1/S checkpoint.

A range of CDK4 antagonists are in clinical development, most in early-phase study, and are fairly nonselective, with

effects on several CDKs.[28] Genetic ablation of CDK2, -4, and -6 in mice seems dispensable in most normal cell cycles, but depends on CDK1.[29] The first generation of nonselective CDK inhibitors was associated with significant toxicities,[28,30] which may be ameliorated by the development of more selective antagonists of CDK4 (e.g., P1446A-05, Piramal Healthcare, Mumbai, India; NCT007728766). The frequent coamplification of *MDM2* and *CDK4* in WDLPS/DDLPS is of particular interest because it presents an opportunity for combined use of targeted therapeutics.[31]

Vascular Endothelial Growth Factor Receptor Pathway

Vascular endothelial growth factor (VEGF) is a protein ligand produced primarily in response to tissue hypoxia in normal cells. VEGF binds to members of the VEGF receptor (VEGFR) family on endothelial cells and stimulates receptor tyrosine kinase activity. Endothelial cell proliferation results, and thus VEGF enhances local delivery of oxygen and other nutrients through neoangiogenesis. Various cancers have been shown to co-opt this pathway, and production of VEGF can accelerate tumor growth. Several agents, including the anti-VEGF antibody bevacizumab and the VEGFR2 small molecule inhibitors sunitinib, sorafenib, and pazopanib, target the VEGF/VEGFR axis and impair tumor progression, and have been approved by regulatory authorities for the treatment of cancers.

Many sarcoma cell lines or tumors have been shown to produce VEGF or show evidence of activation of VEGFR, although for most cases the precise mechanisms remain unclear.[32] Some sarcoma subtypes are highly vascular on gross or microscopic examination, and several agents have been studied for their efficacy against sarcomas. When examined against sarcomas as a whole, VEGFR inhibition seems to have minimal impact on sarcoma growth. A phase II study of 17 patients treated with combination doxorubicin and bevacizumab, for example, observed only 2 responses (12%), and 13 patients had stable disease for more than 12 weeks,[33] not significantly different from what might be expected from doxorubicin alone.

However, some select subtypes may be uniquely sensitive to VEGFR inhibition, and if confirmed in larger studies this may lead to new histotype-specific treatment advances and a better molecular genetic understanding of tumor pathogenesis. In a phase II study of sunitinib, for example, 10 of 49 patients (20%) developed stable disease for more than 16 weeks, including 2 of 3 patients with solitary fibrous tumor/hemangiopericytoma (SFT/HPC) who had disease control for 24 and greater than 59 weeks, respectively.[34] Although sunitinib inhibits several kinases other than VEGFR, the potential for a role of VEGFR in SFT/HPC is strengthened by the results of a retrospective analysis of patients with this disease who were treated with temozolomide and bevacizumab.[35] In this case series, 11 of 14 (79%) patients experienced a partial response according to Choi criteria, and 2 other patients (14%) had stable disease. The role of each individual drug compared with the combination is unclear, but these observations, in conjunction with the suggestive results from the prospective phase II study of sunitinib, suggest that blockage of the VEGF/VEGFR axis may be an effective strategy for treating SFT/HPC.

Angiosarcoma, a mesenchymal cell–derived neoplasm with endothelial differentiation, is also an attractive target for VEGFR-directed therapy. Many angiosarcomas express VEGF or its receptors.[36] Complete pathologic responses were observed in 2 patients treated with radiation and bevacizumab.[37] Among 27 evaluable patients in an ongoing phase II study of single-agent bevacizumab, preliminary best results show 4 patients (15%) experiencing partial response and 13 (48%) with stable disease.[38] In a phase II study of the multitarget kinase inhibitor sorafenib, 5 of 37 patients (14%) with angiosarcoma experienced partial responses and 21 (57%) developed stable disease, whereas patients with other sarcoma subtypes showed minimal activity.[39]

One study found that VEGFR2 and other vascular-specific tyrosine kinases were upregulated in angiosarcomas of the breast (mammary-type or radiation-associated), and mutations in the *VEGFR2* gene were identified in 4 of these specimens, accounting for 10% of samples analyzed.[39] Laboratory assessment showed that these *VEGFR2* mutations result in constitutive activation of the receptor, which can be blocked by the small-molecule inhibitors sunitinib and sorafenib. Whether the presence of these mutations is required for or predictive of response to treatment in vivo remains to be determined in clinical studies.

