

Targeted therapy for sarcomas

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Abstract: Sarcomas are tumors of mesenchymal origin that make up approximately 1% of human cancers. They may arise as primary tumors in either bone or soft tissue, with approximately 11,280 soft tissue tumors and 2,650 bone tumors diagnosed each year in the United States. There are at least 50 different subtypes of soft tissue sarcoma, with new ones described with ever-increasing frequency. One way to look at sarcomas is to divide them into categories on the basis of their genetic make-up. One group of sarcomas has an identifiable, relatively simple genetic signature, such as the X:18 translocation seen in synovial sarcoma or the 11:22 translocation seen in Ewing's sarcoma. These specific abnormalities often lead to the presence of fusion proteins, such as EWS-FLI1 in Ewing's sarcoma, which are helpful as diagnostic tools and may become therapeutic targets in the future. Another group of sarcomas is characterized by complex genetic abnormalities as seen in leiomyosarcoma, osteosarcoma, and undifferentiated sarcoma. It is important to keep these distinctions in mind when contemplating the development of targeted agents for sarcomas. Different abnormalities in sarcoma could be divided by tumor subtype or by the molecular or pathway abnormality. However, some existing drugs or drugs in development may interfere with or alter more than one of the presented pathways.

Keywords: sarcoma, targeted agents, tyrosine kinase inhibitors, mTor inhibition

Angiogenesis

c-kit, PDGFRA, and gastrointestinal stromal tumor

Gastrointestinal stromal tumor (GIST) is a malignant sarcoma felt to arise from the interstitial cell of Cajal and is characterized most commonly by activating mutations in c-kit, and less commonly in platelet-derived growth factor receptor alpha (PDGFRA). Approximately 5,000 cases are diagnosed in the United States each year, with the stomach being the most common location. Imatinib, a tyrosine kinase inhibitor initially developed as an agent for chronic myelogenous leukemia and designed to target the product of its fusion protein Bcr-Abl, was also found to inhibit c-kit. The initial report of activity in 2001^{1,2} was followed by trials in both the United States and Europe that demonstrated objective response rates in the range of 50% to 70%.^{3,4} Interestingly, patients with complete responses, partial responses, and stable disease have similar rates of progression-free survival (PFS) compared with patients with stable disease using imatinib when using conventional response criteria such as Response Evaluation Criteria in Solid Tumors (RECIST) with traditional computed tomography scanning.⁵ Approximately 50% of patients with responsive disease are still alive at 5 years compared with less than 10% survival at 2 years for nonresponders. This observation has prompted a search for alternative assessment schemas and has led

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some to argue that “we should desist from using RECIST in GIST.”⁶ The most common mutation site is at exon 11 and is usually sensitive to treatment with imatinib at 400 mg. Other mutations, such as exon 9, may benefit from higher doses of imatinib.^{7,8} A smaller percentage of GISTs have mutations in the platelet-derived growth factor receptor alpha, and these tumors may also be sensitive to imatinib. Wild-type GISTs, without a mutation, are less sensitive to imatinib.

Patients with advanced disease should continue to receive imatinib until disease progression. This issue was addressed in a French discontinuation study in which patients with responsive GIST were randomly assigned to continue or stop imatinib at 1 year.⁹ The majority of patients developed recurrence of disease within 6 months on discontinuation of imatinib, but disease control could often be achieved on resumption of the drug. This finding was also observed with further randomization at 3 years.¹⁰ The study did suggest that brief “honeymoon” periods off imatinib could be possible without undue patient risk.

For those whose GISTs progress while receiving imatinib, sunitinib is approved for second-line therapy. Of note, after initial progression on standard-dose imatinib, the next recommended treatment is increasing the dose to 800 mg. The dose of sunitinib is 50 mg/day for 4 weeks with a 2-week rest period. Although the objective response rate to sunitinib is 7%, the time to progression on this agent is prolonged significantly compared with placebo, at 27.3 weeks with sunitinib versus 6.4 weeks for placebo.¹¹

Other agents are in the process of evaluation for patients whose tumors progress on imatinib. Regorafenib, an oral multikinase inhibitor, has shown activity in both Phase II and Phase III trials in patients progressing on both imatinib and sunitinib, with a clinical benefit rate of 54% at 16 weeks (two partial response, 10 stable disease) in the Phase II trial¹² and a median PFS of 4.8 months compared with 0.9 months for placebo in the Phase III trial.¹³ This agent blocks vascular endothelial growth factor receptor 2–3 (VEGFR2-3), c-kit, TIE2, PDGFR beta (PDGFRB), fibroblast growth factor receptor 1, RET (rearranged during transfection), RAF, and p38 mitogen-activated protein kinase. It is now approved for use in advanced GISTs after progression on imatinib and sunitinib. Masitinib, a newer tyrosine kinase inhibitor, has been compared with sunitinib in patients with imatinib-resistant GIST. Masitinib was administered at a dose of 12 mg/day versus 50 mg/day sunitinib. Although median PFS rates were similar for the two agents, at 3.9 months for masitinib and 3.8 months for sunitinib, the adverse effect profile was more favorable for

the masitinib group.¹⁴ A smaller study of 30 patients has evaluated masitinib in imatinib-naïve patients with a 20% response rate (RR) by RECIST and an 86% RR by fluoro-deoxyglucose positron emission scanning. Disease control rate in this study (complete response, partial response, stable disease) was 96.7%.¹⁵

Dasatinib, another tyrosine kinase inhibitor with activity against KIT (CD117), PDGFR, ABL, and SRC, was evaluated in a Phase II study. Although the drug demonstrated activity by overall response rate with a partial response of 32% (15/47) by Choi criteria, it did not meet the target progression-free rate of more than 30% at 6 months.¹⁶

Sorafenib, which targets KIT, VEGFR, PDGFRB, and BRAF, has also been studied in refractory GIST. In 38 patients refractory to either imatinib alone or both imatinib and sunitinib, partial response was observed in 13% (1 imatinib resistant, 4 imatinib and sunitinib resistant), and stable disease was seen in 55% (3 IM-RES, 18 IM-SU RES). Median progression-free survival was 5.2 months and median overall survival was 11.6 months with 1-year survival of 50% and 2-year survival of 26%. With an overall disease control rate of 68%, sorafenib was felt to have definite activity in IM-SU-resistant GIST.

