Updating progress in sarcoma therapy with mTOR inhibitors

J.-Y. Blay*

Department of Medical Oncology, Centre Léon Bérard, Lyon, France

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Background: Sarcomas are a diverse group of difficult-to-treat connective tissue neoplasms. The mammalian target of rapamycin (mTOR) pathway has been identified as a therapeutic target in many sarcomas and this article reviews the role of this pathway and updates clinical data for the available mTOR inhibitors.

Design: Reference sources were selected by the author for searches in PubMed and EMBASE, with search terms dependent on the particular subtopic.

Results: mTOR is a protein kinase that regulates cell growth and proliferation and is abnormally activated in many human tumours. Several disruptions of phosphatidylinositol-3’ kinase (PI3K)–Akt signalling are associated with different sarcoma types. The macrolide antibiotic rapamycin and synthetic derivatives sirolimus, temsirolimus, everolimus and ridaforolimus have been investigated in several tumour types and their potential for the treatment of sarcoma is being explored, with varying degrees of success. The PI3K–Akt–mTOR pathway is also implicated in resistance mechanisms to antineoplastic therapies, and mTOR inhibitors therefore have the potential to restore sensitivity to patients with treatment-resistant disease.

Conclusions: The PI3K–Akt–mTOR pathway is an exciting target for therapy in many types of solid malignancies and its blockade represents an opportunity to improve outcomes in poor-prognosis sarcoma.

Key words: gastrointestinal stromal tumour (GIST), mammalian target of rapamycin (mTOR), PI3K–Akt–mTOR, ridaforolimus, sarcoma, sirolimus

introduction

Sarcoma is a term that describes a rare and diverse group of cancers that occur in connective tissue. Predominantly, sarcoma refers to mesodermal proliferation and occurs in both young and old patients. Sarcoma comprised ~1% of malignancies in adults and ~15% of cancers diagnosed in patients under 20 years old in North America in 2006 [1, 2] and 8.5% of cancers in European patients aged 15–24 years diagnosed from 1990 to 1994 [3]. Sarcomas are named according to their tissue of origin, usually bone/joint (e.g. osteosarcoma, chondrosarcoma) or soft tissue (e.g. leiomyosarcoma, liposarcoma). Malignant fibrous histiosarcoma and Ewing’s sarcoma can occur both in soft tissue and in joints/bones.

As the incidence of sarcoma is relatively low compared with other cancers, subtypes are often pooled in studies that enrol patients with sarcoma, and it can be difficult to obtain large series of prospectively collected clinical data for the treatment of individual histologies. Surgery, chemotherapy and radiotherapy are standard interventions for sarcoma, with an aggressive approach taken for high-grade tumours. The choice of chemotherapy depends on the sarcoma subtype, and several cytotoxic treatments have been investigated, including doxorubicin, ifosfamide, trabectedin, gemcitabine, vinorelbine and taxanes as well as combinations of these agents. Only the first three of these agents are registered for these indications worldwide; ifosfamide and trabectedin are registered only in the European Union. It is commonly accepted that chemotherapy is not effective for the treatment of gastrointestinal stromal tumour (GIST) [4]. The prognosis for patients with advanced metastatic soft tissue sarcoma is poor, with a 5-year disease-free survival of <10% and clinical response rates for chemotherapy of ~20% [5].

Further options for the treatment of sarcoma are needed, not only to improve the rate of response to treatment but also to improve the quality and duration of elicited responses and disease stabilisation. Increased expression of several elements in the phosphatidylinositol-3’ kinase (PI3K)–Akt–mammalian target of rapamycin (mTOR) pathway has been identified in many sarcoma subtypes, and the interruption of signalling through this pathway has consequently been investigated as an option in sarcoma therapy. In this review, we will describe the potential of the PI3K–Akt–mTOR pathway in sarcoma therapy and review current data and other issues in the treatment of this malignancy.