In a series of 4 evaluable patients with advanced alveolar soft part sarcoma (ASPS), treatment with sunitinib resulted in radiographic responses in 2 patients and stable disease in 1.[40] A biochemical analysis of frozen samples from these patients showed activation of VGFR2 in only 1 tumor, whereas other kinases sensitive to sunitinib were active, suggesting that the VEGFR pathway may not be a therapeutic target in this disease. However, early clinical studies of the more-selective VEGFR inhibitor cediranib have shown this agent to have significant activity against ASPS.[41] Of 7

patients treated in 2 studies, 4 experienced partial responses, 2 experienced minor responses, and 1 had stable disease. These observations suggest that further study of the role of VEFGR inhibition in ASPS is warranted.

Other small molecule inhibitors of VEGFR, including brivanib and pazopanib, are currently in phase II and III sarcoma-specific studies, respectively. Results from these trials may identify other sarcoma subtypes that may be particularly sensitive to the VEGFR blockade.

Mesenchymal-Epithelial Transition Factor Pathway

The mesenchymal-epithelial transition factor (MET) is a receptor tyrosine kinase that transduces extracellular signals mediated by hepatocyte growth factor (HGF) to the cytoplasm and nucleus through canonical signaling pathways. HGF is commonly produced by stromal cells and activates MET on epithelial cells, leading to cellular proliferation, survival, and migration. Although activating mutations in *MET* have been described in gastric, lung, and renal cancers, these alterations have not been observed in sarcomas. However, the coexpression or juxtaposition of HGF and MET in mesenchymally derived sarcoma cells could lead to autocrine or juxtracrine stimulation and promote tumor growth and metastasis. Investigational agents that could potentially disrupt the HGF/MET axis, including anti-HGF antibodies, anti-MET antibodies, and small molecule MET kinase inhibitors, are currently in clinical development.[42]

MET expression and activation has been shown in several sarcoma subtypes, including clear cell sarcoma (CCS), ASPS, alveolar rhabdomyosarcoma (aRMS), and osteosarcoma.[43–54] With CCS and ASPS, MET expression seems to be driven at least partly by the activity of the MITF or TFE3 transcription factor oncogenes. In CCS, MITF is

Signals from the cell surface transduced by diverse receptor tyrosine kinases converge on common cytoplasmic signaling pathways, including the serine/threonine kinase mammalian target of rapamycin (mTOR). Activation of mTOR plays critical roles in the control of cell metabolism and protein translation, integrating signals from PI3 kinase, hypoxia, amino acid and nutrient concentration, cell stress, and other modifiers of the cellular milieu.[60] Additionally, mTOR is activated in malignancies through various genetic mechanisms, including amplification or mutation of upstream stimulatory proteins, such as growth factors, receptors, PI3 kinase, LKB1, and RHEB, or loss or inhibitory mutations of tumor suppressors, such as *PTEN*, *TSC1*, and *TSC2*.[61] Because of its key role as an integrator of proliferative and survival signals, inhibitors of mTOR have been studied for efficacy in the treatment of malignancies, and 3 are currently available commercially: sirolimus (approved for post-renal transplant immunosuppression), temsirolimus, and everolimus (CCI-779 and RAD001, respectively; both approved for treatment of advanced renal cancer), with the latter 2 being derivatives of sirolimus, or “rapalogues.” These drugs and the investigational agent ridaforolimus (AP23573) inhibit mTOR through interaction with FKBP12 in the mTORC1 complex, and all have been studied for their efficacy in the treatment of sarcomas.

