Angiosarcomas and Other Sarcomas of Endothelial Origin

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KEYWORDS

- Angiosarcoma • Epithelioid hemangioendothelioma • Vascular sarcoma
- Kaposi sarcoma • VEGF • KDR • FLT4 • Translocation • Organ transplant

KEY POINTS

- Vascular sarcomas are rare and collectively affect fewer than 600 people a year in the United States (incidence approximately 2/million).
- Because angiosarcomas, hemangioendotheliomas, and other vascular tumors have unique embryonal derivation, it is not surprising that they have a unique sensitivity pattern to chemotherapy agents.
- Surgery, when possible, remains the primary treatment for angiosarcomas.
- Adjuvant radiation for primary disease seems prudent for at least some angiosarcoma, given the high local-regional recurrence rate of these tumors. Angiosarcomas also have a high rate of metastasis, but it is not clear that adjuvant chemotherapy improves survival.
- Epithelioid hemangioendothelioma is a unique form of sarcoma often presenting as multifocal disease. Most patients can do well with observation alone, although a fraction of patients have more aggressive disease and have difficulties in both local control and metastatic disease.

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- Anthracyclines, alkylating agents such as ifosfamide, are active against at least some vascular sarcomas. Angiosarcomas demonstrate a unique sensitivity to taxanes, and gemcitabine, vinorelbine, and vascular endothelial growth factor (VEGF) or vascular endothelial growth factor receptors (VEGFR) antagonists all have at least some activity against these tumors.
- New targets to consider for therapy include angiopoietin antagonists as well as inhibitors notch or ephrin signaling pathways.

INTRODUCTION

Of the 14,000 cases of sarcoma diagnosed in the United States annually, sarcomas arising from endothelium and other elements of blood vessels constitute ∼2% to 3%, and thus it is likely that fewer than 600 people in the United States are affected each year.[1] This fact is surprising, given the common nature of the benign counterpart of these tumors, hemangiomas, arteriovenous malformations, and other lesions in the population.

In this review, examined are some of the unique characteristics and therapeutic options for patients with tumors that arise from endothelium or its precursors, highlighting the potential of new agents for these tumors. Given the activity of antiangiogenic therapy in both vascular sarcomas and other cancers, new agents will have an impact on both vascular sarcomas and more common cancers.

SCOPE OF THE DIAGNOSES DISCUSSED

The World Health Organization (WHO) fascicle for soft tissue sarcomas was updated in 2013. The terminology for soft tissue vascular sarcomas is largely unchanged from the prior 2002 version. For bone vascular tumors, changes are anticipated to make terminology for both groups of vascular tumors more consistent. Technically, leiomyosarcoma could be considered vascular sarcomas, because they frequently arise from branches of veins, presumably from smooth muscle cells of blood vessels or their precursors, but they are not discussed here. For space considerations, also not addressed are other tumors that arise from other cellular structures associated with blood vessels (eg, solitary fibrous tumor or intimal sarcoma, each of which has unique biology and sensitivity to systemic therapeutics as well). Finally, there are also vascular components of other tumors such as angiomyolipoma, but these are also not discussed in this review.

DEMOGRAPHICS

Kaposi sarcoma (KS) is an AIDS (acquired immune deficiency syndrome)-defining diagnosis and happily has been observed less frequently, with the advent of newer generations of anti-retroviral therapy for people with human immunodeficiency virus (HIV) infections. KS also arises in approximately 1 in 200 patients with organ transplants due to immunosuppressive drugs. KS is also seen in an endemic form in patients from the Mediterranean basin and endemically in Africa and the Mideast as well. In the United States, what was a rare cancer became common with the advent of AIDS, with a peak incidence of 10 to 20/1000 HIV-positive patients per year in the United States, but an ∼80% decrease with the broad use of multitargeted anti-retroviral therapy.[2] Nonetheless, KS remains more common than other vascular sarcomas.

Angiosarcoma may arise in any part of the body but is more common in soft tissue than in bone. The peak age of incidence seems to be the 7th decade, and men are affected more than women.[1] The head and neck area is probably the most common site of diagnosis, and the most common site of radiation-induced angiosarcoma development is the breast. With an increasing incidence of breast cancer, an increase in angiosarcoma of the breast has also been observed with a cumulative incidence of 0.9 per 1000 breast cancer cases over 15 years.[3] The median latency is 4 to 8 years after treatment.