*Correspondence to: Prof. J.-Y. Blay, Department of Medical Oncology, Centre Léon Bérard, 28 Rue Laennec, 69008 Lyon, France. Tel: +33-4-78-78-27-57; Fax: +33-4-78-78-27-16; E-mail: BLAY@lyon.fnclcc.fr

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**targeted therapy in the treatment of sarcoma**

While the majority of sarcomas remain difficult to treat, targeted therapy has been very successful in the treatment of GIST, a distinctive mesenchymal tumour of the gastrointestinal tract. Between the early 1990s and 2004, GIST had an annual incidence of 0.68–1.4/100 000 population where studied [6–8]. GIST predominantly occurs following mutations in the transmembrane KIT receptor, a tyrosine kinase that triggers the mitogen-activated protein kinase, signal transducers and activators of transcription (STAT) and PI3K–Akt pathways [6].

Imatinib mesylate (Gleevec®, Novartis) is a tyrosine kinase inhibitor (TKI) that is selective for several tyrosine kinase enzymes (including KIT) and has revolutionised the treatment of GIST. Imatinib can achieve tumor control in patients with resistance to imatinib, other TKIs, with slightly different activity respectively, after treatment [9]. Following the development of studies, which included 1640 patients, estimated progression-free and overall survival at 3 years are 30%–34% and 60%–61%, respectively, after treatment [9]. Following the development of resistance to imatinib, other TKIs, with slightly different activity profiles, are available such as sunitinib malate (Sutent, Pfizer).

Other sarcomas subtypes with well-defined activated pathways have afterwards been identified as proper models for targeted therapies. These include dermatofibrosarcoma protubersans, with a canonical platelet-derived growth factor subunit A-collα1 fusion protein [10], and Ewing sarcomas, with EWS–Fel1 protein transactivating elements of the insulin-like growth factor 1 receptor (IGF-1R) transduction pathways, in particular through a blockade of insulin-like growth factor (IGF)/BP3 expression, fostering the use of IGF-1R antibodies for therapeutic use [11, 12]. In locally aggressive connective tissue tumours, receptor activator for nuclear factor κ B ligand (RANKL) pathway inhibition in giant cell tumour of the bone [13] and to a lesser extent macrophage colony-stimulating factor receptor pathway inhibition in pigmented villonodular synovitis (PVNS) have also been reported [14].

Therapies that target overactive metabolic processes have broad potential in multiple tumour types and several targets downstream of cell surface receptors exist, offering a variety of approaches for potential therapy candidates. We will examine the role of mTOR inhibitors in sarcomas.

**the role of mTOR in cell growth**

mTOR is a protein kinase that regulates cell growth, proliferation, protein synthesis and transcription in response to insulin and various endogenous growth factors via the PI3K–Akt pathway and cellular nutrient and energy levels and redox status via serine threonine kinase 11 (LKB1) (Figure 1). Downstream targets of mTOR are shown in Table 1. The signalling pathways up- and downstream of mTOR have been described in detail elsewhere [15–17]. Briefly, phosphorylated growth factor receptor tyrosine kinases recruit PI3K to the cell membrane, which then phosphorylates phosphatidylinositol-4,5-bis-phosphate (PIP2) to phosphatidylinositol (3,4,5)-trisphosphate (PIP3) [phosphatase and tensin homologue deleted on chromosome ten (PTEN) is an important regulator of this process and dephosphorylates PIP3 back to PIP2]. PIP3 recruits Akt and 3-phosphoinositide-dependent protein kinase 1 at the cell membrane, resulting in the partial activation of Akt; the further phosphorylation required to fully activate Akt is carried out by mammalian target of rapamycin complex 2 (MTORC2) (produced later on in the cascade).

Activated Akt regulates mTOR via the direct phosphorylation and inhibition of tuberous sclerosis complex 2 (TSC2). TSC2 usually forms a heterodimer with TSC1, which inhibits Ras homologue enriched in brain (Rheb), a small guanosine triphosphate necessary for mTOR activation. In contrast, LKB1 in the energy-sensing pathway stimulates AMP-activated kinase, which activates the TSC1–TSC2 heterodimer to inhibit mTOR activation [15, 17, 18].