Another approach under evaluation for imatinib-resistant GIST is to combine other agents with imatinib. Everolimus (RAD001), an m-Tor inhibitor, has been combined with imatinib. Patients were stratified as to whether they had progressed on imatinib alone (stratum 1) or on imatinib and sunitinib (stratum 2). Everolimus was administered at 2.5 mg/day, and imatinib was given at 600 mg/day. Four of 23 patients in stratum 1 were progression free at 4 months, as were 13 (37%) of 35 patients in stratum 2.¹⁷ The authors concluded that the combination of everolimus and imatinib was worthy of further investigation in GIST.

After the dramatic effect of imatinib in advanced GIST, several studies were initiated to evaluate the use of imatinib in the adjuvant setting for resected GIST. The first published study, performed by the American College of Surgeons Oncology Group, randomly assigned patients with KIT-positive GIST of at least 3 cm in size who underwent complete resection to receive imatinib at 400 mg daily ($n = 359$) versus placebo ($n = 354$) for 1 year in a double-blind manner. With a primary endpoint of recurrence-free survival (RFS), at 19.7 months, 30 patients (8%) in the imatinib group and 70 (20%) in the placebo group had tumor recurrence. The RFS rate was 98% in the imatinib group and 83% in the placebo group at 1 year, with a hazard ratio of 0.35 (one-sided $P < 0.0001$).¹⁸ As patients receiving the placebo were eligible

to crossover to imatinib on progression, an overall survival advantage for imatinib could not be evaluated.

A subsequent study¹⁹ conducted by the Working Group for Medical Oncology and the Scandinavian Sarcoma Group compared 12 versus 36 months of imatinib in the adjuvant setting for high-risk GIST. The primary endpoint of RFS for the 36-month group was 65.6% versus 47.9% for the 12-month group with a hazard ratio of 0.46 ($P < 0.0001$). In addition, overall survival was superior in the 36-month imatinib group compared with the 12-month group (92% versus 81.7%; hazard ratio, 0.45; $P = 0.019$).¹⁹ On the basis of this study, the use of adjuvant imatinib for 36 months is now considered the standard of care for high-risk gastrointestinal stromal tumors.

Neoadjuvant imatinib administration is being employed with the goal of downsizing tumors and increasing the potential resectability of advanced GIST. This indication is not a standard practice in GIST, but it is used in some cases with locally advanced tumors. In the Radiation Therapy Oncology Group/American College of Radiology Imaging Network trial,²⁰ neoadjuvant imatinib was given at 600 mg/day. Thirty patients with localized GIST had RECIST responses of 7% partial response, 83% stable disease, and 10% unknown. Twenty-two patients with metastatic GIST had RECIST responses of 4.5% partial response, 91% stable disease, and 4.5% progression. Two-year PFS was 83% for those with localized disease and 77% for those with metastatic disease.²⁰ Other trials have included both preoperative and postoperative imatinib demonstrating radiographic and pathologic responses with 3–7 days of preoperative imatinib.²¹

PDGFRB and dermatofibrosarcoma protuberans

Dermatofibrosarcoma protuberans (DFSP) is a skin sarcoma that is typically a localized problem but in rare cases may metastasize and can undergo fibrosarcomatous transformation. It is associated with a translocation at t(17;22), which fuses the *COL1A1* gene with the *PDGF-B* gene, leading to overexpression of PDGF-B. Two Phase II trials were conducted, one by the European Organisation for Research and Treatment of Cancer (EORTC) and the other by the Southwest Oncology Group, and the data from these trials were combined for analysis.²² The conclusion was that imatinib was active in DFSP with an objective response rate approaching 50%. Responses were observed in both standard DFSP and in DFSP undergoing fibrosarcomatous transformation. Doses in these studies were from 400–800 mg. Additional studies have explored the use of imatinib in DFSP as preoperative therapy.²³ Imatinib was administered at a dose

of 600 mg/day for 2 months before reevaluation. Overall response rate was 36%. Imatinib has been approved for use in DFSP at a dose of 800 mg.

PDGFRB and chordoma

Chordoma is a tumor that arises from primitive notochordal remnants, that can behave in an aggressive local fashion, and that in rare cases may metastasize. These tumors are felt to be chemotherapy-insensitive. After tumor evaluations demonstrating either expression or phosphorylation of PDGFRB, imatinib was instituted in six patients with advanced chordoma at a dose of 800 mg daily.²⁴ This initial study, which suggested a clinical benefit for imatinib, has been confirmed by a larger Phase II study of 50 patients. The larger study using overall response rate by RECIST showed a single partial response (2%) and 35 patients with stable disease (70%), and a clinical benefit rate of 64%.²⁵ Median PFS was 9 months. Responses can be associated with tumor liquefaction and/or hemorrhage.²⁶

ASPS/transcription factor E3 fusion, VEGF, and ASPS

Alveolar soft part sarcoma (ASPS) is a chemotherapy-insensitive tumor associated with a specific genetic translocation at t(17-X), which results in the ASPS/transcription factor E3 fusion protein. It often grows slowly but inexorably and is frequently associated with lung metastases. Given its long natural history, brain metastases are not infrequent. Recently, several targeted agents have demonstrated responses in this disease. Both sunitinib and cediranib have elicited responses. In one series, two of five patients with ASPS had partial response by RECIST criteria, with an additional patient showing stable disease with sunitinib at 37.5 mg/day.²⁷ Analysis of tumor samples showed activation of PDGFR, epidermal growth factor receptor, MET, and RET. An additional study from this group confirmed activity for sunitinib mediated by PDGFRB, VEGFR2, and RET.²⁸ Promising activity for cediranib, a selective VEGF signaling inhibitor, has also been reported.²⁹ Seven patients were treated with cediranib at an initial dose of 45 mg daily. Four patients had partial responses, two patients had minor responses, and one had stable disease.²⁹ Additional confirmative studies with this agent in this disease are in progress.³⁰

VEGF inhibition, insulin-like growth factor I receptor inhibition, and solitary fibrous tumor

Hemangiopericytoma/solitary fibrous tumors are tumors of uncertain histogenesis that are often localized and low

grade but that may be multifocal and/or metastatic. Their behavior is often unpredictable. Recent reports have suggested activity for the use of VEGF inhibitors in conjunction with chemotherapy for this entity. At the University of Texas MD Anderson Cancer Center, 14 patients with hemangiopericytoma/solitary fibrous tumor received chemotherapy with temozolomide at 150 mg/m² orally on days 1–7 and 15–21 with bevacizumab at 5 mg/kg on days 8 and 22.³¹ Eleven (79%) of 14 patients had partial response by Choi criteria,⁵ two patients had stable disease, and one patient had progressive disease. Median PFS was estimated to be 9.7 months.