Overall, response rates for nonselected sarcomas have been relatively low. A phase II study of temsirolimus in 41 patients with sarcoma observed only 1 partial response in a patient with fibrosarcoma. The median time to progression in this study was 2 months,[62] and 23 patients had grade 3 toxicities. Results of a phase I study of ridaforolimus involving 7 patients with sarcoma showed a partial response of more than 4 years in a patient with malignant mixed müllerian tumor (carcinosarcoma) and a partial response in a patient with Ewing’s sarcoma.[63] Six patients had a progression-free survival of greater than 6 months, prompting a sarcoma-specific phase II study involving 212 patients.[64] This study showed 4 partial responses among 54 patients with bone sarcomas, and 1 partial response among 57 patients with soft tissue sarcoma, but overall 29% of participants experienced either a partial response or stable disease of more than 4 months.

To more fully evaluate whether ridaforolimus alters the rate of disease progression, a phase III placebo-controlled study is currently underway to study its efficacy in maintaining disease control after conventional chemotherapy.

The apparent lack of efficacy of mTOR inhibitors in the treatment of sarcoma seems at odds with in vitro models and strong rationale in subtypes driven, for example, by activating mutations in tyrosine kinase receptors such as *KIT* in GIST. Correlative studies have validated adequate plasma drug levels and target modulation in surrogate tissues.[62,63] Biomarkers, such as the presence of phosphorylation of S6 in archival tumor specimens, may predict responsiveness to mTOR inhibition.[65] Although more upstream oncogenic signals also may activate multiple parallel pathways that supersede inhibition of just one pathway controlled by mTOR. Dramatic responses to mTOR inhibition have been observed in select subtypes of sarcoma with genetic or biochemical alterations more directly tied to mTOR, such as with loss of the mTOR inhibitory proteins TSC1 and TSC2 in malignant PEComas.[66] These findings suggest that mTOR inhibitors may have substantial activity in the appropriate histologic or genetic context.

Lastly, compensatory upregulation of AKT signaling has been reported as a possible mechanism of resistance after treatment with rapalogues.[67,68] In certain cell models, this may be blocked by inhibition of IGF1R signaling,[61] and clinical studies of anti-IGF1R antibodies in combination with mTOR inhibitors against sarcomas are currently underway. Additionally, the efficacy of combined PI3 kinase/mTOR inhibitors and mTORC1/mTORC2 inhibitors will be interesting to evaluate in sarcomas, because drugs of this kind are currently in early clinical development and may abrogate feedback upregulation of AKT.

Conclusions

The paradigm of oncogene addiction is widely believed to explain why the presence of mutations in key driver genes predicts for clinical response in patients treated with cognate molecular therapeutic agents. This paradigm has held true for several sarcomas and other connective tissue tumors, including GIST, DFSP, and perhaps also PVNS. However, additional targets were recently identified that reflect key roles in the biology of the tumor, even when the targets themselves are not directly mutated. This class of targets, which may be termed lineage-addicted, also seem to predict for response to treatment in diseases, such as GCT of bone and a subset of angiosarcomas. Finally, another set of targets seems to exist with roles that are not well understood, either because they operate in nonredundant pathways in which the activating mutations remain to be identified, or because their obligatory role in the tissue of origin is not well understood. Why the tumor behavior depends on these pathways is important to understand, because how to

predict which individuals will experience a dramatic response to a drug is not yet known. In an age of personalized medicine, biomarkers predictive of response (or nonresponse) will be critical to optimize outcomes and direct the appropriate use of high-cost therapeutic agents.