In addition, it is worth noting that after rhabdomyosarcoma, angiosarcoma is likely the second most common sarcoma to arise from germ cell tumors.[4,5] In all, angiosarcoma and epithelioid hemangioendothelioma (EHE) represent under 2% to 3% of all sarcoma diagnoses.

Epithelioid hemangioendothelioma (EHE) is substantially less common than angiosarcoma, but given the more indolent nature of the tumor, there is a relatively larger prevalent population. It occurs in a younger population, with a peak incidence in the 4th to 5th decade.[6] Women seem to be affected more commonly than men. In a survey of EHE patients from an EHE support group, overall survival was 73% at 5 years.[7]

ANGIOGENESIS VERSUS VASCULOGENESIS AND THE GROWTH OF ENDOTHELIAL TUMORS

There is significant confusion in the literature regarding the terms vasculogenesis and angiogenesis. Vasculogenesis typically has been a term applied to de novo blood vessel formation during embryonic development. Conversely, classically, angiogenesis was described to be the formation of new capillaries by sprouting or splitting of preexisting vessels. In common oncological parlance today, angiogenesis is used to describe the growth of any new blood vessel of any size. It has been proposed that capillarogenesis is a more accurate term to describe the "universal formation of new capillaries, during development and in the adult, without any implications regarding possible underlying mechanisms, processes, or the cells that give rise to this outcome" and distinguishable from the growth and maturation of these smallest of vessels into larger ones.[8]

Clearly, KS, angiosarcomas, and hemangioendotheliomas fall into the categories of tumors of endothelial cells or their precursors. Clinicians see both nodular masses and superficial spreading versions of endothelial tumors (**Fig. 1**). Pathologists have described some microscopic features of cutaneous angiosarcomas as having areas that are more solid (which one can hypothesize as being local aggressiveness of the tumor) as well as a characteristic dissecting pattern among existing collagen bundles, which could be construed as an aberrant version of capillarogenesis. These features seem to correlate with the gross pictures of tumor growth. The dissecting features may also account for the very common marginal recurrence of these tumors after primary resection. The authors further hypothesize that the multifocal pattern of these tumors, seen in particular in some versions of EHE, may arise from an unusual pattern of self-seeding as described by Comen and colleagues and Kim and colleagues.[9,10]

Like angiosarcoma, KS is described as evolving between a patch stage, a plaque stage, and frankly nodular disease, again harkening to the pattern of growth seen in other endothelial tumors in which aberrant capillarogenesis is involved.

CAUSE OF SARCOMAS OF ENDOTHELIAL ORIGIN

The most common cause of angiosarcoma seems to be therapeutic radiation, which was a well-recognized cause of hepatic angiosarcoma in the era when the

Fig. 1. Nodular (*left,* most notable on the bridge of the nose) and spreading (*right*) patterns of spread of cutaneous angiosarcoma of the head and neck.

thorium-containing contrast agent Thorotrast was used.[11] Presently, the breast is the most common anatomic site affected by radiation-induced angiosarcoma, raising the question of the use of lumpectomy and radiation for ductal carcinoma in situ, a noninvasive form of breast cancer in which this recommendation is often made in lieu of wide surgical resection.[3,12]

Angiosarcomas also arise after exposure to vinyl chloride, although they remain rare tumors even in an exposed population.[13,14] Angiosarcomas are also observed after lymphedema from any cause, be it surgical, filarial, or congenital, and carries the term Stewart-Treves syndrome from the pathologists who first described it.[15]

Whether arising in its epidemic HIV-associated form or endemic form, KS is caused by human herpesvirus-8 (HHV8), a γ-2 herpesvirus also termed Kaposi sarcoma herpesvirus. HHV8 functions at least in part through stimulation of chemokines, a viral version of interleukin-6, and anti-apoptotic proteins for its growth and transmission.[16–19] The role of microRNA networks in its propagation as well as change from latent to lytic state is under scrutiny.[20]

GENETIC CHANGES IN ENDOTHELIAL-BASED SARCOMAS

Specific sarcomas of endothelial derivation are described in **Table 1**, along with genetic alterations observed for each subtype. The specifics of HHV8 biology are beyond the scope of this review, but point to specific genes that may be important in the conversion of an endothelial cell to a sarcoma cell, for example, cyclin D homologues and a G-protein-coupled receptor.[21] Also not discussed here are the very interesting findings with respect to genetic knockout mice and vascular development; arteriovenous malformations arise in several of these mice and understanding of these pathways could affect therapy for patients with vascular sarcomas.[22–24]