Another study of targeted therapy in solitary fibrous tumors evaluated sunitinib in eleven patients at a dose of 37.5 mg/day and in one patient who received figitumumab, an insulin-like growth factor receptor inhibitor.³² Ten patients were evaluable for response, with six showing partial response with Choi criteria (all with stable disease by RECIST), one showing stable disease, and three showing progressive disease. Response duration was more than 6 months in five patients. PDGFR, RET, VEGFRi/2, and insulin-like growth factor 1 receptor (IGF1R) were activated in these tumors. The single patient who progressed on sunitinib appears to have experienced disease stabilization on figitumumab.

VEGF inhibition and angiosarcoma

Given the vascular nature of angiosarcoma, it is tempting to assume that these tumors should be the ideal targets for VEGF inhibitors. Several recent studies have been performed evaluating VEGF inhibition in this disease. A study from the French Sarcoma Group evaluated sorafenib in advanced sarcoma using a primary endpoint of progression-free rate at 9 months according to RECIST. Patients received sorafenib at 400 mg twice a day. Two strata were evaluated: one for superficial disease (26 patients) and one for visceral angiosarcoma (15 patients). The progression-free rate at 9 months was 3.8% in the superficial angiosarcoma group and 0% in the visceral disease group. Median PFS rates were 1.8 months and 3.8 months. Thirty patients (78%) had received prior chemotherapy. No responses were observed in the chemotherapy-naïve group, but a 40% tumor control rate and a 23% response rate were seen in pretreated patients. The researchers' conclusion was that sorafenib showed limited antitumor activity in angiosarcoma.³³ Another study of sorafenib that included 40 patients with vascular sarcomas showed a response rate of 13%, a 3-month PFS rate of 64%, and a median PFS time of 4 months.³⁴ A study of bevacizumab in angiosarcoma

and epithelioid hemangioendothelioma enrolled 32 patients receiving bevacizumab at 15 mg/kg every 21 days. Thirty patients were evaluable with four having a partial response (two angiosarcoma and two hemangioendothelioma). Fifteen patients had stable disease (50%), with a mean time to progression of 26 weeks.³⁵ These studies taken together suggest that further progress is needed in these highly aggressive sarcomas and that VEGF inhibition with currently available agents alone is inadequate.

VEGF inhibition and pazopanib

Pazopanib is an oral angiogenesis inhibitor that targets VEGF receptors, PDGF receptor, and c-kit. It has been tested in Phase II and Phase III trials in sarcomas. In the Phase II trial, 142 patients were enrolled in four different strata: adipocytic soft tissue sarcoma, leiomyosarcoma, synovial sarcoma, and other sarcomas. The primary endpoint was progression-free rate at 12 weeks. Pazopanib was administered at 800 mg/day. The adipocytic group was closed after the first stage because of insufficient activity; the progression-free rate was 26%. The progression-free rates in the other groups were 44% for leiomyosarcoma, 49% for synovial sarcoma, and 39% for other sarcoma subtypes.³⁶

This study was followed by a Phase III trial evaluating pazopanib in metastatic nonadipocytic soft tissue sarcomas after failure of standard chemotherapy. Patients were randomly assigned to receive pazopanib at 800 mg/day or placebo in a 2:1 ratio. The study was double-blinded without crossover. The primary endpoint was PFS. Of the patients, 369 were evaluable. Median PFS was 4.6 months with pazopanib and 1.6 months for placebo. The hazard ratio was 0.31 ($P < 0.0001$). Overall survival was 12.5 months for the pazopanib group and 10.7 months for the placebo group.³⁷ On the basis of the results of this trial, pazopanib has been approved to use in refractory, metastatic sarcomas in the US.

M-CSF, COL6A3, and pigmented villonodular synovitis

Pigmented villonodular synovitis is a benign process that can be locally destructive and that is associated with frequent local recurrences. It is characterized by a t(1;2) translocation, which results in the fusion of *COL6A3* and *M-CSF* genes. Both imatinib and nilotinib have demonstrated activity in this disease. A complete response has been observed with imatinib,³⁸ and nilotinib demonstrated a 12-week progression-free rate of 85.7% in 33 patients at a dose of 800 mg/day, although no objective responses were seen.³⁹

Anaplastic lymphoma kinase and inflammatory myofibroblastic tumor

Inflammatory myofibroblastic tumor combines a spindle cell proliferation with an inflammatory infiltrate. These tumors may have aberrant expression of ALK, the anaplastic lymphoma kinase. Recently, an ALK inhibitor, crizotinib, was shown to be active in non-small-cell lung cancer with ALK gene rearrangements and was approved for use in that entity. Two patients with inflammatory myofibroblastic tumor have been treated with crizotinib, with a partial response of 6 months' duration in a single patient with ALK-rearranged disease.⁴⁰

IGF1R belongs to the family of receptors that are known to activate cellular proliferation, differentiation, and growth, as well as prevention from apoptosis through interaction with the ligands insulin, and IGF1 and IGF2. IGF1R has been implicated in the pathogenesis of both soft and bone sarcomas.⁴¹

IGF1R and Ewing's sarcoma

Ewing's sarcoma is the second most common bone tumor in children and young adults. It is associated with t(11;22), which produces the EWS-FLI1 fusion protein. This fusion protein binds to IGF binding protein 3, which upregulates IGF1.⁴² Several agents have been studied in attempting to target this pathway. R1507 is a monoclonal antibody directed at IGF1R. One hundred eleven patients with Ewing's sarcoma were treated with R1507 weekly at 9 mg/kg. A response rate of 14.4% with single complete response and nine partial responses was seen with a median survival of 6.9 months. A small subset of patients treated with this agent has experienced durable remissions.⁴³ Unfortunately, clinical development of this agent has been discontinued.