The mTOR catalytic unit exists in two complexes in mammals. MTORC1 consists of mTOR, mLST8 (also called GβL) and regulatory-associated protein of mTOR (raptor) and is responsible for sensing nutrient and growth factor signals. MTORC2 consists of mTOR, mLST8, rapamycin-insensitive protein 1 (rictor) and mitogen-activated-protein-kinase-associated-protein 1 (mSin 1) and is responsible for actin remodelling. As their components suggest, MTORC1 is susceptible to inactivation via rapamycin (and its analogues), while MTORC2 is not. These complexes are interlinked further in that MTORC2 phosphorylates partially activated Akt earlier in the PI3K–Akt pathway, ultimately leading to activation of MTORC1. Activation of MTORC1 leads to cell growth and proliferation via protein S6 kinase 1 (S6K1) and eukaryotic initiator factor 4E-binding protein-1 (4E-BP1) [15, 17, 18].

The fundamental role of the PI3K–Akt pathway in cell growth and proliferation is reflected in the number of its constituent proteins that are coded for by proto-oncogenes or tumour suppressors. The over- or under-expression of such elements following genetic aberrations are associated with a broad range of sarcomas and other cancers, for example PI3K [19, 20], PTEN [21], KIT [22, 23], Akt [24], receptor TKs [23, 25, 26], TSC [27], LKB1 [28, 29] and Ras [30, 31]. This pathway is therefore an important target for cancer therapy.

**sarcoma and mTOR signalling**

The control of cell growth and proliferation by the PI3K–Akt–mTOR pathway is abnormally activated in many human tumours, and several disruptions of PI3K–Akt signalling are associated with different sarcoma types [32]. Rhabdomyosarcoma has been associated with increased levels of receptor and nonreceptor tyrosine kinases, epidermal growth factor receptor (EGFR), ErbB-2, insulin-like growth factor-2 and S6 and phosphorylated forms of 4E-BP1 and Akt, the latter of which plays an important role in the regulation of PTEN [16, 33]. In Kaposi’s sarcoma, the Kaposi’s sarcoma-associated herpesvirus G protein-coupled receptor has been shown to phosphorylate and thereby inactivate TSC2, leading to increased mTOR activity [34]. Inactivation of PTEN has been shown to prompt the development of leiomyosarcoma in animal models [35]. Overexpression of IGF-1R is associated with an aggressive phenotype in synovial sarcoma [36]. Expression of fibroblast growth factor receptor is a common feature of Ewing’s sarcoma and is important for the maintenance of an aggressive phenotype in this disease [37].
EGFR and human epidermal growth factor receptor 2 contribute to osteosarcoma pathogenesis [38]. Overall, dysregulation of the mTOR pathway is commonly described in several types of sarcoma; therefore, this pathway is an important potential target for sarcoma therapy.

**mTOR inhibitors**

Rapamycin is a macroline antibiotic produced by *Streptomyces hygroscopicus* found in the soil of the island of Rapa Nui. *In vivo*, rapamycin forms a complex with the intracellular immunophilin FKBP12, and this complex binds to MTORC1, preventing the downstream phosphorylation of S6K1 and 4E-BP1 and associated cellular growth and proliferation [17]. Rapamycin itself has been studied as a therapeutic product (sirolimus), initially as an immunosuppressant, but more recently its potential has been investigated in several different tumour types. Synthetic versions of rapamycin have also been developed, which have more favourable physicochemical properties for drug delivery [39]. Tacrolimus (FK-506) is a related macrolide immunosuppressant which also binds to FKBP12 and has been used following organ transplantation and has more recently been investigated in ulcerative colitis.

**sirolimus**

Sirolimus is currently licensed for immunosuppression following organ transplantation, but there has been much interest in its properties as an antineoplastic agent, both in transplant-related neoplasms (such as Kaposi’s sarcoma) [40, 41] as well for lesions related to mutations in the tuberous sclerosis complex, such as lymphangioleiomyomatosis and angiomyolipoma [42–47]. In a report of four cases of progressive metastatic sarcoma in patients who have progressed after 2–6 lines of chemotherapy, treatment with sirolimus...
resulted in minor radiographic improvement in three cases [48]. Myxoid chondrosarcoma has also been reported to respond well to sirolimus in combination with cyclophosphamide [49].

temsirolimus
Temsiorilimus (CCI-779; Wyeth Pharmaceuticals) is a water-soluble prodrug ester of sirolimus and is indicated for the treatment of advanced renal cell carcinoma in both Europe and the United States. In a phase III trial including 626 patients with poor prognosis, previously untreated advanced renal cell carcinoma, temsirolimus significantly prolonged overall survival compared with interferon-alpha alone (10.9 versus 7.3 months, \( P < 0.008 \)); overall survival with the combination of interferon-alpha and temsirolimus was 8.4 months [50]. Also, approval for the use of temsirolimus in relapsed or refractory mantle cell lymphoma was recently granted in Europe [51].