Angiosarcomas are largely aneuploid tumors, which for at least some of them makes sense, given their association with therapeutic irradiation. Because there are only rare cases of angiosarcomas that seem to arise from a benign lesion such as a hemangioma,[25] the pathway leading to the 2 types of vascular lesions seems distinct, although clearly a genetic examination of such rare compound lesions would be of

Table 1
Genetics of sarcomas of apparent endothelial cell origin

Histology	Characteristic Genetic Changes/etiology
Kaposi sarcoma	HHV-8/Kaposi sarcoma herpesvirus
Angiosarcoma	*MYC* amplification (in radiation-induced angiosarcoma more than primary angiosarcoma) *KDR/VEGFR2* mutations, *FLT4/VEGFR3* amplifications (frequency well under 50%)
Epithelioid hemangioendothelioma	t(1;3) (p36.3;q25) *WWTR1-CAMTA1* (more common) t(X;11) (p11.23;q22.1) *YAP1-TFE3*
Pseudomyogenic hemangioendothelioma	t(7;19) (q22;q13); frequency unknown

Data from Refs.[19,20,26–28,30–34,41,77,82–84]

great interest to understand angiosarcomagenesis. ERG (ETS [E twenty six]-related gene) is overexpressed in most angiosarcomas as well as other benign and malignant vascular tumors and seems to be a consistent endothelial lineage marker.[26] *MYC* amplification seems to be more common in secondary than primary angiosarcomas.[27–29] *miR17-92* seems to be up-regulated with *MYC* in radiation-induced angiosarcomas as well, with concurrent downregulation of anti-angiogenic gene *THBS1.*[27] *KDR* mutation and *FLT4* amplification have been observed in a fraction of angiosarcomas.[28,30] There does not sem to be a correlation between mutation status and outcome with vascular endothelial growth factors (VEGFs).

EHE has been found to be associated with the t(1;3) (p36.3;q25) *WWTR1-CAMTA1* translocation,[31,32] and less commonly t(X;11) (p11.23;q22.1) *YAP1-TFE3.*[33] *WWTR1*, also called *TAZ*, is a gene involved in 14-3-3 transcriptional factor activation and signaling in the hippo pathway that is normally highly expressed in endothelial cells. *CAMTA1* is part of a family of calmodulin-binding transcription activators, normally found only in brain. *YAP1* is another gene in the hippo pathway, thus closely EHE to hippo signaling in all cases examined to date. These fusions are not directly targetable with present day therapeutics but may reveal downstream targets. Of note, the multiple lesions examined from a single patient all seem to have the same translocation, providing evidence that this is a matter of tumor metastasis or self-seeding at an early stage of development.[34]

PATHOLOGIC ABNORMALITY OF ENDOTHELIAL TUMORS

All angiosarcomas are presently considered high-grade neoplasms, regardless of degree of vascular differentiation or cytology, save primary breast angiosarcomas, where the Rosen 3-tier grading scheme is used. The concept angiosarcoma grading was challenged in one analysis of what was largely consultation material. In this study of 49 patients Rosen grade was not prognostic, in keeping with outcomes from other primary sites of disease.[35]

As noted above, angiosarcomas demonstrate a dissecting pattern of blood vessel formation and bear the endothelial markers characteristic of this cell lineage. There are variations of the histology based on anatomic site, with cutaneous lesions demonstrating dissecting and solid patterns of growth, and some tumors of visceral origin more commonly displaying epithelioid features. In comparison to benign lesions, areas with multilayered endothelial growth are characteristic of angiosarcoma, and there is at least some evidence of cytologic atypia. Mitotic rate is variable, but greater than that seen for hemangiomas.