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References

1. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472–480.
2. McArthur GA, Demetri GD, van Oosterom A, et al. Molecular and clinical analysis of locally advanced dermatofibrosarcoma protuberans treated with imatinib: Imatinib Target Exploration Consortium Study B2225. J Clin Oncol 2005;23:866–873.
3. Maki RG, Awan RA, Dixon RH, et al. Differential sensitivity to imatinib of 2 patients with metastatic sarcoma arising from dermatofibrosarcoma protuberans. Int J Cancer 2002;100:623–626.
4. Rubin BP, Schuetze SM, Eary JF, et al. Molecular targeting of platelet-derived growth factor B by imatinib mesylate in a patient with metastatic dermatofibrosarcoma protuberans. J Clin Oncol 2002;20:3586–3591.
5. Sims NA, Gooi JH. Bone remodeling: multiple cellular interactions required for coupling of bone formation and resorption. Semin Cell Dev Biol 2008;19:444–451.
6. Dougall WC, Glaccum M, Charrier K, et al. RANK is essential for osteoclast and lymph node development. Genes Dev 1999;13:2412–2424.
7. Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 1998;93:165–176.
8. Simonet WS, Lacey DL, Dunstan CR, et al. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell 1997;89:309–319.
9. Anderson DM, Maraskovsky E, Billingsley WL, et al. A homologue of the TNF receptor and its ligand enhance T-cell growth and dendritic-cell function. Nature 1997;390:175–179.
10. Kong YY, Yoshida H, Sarosi I, et al. OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. Nature 1999;397:315–323.
11. Takahashi N, Udagawa N, Suda T. A new member of tumor necrosis factor ligand family, ODF/OPGL/TRANCE/RANKL, regulates osteoclast differentiation and function. Biochem Biophys Res Commun 1999;256:449–455.
12. Garsed DW, Holloway AJ, Thomas DM. Cancer-associated neochromosomes: a novel mechanism of oncogenesis. Bioessays 2009;31:1191–1200.
13. Morgan T, Atkins GJ, Trivett MK, et al. Molecular profiling of giant cell tumor of bone and the osteoclastic localization of ligand for receptor activator of nuclear factor kappaB. Am J Pathol 2005;167:117–128.
14. Atkins GJ, Haynes DR, Graves SE, et al. Expression of osteoclast differentiation signals by stromal elements of giant cell tumors. J Bone Miner Res 2000;15:640–649.
15. Fletcher CD, Unni KK, Merlens F, eds. World Health Organization classification of tumours: pathology and genetics of tumours of soft tissue and bone. Lyon, France: IARC Press; 2002.
16. Thomas DM, Skubitz KM. Giant cell tumour of bone. Curr Opin Oncol 2009;21:338–344.
17. Miller PD. Denosumab: anti-RANKL antibody. Curr Osteoporos Rep 2009;7:18–22.
18. Thomas D, Henshaw R, Skubitz K, et al. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. Lancet Oncol 2010;11:275–280.
19. West RB, Rubin BP, Miller MA, et al. A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. Proc Natl Acad Sci U S A 2006;103:690–695.
20. Blay JY, El Sayadi H, Thiesse P, et al. Complete response to imatinib in relapsing pigmented villonodular synovitis/tenosynovial giant cell tumor (PVNS/TGCT). Ann Oncol 2008;19:821–822.
21. Toledo F, Wahl GM. Regulating the p53 pathway: in vitro hypotheses, in vivo veritas. Nat Rev Cancer 2006;6:909–923.
22. Fulci G, Labuhn M, Maier D, et al. p53 gene mutation and ink4a-arf deletion appear to be two mutually exclusive events in human glioblastoma. Oncogene 2000;19:3816–3822.
23. Montes de Oca Luna R, Wagner DS, Lozano G. Rescue of early embryonic lethality in mdm2-deficient mice by deletion of p53. Nature 1995;378:203–206.
24. Momand J, Jung D, Wilczynski S, Niland J. The MDM2 gene amplification database. Nucleic Acids Res