Ganitumab is another monoclonal antibody directed against IGF1R. It has been evaluated in a Phase II trial of patients with metastatic Ewing's sarcoma or desmoplastic small cell tumors, which also contain fusions of the EWS gene. Thirty-eight patients were treated at 12 mg/kg every 2 weeks, with 35 patients evaluable for response. There were two partial responses (6%), and 17 patients with stable disease (49%). Four patients had stable disease longer than 24 weeks, yielding a clinical benefit response of 17%. No apparent relationship was observed between tumor response and IGF1 levels of EWS gene translocation.⁴⁴

Figitumumab is a fully human IgG2 monoclonal antibody that targets IGF1R. A Phase I study that included 16 patients with Ewing's sarcoma had two patients with objective responses, one complete response, and one partial response,

and an additional six patients had stable disease lasting at least 4 months.⁴⁵ A Phase 2 study of figitumumab has also been conducted in which 106 evaluable patients were treated with figitumumab at 30 mg/kg every 4 weeks. Fifteen patients (14.2%) had partial response and 25 had stable disease. Median overall survival was 8.9 months. High pretreatment levels of IGF1 were associated with a survival benefit.⁴⁶

Despite the initial enthusiasm for this group of agents, their activity in Ewing's sarcoma appears to be modest, with relatively low response rates and responses often of brief duration. One explanation for this observation may be the development of alternate pathways for growth in these tumors. One recent paper studying two patients with initial responses to IGF1R antibody followed by progression, revealed upregulation of p-Akt and p-m-Tor, with a subsequent response to combined IGF1R inhibition with m-Tor inhibition. A second patient was found to have activation of the ERK pathway at emergence of resistant tumor.⁴⁷ The implication of this study may be that multiple pathways may need to be inactivated for more durable responses.

RANKL and giant cell tumor of bone

Giant cell tumor of bone is a benign condition that presents as an intraosseous lytic lesion that may be associated with a soft tissue component. It can recur locally and can rarely metastasize. Surgery is the usual treatment of choice. Receptor activator of nuclear factor kappa-B ligand (RANKL) is the ligand for tumor necrosis factor receptor, RANK. The stromal cells of giant cell tumor express RANKL, and denosumab is a monoclonal antibody directed against RANKL. A recent study of denosumab in 37 patients with recurrent or unresectable giant cell tumor of bone demonstrated responses in 30 of 35 evaluable patients. Response was defined as elimination of at least 90% of giant cells or no radiological progression of the target lesion up to week 25. Denosumab was administered at 120 mg subcutaneously every 28 days, with a loading dose given on days 8 and 15 of cycle 1. Adverse events were reported in 33 of 37 patients, most commonly pain or headache.⁴⁸ Histologic evaluation of tumor samples demonstrated a decrease of 90% or more in 20/20 samples evaluated, as well as a reduction in tumor stromal cells.⁴⁹

MDM2, CDK4, and liposarcoma

CDK4 and MDM2 are amplified in most well-differentiated/dedifferentiated liposarcomas. Their presence can help confirm the diagnosis of liposarcoma and serve to distinguish benign lipomas (which do not express CDK4 or MDM2)

from true sarcomas. PD0332991 is a CDK4 inhibitor. A recent Phase II trial using oral PD0332991 at 200 mg/day for 14 days in a 21-day cycle enrolled 29 patients, of whom 27 were evaluable for the primary endpoint of PFS higher than 40% at 12 weeks. PFS was 70% at 12 weeks, and median PFS was 18 weeks.⁵⁰ On the basis of these results, a Phase III trial is planned.

Hedgehog signaling and chondrosarcoma

Hedgehog signaling plays a role in cartilage tumorigenesis and is activated in chondrosarcoma. GDC-0449 is an inhibitor of the hedgehog pathway. A Phase II trial⁵¹ has been performed with GDC-0449 in advanced chondrosarcoma, using a dose of 150 mg daily. The primary endpoint of the trial is 6-month nonprogression rate according to RECIST, with a 40% nonprogressive disease rate. At the planned interim analysis, four of 17 patients had stable disease. Accrual is now at 40 patients. The drug appears to be well-tolerated.⁵¹ Additional trials with this agent in combination with a Notch inhibitor, RO4929097, in advanced sarcomas are in progress.⁵²

Because of the importance of the mammalian target of rapamycin (mTOR) pathway, the abnormalities and over-expression found in different types of sarcomas, as well as the numerous studies of mTOR inhibitors as single agents or in combination in sarcomas, the mTOR pathway, interactions with other pathways, and ongoing clinical studies are presented separately.

mTOR inhibitors

mTOR was identified in 1995 as the principal protein kinase targeted by RAPAMYCIN. The natural product RAP (sirolimus; Rapamune®; Wyeth-Ayerst, Philadelphia, PA, USA) is a lipophilic macrolide isolated more than 20 years ago from a strain of *Streptomyces hygroscopicus* found in the soil of Easter Island (Rapa Nui). Initially,^{53–55} the antiproliferative effect of RAP was principally attributed to its ability to modulate the synthesis of critical proteins required for ribosome biosynthesis, protein translation, and G₁ to S cell cycle phase traverse, with the final result being cell cycle arrest in G₁ phase.⁵⁶

RAP and other therapeutics targeting mTOR are particularly active against malignancies driven by activated PI3K, Akt, or both, as well as by *PTEN* (phosphatase and tensin homologue deleted from chromosome 10) gene mutations as the tumor becomes dependent on this pathway for growth. PTEN protein, the product of the PTEN tumor suppressor gene, opposes the activation of PI3K.⁵⁷ Studies in PTEN

knockout mice have demonstrated that PTEN-deficient tumor cells are very sensitive to the growth inhibitory effects of RAP and its analogs.⁵⁸