Immunohistochemical markers for angiosarcoma include CD31, ERG, and CD34, among others. Although FLT4/vascular endothelial growth factor receptor3 was proposed as a lymphatic-specific marker based on in situ hybridization in developing mice,[36] a significant number of angiosarcomas express one or more lymphatic markers, without direct correlation with FLT4 gene amplification.[28] It is hoped that work on the association of ephrin B2 and EphB4 expression in arterial versus venous development will shed some light on this fundamental issue regarding the nature of these tumors.[37–40]

EHE are characterized by endothelial cells arranged in single files, nest, or more solid growth, and distinct lack of vessel formation that is characteristic of angiosarcomas. Intracytoplasmic vacuoles are often seen, and some of these may have red blood cells in them as well. Like angiosarcomas, EHE are positive for CD31, CD34, and ERG, and often are keratin positive.

KS usually shows a greater number of spindle-shaped cells than angiosarcoma and also forms vascular channels containing red blood cells, like angiosarcoma. Lymphoplasmacytic infiltrates may be observed. Eosinophilic hyaline inclusions can be observed in more advanced lesions. Although CD31 and CD34 immunohistochemicals are also common in KS, HHV8 latent nuclear antigen-1 is only positive in KS and not in the other diagnoses.

The 2013 WHO classification adds the unifying entity pseudomyogenic hemangioendothelioma, which has also been called epithelioid sarcoma-like hemangioendothelioma.[41–43] It will be included in the "rarely metastasizing" category of the WHO soft tissue sarcoma classification. Like EHE, it can be multifocal, and at least some cases are associated with a t(7;19) (q22;q13) translocation, distinct from other forms of hemangioendothelioma described above. There are presently no data regarding chemotherapy sensitivity of this unique vascular sarcoma subtype.

PRIMARY THERAPY
Kaposi Sarcoma

For KS, observation alone, in particular in someone with improving CD4 counts after the institution of anti-retroviral therapy, seems prudent except for those patients with obvious symptoms. For transplant-related KS patients cautious decrease or withdrawal of immunosuppressive therapy is often effective, but this benefit comes at the risk of allograft rejection.[44,45] The switch of the immunosuppressive regimen from calcineurin inhibitors to target rapamycin inhibitor sirolimus has been reported to induce significant regression of KS lesions.[45,46]

KS lesions are usually not isolated, and thus "primary therapy" takes on a different tone. Intralesional chemotherapy such as vinblastine can be used for symptomatic isolated lesions,[47,48] as can topical retinoids. Radiation therapy is usually used as primary therapy disease that is symptomatic and too extensive to treat with more localized treatments.

Angiosarcoma and EHE

When feasible, primary treatment of angiosarcoma or EHE is surgical. However, for the relatively common site of head and neck it is not uncommon to encounter unresectable disease that covers too large an area of the scalp to treat surgically, in which case electron beam radiation sometimes can be used for local control. In the situation of radiation-induced angiosarcoma of the breast, the local recurrence risk of these lesions highlights the need for resection of irradiated parenchyma and skin as primary therapy to attempt to improve the local control rate.[3,49]

For primary therapy of EHE or angiosarcoma involving the liver, embolization can be useful, taking advantage of the differences between tumor and normal tissue tolerance for hypoxia. Shamefully, there remain no comparative data on chemoembolization versus bland embolization, despite thousands of patients with a variety of diagnoses being treated with either modality.

After primary therapy for angiosarcoma (or potentially EHE in the correct anatomic location), general principles regarding adjuvant therapy in sarcoma apply, with some caveats. If an angiosarcoma was caused by radiation, it is oftentimes not possible to administer adjuvant radiation. In some cases a way to boost local doses of radiation can be considered, such as brachytherapy, but these are considered on a case-by-case basis.

In terms of adjuvant chemotherapy, the low response rate to chemotherapy in EHE makes it a relatively unattractive prospect. In addition, the small number of people with localized disease with EHE at presentation makes this clinical situation uncommon.

As for adjuvant chemotherapy for angiosarcoma, meta-analysis data indicate that patients with unselected sarcomas have a survival benefit from ifosfamide-based chemotherapy.[50] However, for the few positive individual studies over the last few decades of adjuvant therapy in soft tissue sarcomas, there are multiple negative individual studies, including the largest such randomized study,[51] making the recommendation of adjuvant anthracycline-ifosfamide a difficult decision. As with all clinical decision-making in which there are conflicting data, decisions should be made on a patient-by-patient basis.