1998;26:3453–3459.
25. Vassilev LT, Vu BT, Graves B, et al. In vivo activation of the p53 pathway by small-molecule antagonists of MDM2. Science 2004;303:844–848.
26. Liu W, He L, Ramirez J, Ratain MJ. Interactions between MDM2 and TP53 genetic alterations, and their impact on response to MDM2 inhibitors and other chemotherapeutic drugs in cancer cells. Clin Cancer Res 2009;15:7602–7607.
27. Burkhart DL, Sage J. Cellular mechanisms of tumour suppression by the retinoblastoma gene. Nat Rev Cancer 2008;8:671–682.
28. Malumbres M, Barbacid M. Cell cycle, CDKs and cancer: a changing paradigm. Nat Rev Cancer 2009;9:153–166.
29. Santamaria D, Barriere C, Cerqueira A, et al. Cdk1 is sufficient to drive the mammalian cell cycle. Nature 2007;448:811–815.
30. Shapiro GI. Cyclin-dependent kinase pathways as targets for cancer treatment. J Clin Oncol 2006;24:1770–1783.
31. Cheok CF, Dey A, Lane DP. Cyclin-dependent kinase inhibitors sensitize tumor cells to nutlin-induced apoptosis: a potent drug combination. Mol Cancer Res 2007;5:1133–1145.
32. DuBois S, Demetri G. Markers of angiogenesis and clinical features in patients with sarcoma. Cancer 2007;109:813–819.
33. 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;23:7135–7142.
34. 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;27:3154–3160.
35. Park MS, Patel SR, Ludwig JA, et al. Combination therapy with temozolomide and bevacizumab in the treatment of hemangiopericytoma/malignant solitary fibrous tumor [abstract]. J Clin Oncol 2008;26(Suppl 1):Abstract 10512.
36. Itakura E, Yamamoto J, Oda Y, Tsuneyoshi M. Detection and characterization of vascular endothelial growth factors and their receptors in a series of angiosarcomas. J Surg Oncol 2008;97:74–81.
37. Koontz BF, Miles EF, Rubio MA, et al. Preoperative radiotherapy and bevacizumab for angiosarcoma of the head and neck: two case studies. Head Neck 2008;30:262–266.
38. Agulnik M, Okuno SH, von Mehren M, et al. Bevacizumab for the treatment of angiosarcoma: an open-label multicenter phase II study [abstract]. Presented at the Connective Tissue Oncology Society Annual Meeting; November 5–7, 2009; Miami, Florida. Abstract 39250.
39. Antonescu CR, Yoshida A, Guo T, et al. KDR activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors. Cancer Res 2009;69:7175–7179.
40. Stacchiotti S, Tamborini E, Marrari A, et al. Response to sunitinib malate in advanced alveolar soft part sarcoma. Clin Cancer Res 2009;15:1096–1104.
41. Gardner K, Judson I, Leahy M, et al. Activity of cediranib, a highly potent and selective VEGF signaling inhibitor, in alveolar soft part sarcoma [abstract]. J Clin Oncol 2009;27(Suppl 1):Abstract 10523.
42. Comoglio PM, Giordano S, Trusolino L. Drug development of MET inhibitors: targeting oncogene addiction and expedience. Nat Rev Drug Discov 2008;7:504–516.
43. Coltella N, Manara MC, Cerisano V, et al. Role of the MET/HGF receptor in proliferation and invasive behavior of osteosarcoma. FASEB J 2003;17:1162–1164.
44. Davis IJ, McFadden AW, Zhang Y, et al. Identification of the receptor tyrosine kinase c-Met and its ligand, hepatocyte growth factor, as therapeutic targets in clear cell sarcoma. Cancer Res 2010;70:639–645.
45. Diomedi-Camassei F, McDowell HP, De Ioris MA, et al. Clinical significance of CXC chemokine receptor-4 and c-Met in childhood rhabdomyosarcoma. Clin Cancer Res 2008;14:4119â€“4127.
46. Ginsberg JP, Davis RJ, Bennicelli JL, et al. Up-regulation of MET but not neural cell adhesion molecule expression by the PAX3-FKHR fusion protein in alveolar rhabdomyosarcoma. Cancer Res 1998;58:3542–3546.
47. Jun HJ, Lee J, Lim DH, et al. Expression of MET in alveolar soft part sarcoma. Med Oncol 2010;27:459–465.
48. Kikuchi K, Tsuchiya K, Otabe O, et al. Effects of PAX3-FKHR on malignant phenotypes in alveolar rhabdomyosarcoma. Biochem Biophys Res Commun 2008;365:568–574.
49. Lazar AJ, Lahat G, Myers SE, et al. Validation of potential therapeutic targets in alveolar soft part sarcoma: an immunohistochemical study utilizing tissue microarray. Histopathology 2009;55:750–755.
50. Patane S, Avnet S, Coltella N, et al. MET overexpression turns human primary osteoblasts into osteosarcomas. Cancer Res 2006;66:4750–4757.
51. Rees H, Williamson D, Papanastasiou A, et al. The MET receptor tyrosine kinase contributes to invasive tumour growth in rhabdomyosarcomas. Growth Factors 2006;24:197–208.
52. Stockwin L, Vistica DT, Kenney S, et al. Gene expression profiling of alveolar soft-part sarcoma (ASPS). BMC