RAP binds intracellularly to FK-BP12, a low-molecular-weight cytosolic protein, and forms a complex with a high affinity for mTOR.^{59,60} The inhibition of the mTOR kinase activity blocks the activation of two downstream signaling elements: the 40S ribosomal protein S6 kinase (p70^{S6k}) and the eukaryotic initiation factor 4E binding protein1 (4E-BP1).^{61,62} By inhibiting mTOR, and therefore the translation of proteins that are essential for cell cycle traverse, cell growth, survival, and cell division, RAP and RAP analogs have antiproliferative and immunosuppressive effects.

mTOR exists in two different complexes, mTORC1 and mTORC2.^{63,64} TORC1 is considered sensitive to rapamycin, whereas TORC2 was until recently believed to be totally rapamycin-insensitive. Recent studies show that prolonged exposure to RAP analogs can lead to inhibition of mTORC2.^{63,65} mTORC1 is a trimeric protein kinase formed of the mTOR catalytic subunit, the regulatory-associated protein of mTOR (raptor), and a mammalian LST8/G-protein β -subunit-like protein (mLST8/G β L).^{63,66–68} The functions of the mTORC1 components are only partly understood. Studies suggest that raptor presents downstream target substrates to the mTOR kinase domain for phosphorylation in the presence of enough nutrients and also stabilizes mTOR; it is also a scaffolding protein, as it binds to downstream targets of mTOR, eukaryotic initiation factor 4E binding protein 1 and protein S6 kinase 1, via TOR signaling motif.^{69,70} The full catalytic activity of TOR requires interaction with LST8, with downregulation of mLST8 resulting in a decrease in mTOR kinase activity.^{71–73} FKBP12-rapamycin when bound to mTORC1 can abrogate mTORC1 kinase activity both in vitro and in vivo.

TORC2 consists of mTOR, rictor (rapamycin-insensitive companion of mTOR), G β L, and mammalian stress-activated protein kinase interacting protein 1.^{74,75} TORC2 can form multimeric supercomplexes, which have been shown to have a more active kinase activity than monomeric TORC2.⁷⁶ Recently, novel components such as Protor 1 (protein observed with Rictor-1) and Protor 2 have been shown to interact with Rictor.⁷⁷ mTORC2 is not bound by FKBP12-rapamycin, and it has been suggested that TORC2 mediates the spatial control of cell growth.^{74,75,78} Knockdown of components of mTORC2 such as rictor or mTOR results in loss of both actin polymerization and cell spreading.^{64,75}

The mTOR pathway, as well as the mechanism of action of mTOR inhibitors, their clinical characteristics, and

suggested mechanism of resistance, have been extensively explored during the last few years, and a large amount of information is now available.^{71,79,80}

There is preclinical evidence supporting the use of mTOR inhibitors in sarcomas. Studies have revealed that PTEN is involved in the pathogenesis of sarcomas including GIST, leiomyosarcomas, and rhabdomyosarcomas.^{81–83} Analysis of 51 cases of soft tissue sarcomas revealed mutations of the *PTEN/MMAC1* gene in two cases (3.9%), both being leiomyosarcoma arising from the intraabdominal cavity.⁸¹ Another study suggests that Akt Ser473 may be a key target residue for PTEN to modulate the effects of IGF2 on activating the PI3K/Akt pathway in rhabdomyosarcoma cells.⁸² Further preclinical studies are warranted to allow a better understanding of the biology of these heterogeneous tumors, thus leading to novel therapeutic options.

Rapamycin analogs in clinical development

RAP's poor aqueous solubility and chemical stability precluded its use at doses susceptible to producing an effect as anticancer agent, and therefore new RAP analogs were developed. The RAP analogs currently used as anticancer agents include temsirolimus (CCI-779; Wyeth, Cambridge, MA, USA), everolimus (RAD 001, Novartis Pharmaceuticals AG, Basel, Switzerland), and ridaforolimus (AP23573, Merck & Co, Inc, Whitehouse Station, NJ, USA). These agents have demonstrated antiproliferative activity against a diverse range of malignancies in preclinical studies, and clinical evaluations have been very successful in a range of malignancies.

Temsirolimus

Temsirolimus (CCI-779) is a water-soluble RAP ester and was the first rapamycin analog selected for clinical development. In preclinical studies, CCI-779 and RAP demonstrated similar growth inhibitory profiles. Both agents elicited tumor growth inhibition rather than tumor regression in a wide variety of human tumor xenografts.

Two intermittent schedules were selected for initial development of CCI-779: a weekly 30-minute intravenous (IV) infusion and a 30-minute IV infusion daily for 5 days every 2 weeks. Main toxicities were mucositis, hypercholesterolemia, thrombocytopenia, rash, and fatigue. The weekly temsirolimus was approved as first-line treatment for poor-prognosis metastatic renal carcinoma.^{84–91}

Everolimus is an orally bioavailable hydroxyethyl ether of RAP. The agent has demonstrated impressive

antiproliferative activity against several human tumor cell lines as well as a broad range of human tumor xenografts.²⁷ Moreover, additional studies have revealed that RAD 001 may have antiangiogenic properties.²⁸ Early clinical trials demonstrated tolerability with a daily dose of 10 mg. Adverse events are similar with what was described with other mTOR inhibitors including mucositis, rash, hyperglycemia and hypercholesterolemia, anemia, thrombocytopenia, fatigue, and rarely, pneumonitis. Everolimus is currently approved for treatment of metastatic renal cell carcinoma (MRCCA) and pancreatic neuroendocrine tumors. Several other studies revealed promising results in other tumor types, including a combination with aromatase inhibitors in breast cancer (Everolimus in Combination With Exemestane in the Treatment of Postmenopausal Women With Estrogen Receptor Positive Locally Advanced or Metastatic Breast Cancer Who Are Refractory to Letrozole or Anastrozole; BOLERO2).^{92–99}