TREATMENT OF RECURRENT DISEASE BY DIAGNOSIS
Kaposi Sarcoma

As noted below for angiosarcoma, anthracyclines and taxanes both demonstrate significant activity in KS. Chemotherapy is generally used for more extensive skin disease, edema, visceral disease, and disease not responding to local therapy. PEGylated liposomal doxorubicin (PLD; Doxil/Caelyx) showed a greater response rate and less toxicity than a combination of vincristine, doxorubicin, and bleomycin in 2 studies, and thus is a good standard of care.[52,53] Liposomal daunorubicin was also shown similar to a combination of vincristine, doxorubicin, and bleomycin in terms of response rate and median survival and is another potential option.[54] In a small study (n = 60), PLD was more active than liposomal daunorubicin, giving further support for its use.[55]

Taxanes also have activity in KS. There are concerns about the interaction of antiretroviral agents and cytochrome p450 metabolism, so care should be taken in their use. In one poorly accruing randomized study (n = 73 evaluable), clinical outcomes were similar with PLD 20 mg/m^2 IV every 3 weeks versus paclitaxel at a dose of 100 mg/m^2 IV every 2 weeks.[56] For patients for whom PLD is not a good option, paclitaxel or other agents such as docetaxel[57] or the yet to be tested nab-paclitaxel may be reasonable second-line options for treatment.

Other agents with some activity in KS include vinorelbine,[58] bevacizumab,[59] or sirolimus[60] (at very low doses due to pharmacokinetic interactions). However, given the lack of data on newer agents, clinical trials are advisable in advanced disease.

Angiosarcoma

Angiosarcoma is one of the few sarcoma diagnoses with a significant response rate to taxanes,[61] as had been noted previously with KS. In a similar fashion, PLD was shown to have activity in angiosarcoma,[62] with less toxicity than that of standard doxorubicin.

A single-center review demonstrated that anthracyclines had slightly greater activity than taxanes.[63] However, prospective studies in angiosarcoma patients have been few and far between. There are no prospective studies of anthracyclines treating angiosarcoma specifically, although there are data from studies involving multiple sarcoma histologies that anthracyclines and/or ifosfamide have activity in angiosarcoma patients (eg, the phase II study of mitomycin-doxorubicin-cisplatin showing 3 of 4 angiosarcoma patients with responses).[64]

Paclitaxel was studied in France in 30 patients, using 80 mg/m^2 IV on days 1, 8, and 15 of a 28-day cycle. The aggressiveness of advanced disease was highlighted by the median time to progression of 4 months and median overall survival of 8 months. For other cytotoxic agents, after small numbers of patients with angiosarcoma in all-sarcoma phase II studies, Stacchiotti and colleagues[65] examined the experience with gemcitabine in a traditional 1000 mg/m^2 schedule days 1, 8, and 15 every 28 days in 25 angiosarcoma patients across several centers in Italy, showing a median progression-free survival (PFS) of 7 months and median overall survival of 17 months. Radiation-induced angiosarcomas seemed to fare as well to therapy as those that arose spontaneously. There are anecdotal data that the combination of gemcitabine-docetaxel is active in angiosarcoma, but it is not clear if it is any more active than, for example, sequential therapy with the 2 agents. Given the relatively short PFS for people on systemic therapy in general, this seems a difficult proposition to prove.

As part of a multi-arm phase II study, Maki and colleagues[66] showed 5 of 37 angiosarcoma patients with Response Evaluation Criteria in Solid Tumors (RECIST) responses to oral daily sorafenib. Median PFS was 3.8 months, and overall survival was 14.9 months for the angiosarcoma patients. These data were quite different from the French experience with sorafenib, in which 26 patients with superficial tumors and 15 with visceral angiosarcomas were enrolled. The median PFS times for cutaneous and visceral disease were 1.8 months and 3.8 months, respectively, and median overall survival times were 12.0 months and 9.0 months, respectively.[67] The reasons for the differences between the 2 studies remain unclear. Differences between specific kinase inhibitors were also highlighted by the SARC001 study, in which there were only 2 patients of 16 treated who did not progress within 16 weeks of starting therapy.[68] Bevacizumab has also been examined prospectively and was shown to have a 15% response rate in 30 evaluable patients with angiosarcoma (n = 23) or EHE (n = 7) in a phase II study.[69] Median PFS was 12 weeks, whereas median overall survival was 52.7 weeks in the angiosarcoma population.