A multicentre phase II study of temsirolimus enrolled patients with soft tissue sarcoma who had received no prior chemotherapy for advanced disease and had no brain metastases [48]. Patients received 25 mg i.v. temsirolimus weekly, and in 41 assessable patients, estimated median time to progression was 2 months. Forty-two per cent of patients experienced grade 3 adverse events, which included hyperglycaemia, anaemia, dyspnoea and nausea. However, these data do not compare favourably with the experience of the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group [52]. This group conducted a retrospective analysis of patients from 12 clinical trials who had received therapy for soft tissue sarcoma to evaluate the magnitude of response in terms of progression-free survival that should be expected of an active investigational therapy. Their conclusion was that as first-line therapy, an active agent should produce a 6-month progression-free rate of at least 30% [52]. Thus, temsirolimus does not appear to hold considerable promise for activity in soft tissue sarcoma.

everolimus
Everolimus (RAD001; Novartis Pharmaceuticals) is an orally available rapamycin derivative that has been investigated as monotherapy in patients with renal cell carcinoma [53] and non-small-cell lung cancer. Everolimus is being investigated in an extensive clinical trial programme of >250 trials encompassing a range of tumours including head and neck cancer, hepatocellular carcinoma, pancreatic cancer, lung cancer, glioma and haematological malignancies [54].

Everolimus is currently approved for treatment of advanced renal cell carcinoma after progression on sunitinib or sorafenib. In a phase III randomised trial of 410 patients with advanced renal cell carcinoma progressing on sunitinib, sorafenib or sequential treatment of both, everolimus 10 mg/day doubled median time to progression compared with placebo (4.0 versus 1.9 months; hazard ratio = 0.30; \( P < 0.0001 \)) [53]. Notably, after 10 months of treatment, 25% of patients treated with everolimus had not experienced disease progression.

A phase II study investigating the efficacy of everolimus in patients with histological evidence of progressive or metastatic bone or soft tissue sarcoma is currently underway (NCT00767819), as is a phase I/II study of everolimus in paediatric patients with recurrent or refractory solid tumours (NCT00187174).

ridaforolimus
Ridaforolimus (AP23573; Ariad Pharmaceuticals, formerly known as deforolimus) is a nonprodrug rapamycin analogue mTOR inhibitor which has shown activity in a variety of tumour types [55, 56]. A phase I dose-escalating study in 32 patients with solid malignancies (including seven patients with sarcoma) who had experienced treatment failure with standard therapy determined a maximum tolerated dose of deforolimus to be 18.75 mg/day i.v. given for 5 days every 2 weeks [57]. Adverse events were generally dose related and largely mild-to-moderate in intensity (grades 1–2). The most common adverse event was mouth sores (grades 1–2, 63%; grades 3–4, 16%), similar to aphthous ulcers, which resolved with treatment and decreased in frequency and severity with prolonged treatment. Erythematous maculopapular rash was also common (grades 1–2, 63% and grades 3–4, 3%). These events occurred most frequently in patients receiving >12.5 mg/day of ridaforolimus. Other adverse events included hyperlipidemia, hyperglycemia, anaemia, stomatitis and myelosuppression. Seven patients with sarcoma were enrolled in this study and all experienced clinical benefit from treatment, including two partial responses (PRs) [57]. Ridaforolimus was also investigated in a phase 1 study using a weekly administration schedule [58]: 46 patients received the drug IV >30 min once weekly at dosages ranging from 6.25 to 100 mg. Again, the most common side effects were fatigue, anorexia and mucositis, the latter being the dose-limiting toxicity; 75 mg was established as maximum tolerated dose. One unconfirmed PR has been reported in a patient with bladder carcinoma.