Ridaforolimus (AP23573) is a nonprodrug of RAP and has demonstrated prominent antiproliferative activity against several cancers in vitro and in vivo. AP23573 has favorable pharmaceutical and pharmacological characteristics, and early studies in human xenograft models have shown a potent inhibition of tumor growth with a five times a day oral administration schedule of AP23573.¹⁰⁰ Two formulations (IV and oral) were subject to clinical testing. For the IV formulation, two schedules of administration were explored: five times a day every other week and weekly.^{101,102} Toxicities included rash, mucositis, hypercholesterolemia, fatigue, and thrombocytopenia. Dose limiting toxicity in both schedules was determined to be mucositis. The recommended dose for Phase II studies is 15 mg IV daily for 5 days every other week and 100 mg IV on the weekly schedules, respectively. Interestingly, at the lowest dose level of 3 mg in the five times a day schedule, one patient with metastatic Müllerian sarcoma experienced a confirmed and durable partial response for more than 36 months. Antitumor activity was seen over the entire dose range on both schedules in several tumor types, including Müllerian sarcoma, GIST, Ewing's sarcoma, renal cell carcinoma, lymphoma and non-small-cell lung cancer. Other hematological studies or combination studies were also performed.^{103,104}

mTOR inhibitors in sarcomas Ridaforolimus Phase II sarcoma study

On the basis of the results seen in the Phase I study, ridaforolimus was tested in a Phase II clinical study in patients with previously treated advanced bone or soft tissue sarcoma.¹⁰⁵

Patients with advanced sarcomas were stratified into four cohorts on the basis of histologic type: bone sarcoma, leiomyosarcoma, liposarcoma, and other soft tissue sarcomas excluding GIST. Patients were eligible regardless of the number of previous therapies. Ridaforolimus was administered at 12.5 mg IV daily for 5 days every 2 weeks on the basis of the results from Phase I studies. The study used a Simon two-stage design. For each cohort, treatment was defined as active if the proportion of patients with clinical benefit response that included partial response, complete response, or stable disease for at least 16 weeks was more than 25%. The use of stable disease and clinical benefit as a study endpoint was decided on the basis of studies revealing that for certain cancers such as sarcomas, sustained, stable disease is increasingly being recognized as a relevant response to treatment.^{106–108} In addition, studies by EORTC have demonstrated that a 6-month PFS of 30% or more can be considered as a reference value to suggest drug activity for first-line therapy.¹⁰⁹ For second-line therapy, a 3-month PFS of 40% or greater would suggest drug activity, and 20% and lower would suggest inactivity.¹⁰⁹ In ridaforolimus, all cohorts met the criteria to enter stage 2 of the trial. A total of 213 patients were treated, with 193 patients evaluable for response. In all four categories of sarcoma, clinical benefit was seen in approximately 25% of patients. The most frequent adverse effects were mucositis, rash, hyperlipidemia,

fatigue, and thrombocytopenia. Overall, 54 (28%) patients had clinical benefit, including 5 with partial response. The antitumor activity of AP23573 in this study is summarized in Table 1.

A subgroup of 76 patients underwent positron emission tomography (PET) with 18F-fluorodeoxyglucose, and the metabolic response was analyzed on days 3 to 5 and 48 to 56, using the EORTC PET study group criteria.¹¹⁰ Partial metabolic responses were seen in 26% of the patients on first evaluation and 46% on second evaluation; stable metabolic response was seen in 69% of patients. Although preliminary, these results are encouraging in determining the role of PET in the evaluation of early response in patients with sarcoma treated with mTOR inhibitors.

The encouraging results of the Phase II study led to a Phase III study in patients with advanced sarcomas the SUCCEED (Sarcoma Multi-Center Clinical Evaluation of the Efficacy of Ridaforolimus) study. The purpose of the study was to evaluate whether maintenance therapy with oral ridaforolimus, by preventing and controlling tumor growth for a prolonged period of time in patients with metastatic soft tissue or bone sarcomas responding to chemotherapy, will result in clinically significant improvement in PFS compared with oral placebo. The study was completed and results were presented in 2011. This was an international, double-blind study randomized 1:1 between ridaforolimus

Table 1 Targets and targeted agents in sarcoma

Disease	Agents	Targets
Gastrointestinal stromal tumor	Imatinib, sunitinib, sorafenib, regorafenib, masatinib (invest)	c-kit, platelet-derived growth factor receptor alpha
Dermatofibrosarcoma protuberans	Imatinib	Col1A1-platelet-derived growth factor receptor beta
Chordoma	Imatinib	Platelet-derived growth factor receptor beta
Alveolar soft part sarcoma	Sunitinib Cediranib	Alveolar soft part sarcoma/ transcription factor E3
Hemangiopericytoma/solitary fibrous tumor	Sunitinib, avastin/temozolomide	Vascular endothelial growth factor
Angiosarcoma	Sorafenib, bevacizumab	Vascular endothelial growth factor
Nonadipocytic sarcomas	Pazopanib	Vascular endothelial growth factor
Inflammatory myofibroblastic tumor	Crizotinib	Anaplastic lymphoma kinase
Pigmented villonodular synovitis	Imatinib Nilotinib	COL6A3-M-CSF
Ewing's sarcoma	Ganitumab, figitumumab	Insulin-like growth factor I receptor
Giant cell tumor of bone	Denosumab	Receptor activator of nuclear factor kappa-B ligand
Liposarcoma	PD03329919	Cdk4
Chondrosarcoma	GDC0449 RO4929097	Hedgehog Notch
Perivascular epithelioid cell tumor	Sirolimus, everolimus, temsirolimus, ridaforolimus	Mammalian target of rapamycin

Notes: This table represents agents with demonstrated activity in various sarcomas. Not all agents are approved by the US Food and Drug Administration for these uses. Some listed agents are still investigational.

(40 mg orally for 5 days/week) and placebo as maintenance therapy in patients with metastatic sarcoma after stable disease or objective response to prior chemotherapy treatment scan. Patients were stratified by sarcoma type and line of previous treatment. The primary endpoint was PFS based on independent radiological review; secondary endpoints include overall survival best target lesion response, cancer-related symptoms, and safety and tolerability.

This large cohort, 711 patients, completed enrollment in less than 3 years. The pre-specified endpoint of the study, the PFS was met with a statistically significant improvement in PFS (hazard ratio= 0.72; $P>0,0001$, stratified log-rank) and 52% gain in median PFS (22.4 weeks for ridaforolimus and 14.7 weeks for placebo). The patients groups were well balanced and the PFS benefit was noted in all pre-specified patient groups. The survival data, although indicating a trend favoring ridaforolimus, was not significantly improved. The incidence of side effects was higher in the ridaforolimus arm, but there were no unexpected events and the overall safety profile was consistent with prior reported data with the same drug and other mTOR inhibitors. Given the lack of overall benefit on overall survival, despite improvement in PFS, the US Food and Drug Administration did not grant approval for ridaforolimus as maintenance therapy after chemotherapy in patients with advanced or metastatic sarcoma.