Epithelioid Hemangioendothelioma

The rarity of EHE has led to little prospective evaluation of this diagnosis in clinical trials. The Agulnik study is the only one to prospectively capture these patients properly, showing median PFS and overall survival of 7 patients of 39.1 and 142.6 weeks, respectively.[69] These data highlight the much more indolent nature of this diagnosis in some patients, with liver or other organ failure in a significant proportion of patients. The authors have observed anecdotal responses to single agents, but no consistent pattern of activity, of PLD, doxorubicin, ifosfamide, vinorelbine, sorafenib, pazopanib, or other agents. For example, a patient on oral cyclophosphamide and prednisolone achieved a complete response,[70] but the authors have been unable to replicate this finding on a consistent basis. In treating a large number of patients with a variety of agents, Stacchiotti and colleagues[71] have found activity of sirolimus in EHE, making this an interesting agent to consider even as first-line therapy, given the lack of consistent responses with other agents. Sirolimus is also an obvious choice of immunosuppressant in patients who have liver transplant for liver-predominant EHE.

For EHE involving the liver, even in the setting of metastasis-proven disease in other organs such as lung, liver transplant is an option for continued survival in the setting of a failing liver if the disease is indolent enough over time. Of course, this means the use of anti-rejection drugs and attendant complications thereafter, but in the proper clinical setting, such a procedure can be life-extending. An evaluation by a liver transplant team during a patient's course is advisable; however, transplant should not be considered as primary therapy for EHE of the liver, because a substantial proportion of patients can have indolent disease that evolves only slowly over a decade or more; the 5-year survival rate in one small series was 67%.[72] Furthermore, recurrence of EHE is common in the transplanted liver.[73,74] It would be a waste to discard a patient's liver that is still even somewhat functional by rushing to liver transplant. The success rate of liver transplant in the literature does not take into account the long survival of patients with primary disease.

EMERGING THERAPEUTIC OPTIONS

Local therapy also may be improving for patients with angiosarcoma or EHE in an end organ. Yttrium 90 is an electron emitter with a 64-hour half-life and has been used in primary hepatocellular carcinoma with some success. Selective internal radiotherapy with Yttrium 90 microspheres is a way to deliver radiation therapy in a measured way to the liver and is a possible consideration for EHE or angiosarcoma metastatic to liver or other end organ, although there are no prospective data available.

A variety of developments in biology may have an impact on angiogenesis in cancer and thus also have an impact on treatment of endothelial tumors such as angiosarcoma. Advances in the developmental biology of blood vessel formation point out new pathways that may be worth pursuing as therapies for KS, angiosarcoma, or EHE.

The finding of the importance of ephrin signaling and the notch pathway in the development of vasculature gives hope that inhibitors of these pathways will be useful.[75–77] Dasatinib is an inhibitor of at least one of the very complex family of ephrins/Eph signaling pathways and has not been examined in detail in angiosarcoma, for example. Unfortunately, γ-secretase inhibitors, which represent one mechanism to block notch signaling, essentially have been abandoned as of 2013 for study in solid tumors. Agents that attack other important steps in angiogenesis are under study as well, such as inhibitors of angiopoietin signaling via receptor TIE2.[78] Given the differences in mechanism of action compared with small molecule tyrosine kinase inhibitors, antibodies to VEGF or platelet-derived growth factor receptors could provide activity alone or in combination with these other agents, trying to mimic the concept of early aggressive blockade of a tyrosine kinase signaling pathways (eg, HER2 in breast cancer, BRAF and MEK in melanoma) to achieve better tumor control.[79–81] Looking for general principles that will apply to more than one type of cancer is one strategy to insure patients with common and rare diseases alike may benefit from new therapeutic strategies.

PERSPECTIVE

Elegant basic science studies of vertebrate development have led to a greater appreciation of the differences between arteries, veins, and lymphatics. These data inform thinking regarding the yin and yang of therapeutic angiogenesis in cardiac disease versus anti-angiogenic therapy in cancer. Given only modest benefit of existing agents in metastatic endothelial tumors such as KS, EHE, and angiosarcoma, these developmental and other mechanistic pathways, such as signaling downstream from ERG or MYC, aim to help guide future generations of studies of this diverse group of

sarcomas. Because proportions of patients respond to therapy directed at the VEGF axis, there are clearly differences in the VEGF dependence of this family of tumors. Perhaps by reconstructing downstream signaling pathways in patient material, it will be bests to discern circumstances in which receptor or downstream signaling inhibitors will benefit patients most.

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