Cancer 2009;9:22.
53. Taulli R, Scuoppo C, Bersani F, et al. Validation of Met as a therapeutic target in alveolar and embryonal rhabdomyosarcoma. Cancer Res 2006;66:4742–4749.
54. Tsuda M, Davis IJ, Argani P, et al. TFE3 fusions activate MET signaling by transcriptional up-regulation, defining another class of tumors as candidates for therapeutic MET inhibition. Cancer Res 2007;67:919–929.
55. Relaix F, Polimeni M, Rocancourt D, et al. The transcriptional activator PAX3-FKHR rescues the defects of Pax3 mutant mice but induces a myogenic gain-of-function phenotype with ligand-independent activation of Met signaling in vivo. Genes Dev 2003;17:2950–2965.
56. Li Y, Chang Q, Rubin BP, et al. Insulin receptor activation in solitary fibrous tumours. J Pathol 2007;211:550–554.
57. Rikhof B, van Doorn J, Suurmeijer AJ, et al. Insulin-like growth factors and insulin-like growth factor-binding proteins in relation to disease status and incidence of hypoglycaemia in patients with a gastrointestinal stromal tumour. Ann Oncol 2009;20:1582–1588.
58. 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;27:5800–5807.
59. Tarn C, Rink L, Merkel E, et al. Insulin-like growth factor 1 receptor is a potential therapeutic target for gastrointestinal stromal tumors. Proc Natl Acad Sci U S A 2008;105:8387–8392.
60. Sabatini DM. mTOR and cancer: insights into a complex relationship. Nat Rev Cancer 2006;6:729–734.
61. Wan X, Helman LJ. The biology behind mTOR inhibition in sarcoma. Oncologist 2007;12:1007–1018.
62. 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]. Proc Am Soc Clin Oncol 2006;24(Suppl 1):Abstract 9504.
63. Mita MM, Mita AC, Chu QS, et al. Phase I trial of the novel mammalian target of rapamycin inhibitor deforolimus (AP23573; MK-8669) administered intravenously daily for 5 days every 2 weeks to patients with advanced malignancies. J Clin Oncol 2008;26:361–367.
64. Chawla SP, Tolcher AW, Staddon AP, et al. Updated results of a phase II trial of AP23573, a novel mTOR inhibitor, in patients (pts) with advanced soft tissue or bone sarcomas [abstract]. Proc Am Soc Clin Oncol 2006;24(Suppl 1):Abstract 9505.
65. Iwenofu OH, Lackman RD, Staddon AP, et al. Phospho-S6 ribosomal protein: a potential new predictive sarcoma marker for targeted mTOR therapy. Mod Pathol 2007;21:231–237.
66. Wagner AJ, Malinowska-Kolodziej I, Morgan JA, et al. Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. J Clin Oncol 2010;28:835–840.
67. O'Reilly KE, Rojo F, She QB, et al. mTOR inhibition induces upstream receptor tyrosine kinase signaling and activates Akt. Cancer Res 2006;66:1500–1508.
68. Sun SY, Rosenberg LM, Wang X, et al. Activation of Akt and eIF4E survival pathways by rapamycin-mediated mammalian target of rapamycin inhibition. Cancer Res 2005;65:7052–7058.

Reprint Address
David M. Thomas, Peter MacCallum Cancer Centre, St. Andrews Place, East Melbourne 3002, Victoria, Australia.
E-mail: david.thomas@petermac.org

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