Temsirolimus Phase II sarcoma study

Forty-one patients with advanced soft tissue sarcomas were enrolled in a first-line Phase II study of temsirolimus (CCI-779) at 25 mg weekly for 3 weeks every 4 weeks.¹¹² Histologic types were diverse and included malignant fibrous histiocytoma, sarcoma not otherwise specified, fibrosarcoma, liposarcoma, leiomyosarcoma, endometrial sarcoma, synovial, hemangio/angiosarcoma, hemangiopericytoma, and neurofibrosarcoma. One patient with fibrosarcoma had a partial response for 36 weeks. Twenty-eight patients have progressed, and the estimated median time to progression was 2 months. The toxicity profile was considered acceptable, with few grade 3 events, including anemia, neutropenia, dyspnea, nausea, stomatitis, fatigue, and hyperglycemia. The authors concluded that CCI-779 failed to demonstrate sufficient activity as first-line therapy in patients with advanced soft tissue sarcoma to justify further development.¹¹²

Sirolimus case reports

Four cases of patients with sarcoma failing two to six lines of chemotherapy who were treated with sirolimus were presented at the American Society of Clinical Oncology

2006 Annual Meeting.¹¹³ Patients with malignant fibrous histiocytoma, leiomyosarcoma, angiosarcoma, and osteosarcoma were treated with 4–8 mg sirolimus daily for a median of 16 weeks with or without daily oral cyclophosphamide 200 mg every other week. Three patients had improvement in tumor-related symptoms, and two had improvement in performance status. Three patients had radiographic improvement and continued receiving treatment at the time of the presentation. The researchers concluded that sirolimus treatment was associated with improvement in tumor-related symptoms, performance status, and biochemical markers of disease activity, and that it inhibited tumor growth in patients with advanced sarcoma failing prior therapies. A formal study of sirolimus in advanced sarcoma is considered.

Combinations studies with mTOR inhibitors Combination everolimus–imatinib in GIST

GISTs historically represent a distinct category of soft tissue sarcoma, with a dramatic evolution and a poor prognosis until the approval of imatinib. This new targeted therapy inhibiting c-kit has impressive efficacy, including prolonged responses and remissions for patients with GIST. Primary resistance to imatinib in advanced GIST is rare; however, ultimately, most patients develop secondary resistance. The Akt-mTOR pathway was incriminated as a potential molecular pathway mediating resistance to imatinib.¹¹⁴ In addition, synergism in vitro between imatinib and everolimus has been seen in human GIST resistant to imatinib. As a result, a Phase I/II trial was performed in patients with GIST refractory to imatinib.¹¹⁵ Thirty-one patients received a continuous dose of imatinib 600 mg/day in combination with everolimus either weekly or daily. Dose limiting toxicity occurred in 3 patients at 25 mg/day everolimus and were stomatitis, thrombocytopenia, and gastritis. The recommended dose of everolimus was 2.5 mg/day in combination with imatinib 600 mg/day. Two patients achieved partial response, and an additional eight patients had stable disease for more than 4 months. Molecular analyses were not available at the time of the presentation, and mature data are expected.

Combination of IGFR inhibitors and mTOR inhibitors in sarcomas

There is growing preclinical evidence that inhibiting IGFR and mTOR pathways together could result in synergistic activity. Two studies of combinations of mTOR inhibitors and IGFR inhibitors were recently presented. One Phase

II study evaluated the combination of cixutumumab (IMC-A12) and temsirolimus in patients with IGFR1-positive and IGFR1-negative bone and soft tissue sarcoma.¹¹⁶ The study design included three cohorts: IGFR1-positive soft tissue sarcomas (group A), IGFR1-positive bone sarcomas (group B), and IGFR1-negative bone and soft tissue sarcomas (group C). An optimal Simon two-stage design was used for each group. A 40% PFS rate was considered promising, and a 20% PFS rate was considered nonpromising. Beginning in February 2010, 383 patients were tested for IGFR and 171 were treated. Cixutumumab was administered at 6 mg/kg and temsirolimus at 25 mg IV weekly. Pre- and posttreatment biopsies and plasma measurements for IGFR1 and IGFB3 were obtained. By intent to treat, each group achieved the primary 12 week PFS (32% group A, 38% group B, and 43% group C). The effect was independent of IGFR1 status by immunohistochemistry. Plasma biomarkers did not correlate with PFS. Although the authors conclude that this combination should be further explored, the extensive progressive disease markers and target screening proved once again that a better understanding of the target and the identification of effective predictive biomarkers for clinical benefit will be key in the rational development of mTOR inhibitors and other targeted therapies.

The second study presented a combination of everolimus and CP-751,871 in patients with advanced sarcomas and other solid tumors.¹¹⁷ This was a Phase I single-center study to determine the tolerability and recommended Phase II dose for the combination. The study demonstrated that a full-dose combination of CP-751,871 and everolimus appears safe and well-tolerated. Sixteen sarcoma patients were enrolled, and the majority experienced stable disease. Further follow-up is needed.

Combination of mTOR inhibitors with chemotherapy in sarcomas

A dose-finding study of temsirolimus and liposomal doxorubicin for patients with advanced sarcomas was reported in 2011.¹¹⁸ Fifteen patients were enrolled and treated at 3 dose levels. The recommended Phase II dose was 30 mg/m² liposomal doxorubicin and 20 mg temsirolimus. The combination was considered tolerable at the indicated dose, and a Phase II study to determine efficacy in advanced sarcomas is ongoing.

Another Phase I study in patients with refractory sarcomas combined irinotecan and temsirolimus.¹¹⁹ Fourteen patients were enrolled. The recommended Phase II dose of this weekly combination was 80 mg/m² irinotecan and 20 mg

temsirolimus. The study is being expanded to a Phase II study, and results are pending.

Activity of mTOR inhibitors in specific sarcoma subtypes

mTOR inhibitors activity in PEComa

Perivascular epithelioid cell tumors (PEComas) are extremely rare tumors only recently recognized as a distinct entity by the World Health Organization. PEComas are part of a family of mesenchymal neoplasm with myelomelanocytic differentiation and share a specific cell type, “the perivascular epithelioid cell,” or PEC. PEComas are a group of neoplasms sharing morphological and immunohistochemical features and include angiomyolipomas, clear-cell “sugar” tumors of the lung, lymphangiomyomatosis, and others, some of them strongly associated with tuberous sclerosis complex. Disorders caused by mutation of the *TSC1* or *TSC2* genes usually result in overactivation of the mTOR pathway, as their gene products regulate negatively mTORC. It is also believed that PEComas share the activation of the mTOR pathway with lymphangiomyomatosis and angiomyolipomas, and therefore all PEComas could be sensitive to mTOR inhibition.

Recently, two publications revealed not only significant radiographic responses and confirmed target inhibition in three and two cases, respectively, but also emphasized the major clinical improvement experienced by the patients.^{120,121} Therefore, based on the preclinical and clinical evidence of efficacy of mTOR inhibitors in PEComas, larger studies are ongoing.

Discussion

The number of active treatments for patients with sarcoma is limited. Therefore, there is a need for more active and less toxic drugs to be included in the panoply of available treatment for sarcomas. The broad spectrum of histopathological and molecular sarcoma subtypes as well as the clinical behavior of these tumors was the reason the clinical studies and preclinical discoveries have been delayed.

Targeted drugs including antiangiogenic agents, mTOR inhibitors, IGFR-inhibitors, and other drugs are currently tested as single agents or in combination for the treatment of sarcomas.

Although there are several ways of altering angiogenesis, and access to small molecules or monoclonal antibodies targeting one or several elements involved in angiogenesis is increasing, the results are not yet practice-altering with the exception of the recent approval of pazopanib. New studies

are ongoing, and results are awaited specifically in sarcoma subtypes in which angiogenesis was proven to represent an essential step for malignant transformation and progression.

Inhibition of signaling received from activation of growth factors such as EGFR and IGFR has been linked to sarcomatous transformation, and many preclinical studies support the use of IGFR inhibitors in sarcomas. Several clinical studies with monoclonal antibodies and small molecules established the tolerability of most of these agents, but their role in sarcoma treatment is still under question, although in selected sarcoma subtypes (Ewing's), the clinical benefit is significant.

The mTOR pathway is one of the most important pathways for tumor transformation and growth and was shown to be altered in sarcomas. Significant clinical evidence is also available. Of the three rapamycin analogs available, ridaforolimus administered IV showed promising results in a Phase II study in patients with advanced sarcomas with a clinical benefit of approximately 25%. The Phase III SUCCEED trial confirmed the role of ridaforolimus as maintenance therapy for patients with sarcoma responding to chemotherapy with a significant increase in PFS compared with in the placebo group. However, the difference in survival did not reach statistical significance; therefore, ridaforolimus did not receive US FDA approval for this setting. Anecdotal responses in patients with sarcoma were also seen with sirolimus either alone or in combination with cyclophosphamide. Therefore, mTOR inhibitors may represent an effective and tolerable therapeutic option for patients with sarcoma. However, there are still some challenges and questions to be addressed in future studies, such as dose, schedule, and appropriate design for Phase III studies as well as identification of biomarkers that would allow prospective selection of patients likely to benefit from treatment with mTOR inhibitors.

Sarcomas are different diseases in terms of pathology, clinical presentation, molecular characteristics, and prognosis. However, because of their rarity, most clinical studies usually include various histological types. Therefore, it is very difficult to analyze subtle differences in response and/or clinical benefit by sarcoma type. Future large randomized studies should take into consideration these issues for study design. The dose and schedule to be used in Phase II and III studies are also of critical importance. An optimal assessment of the treatment effect on disease progression should remain the main focus in clinical trials, as these agents are more likely to behave as cytostatic drugs, and therefore may produce a significant difference in PFS or overall survival in Phase III studies, even if the response rate in Phase II

studies is relatively low. Also, as noted previously for several targeted drugs, even low doses demonstrated improvement in overall survival in selective patients. Therefore, for targeted "cytostatic" drugs, it is crucial to define in Phase I and II studies the optimal dose that produces biological activity with minimal adverse effects, thus offering the option of prolonged drug administration without detrimental influence on patient's quality of life. It is also essential that the schedule of administration for most of the orally administered targeted drugs be defined in early clinical trials, as protracted, uninterrupted administration may result in less common adverse effects such as lung toxicity. Intermittent schedules of administration may be therefore more tolerable and more compatible with a prolonged treatment. When deciding the use of different tyrosine-kinase inhibitors for different sarcoma subtypes, it is critical to assess the intracellular targets and pathways to better evaluate possible efficacy. The most recent promising results in patients with PEComas support a better understanding of molecular biology in these rare tumors in finding new cures.

Furthermore, mainly for targeted therapies, determining the select patient population that could significantly benefit from treatment is the next critical step for the development of these drugs. It is clear from several studies that these agents are effective and probably have more than cytostatic effects in selected patients. Identifying the predictive biomarkers of response and tolerability will allow not only a better patient selection but also improvement of the therapeutic index, as well as of the use and indication of the mTOR inhibitors.

Conclusion

Significant advances in molecular biology and genetic research have allowed better identification of molecular differences between the types of sarcomas. These molecular signatures are important now not only for appropriate diagnosis but also for identification and use of targeted therapies. mTOR inhibitors, IGFR inhibitors, tyrosine kinase inhibitors, and antiangiogenic agents represent promising drugs for the treatment of sarcomas. However, several questions still remain to be answered, particularly regarding optimal dose and schedule, as well as the optimal design for future Phase III trials. Despite a significant number of Phase II studies (either completed or ongoing), a limited number of agents are moving into Phase III testing in sarcoma. The next step for targeted agents is to identify biomarkers and validate screening to fully validate the targets and determine the optimal treatment strategy.

Disclosure

The authors report no conflicts of interest in this work.

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