A phase II trial enrolled 216 patients with advanced sarcoma and categorised them by sarcoma histology. There were no restrictions on prior therapy. A total of 212 patients were treated the following: bone sarcoma \((n = 54)\), leiomyosarcoma \((n = 57)\), liposarcoma \((n = 44)\) and other soft tissue sarcomas \((n = 57)\) [59]. Responses were identified according to classical volumetric RECIST criteria. Patients received ridaforolimus 12.5 mg i.v. daily as single-agent therapy for 5 days every 2 weeks and a clinical benefit rate (CBR) of 29% was observed, which included five PRs. The majority of responses were stable disease (SD) >16 weeks, and there was no significant difference in the outcome between the four identified subgroups. Median overall survival was 40.1 weeks [59].

In an effort to improve patient convenience, an oral formulation of ridaforolimus was also developed and tested in a large phase 1 study [60]. One hundred forty-seven patients with advanced/metastatic solid tumours refractory to therapy were enrolled; in light of the phase 2 study reported in sarcoma, a large fraction (85 patients) of these patients had sarcoma.

Seven regimens, all over a 28-day cycle were investigated [daily for 4 days, weekly; daily for 5 days, weekly (qd5); daily for 6 days, weekly; twice daily for 4 days, weekly; loading dose followed by daily for 5 days; continuously for 21 days and continuously for 28 days]. The dose-limiting toxicity for all regimens was stomatitis which was reversible by dose reduction or symptomatic therapy. The maximal tolerated dose was
increased with the addition of a weekly dose holiday interval; the maximum tolerated doses were 50, 40 and 30 mg/day daily for 4 days, daily for 5 days (qdx5) and daily for 6 days, respectively, as opposed to 15 and 10 mg for the continuous treatment for 21 and 28 days, respectively. Similarly, higher cumulative pharmacokinetic exposure was achieved with the schedules including a dose holiday interval, while maintaining convenience and tolerability. Antitumour activity was evaluated by modified RECIST criteria: the CBR was 25% overall and 27% in patients with sarcoma. Of 24 patients who received 40 mg qdx5/week, 13 had sarcoma; the CBR in this group was 23% and 2 patients (liposarcoma, dendritic cell sarcoma; 15.4%) achieved a PR. Pharmacodynamic analysis showed potent inhibition of mTOR. The conclusion of the study was that oral ridaforolimus has a safety and antitumour activity profile consistent with the i.v. form; 40 mg QDx5 each week appears to an active well-tolerated regimen. This regimen has been selected for further clinical development.

These data prompted the initiation of a phase III placebo-controlled study of maintenance therapy with an oral formulation of ridaforolimus in patients with metastatic soft-tissue or bone sarcomas who have an ongoing favourable response to chemotherapy [the Sarcoma mUlti-Center Clinical Evaluation of the Efficacy of rIaDaforolimus (SUCCEED) study, NCT00538239]. The successful maintenance of an ongoing response and postponement of progression may represent an alternative method of extending clinical benefit to patients.

### resistance to therapy and future developments

Given that the PI3K–Akt–mTOR pathway is crucial to the growth and development of many tumours, it is not surprising that it is also implicated in resistance mechanisms to antineoplastic therapies and therefore is a potential target to restore sensitivity in patients with treatment-resistant disease. Up-regulation of signalling through the PI3K–Akt–mTOR, either by overexpression of PI3K or Akt, or via the loss of PTEN is a common mechanism for both the development of cancer and for the emergence of resistance when other pathways have been blocked [61–65]. The strategy of using an mTOR inhibitor to circumvent resistance to both cytotoxic and targeted therapies has been the subject of much research.

Several combinations of temsirolimus and other agents are currently being investigated in clinical trials, including temsirolimus plus pegylated liposomal doxorubicin in resistant solid malignancies (NCT00703170), temsirolimus plus docetaxel in resistant solid malignancies (NCT00703625) and temsirolimus plus carboplatin and paclitaxel in patients with advanced solid tumours (NCT00400655). A phase II/II trial of everolimus and imatinib (a TKI), in patients with GIST who had previously responded to imatinib monotherapy but had become resistant, has also been reported [66]. Of 31 treated patients, two experienced PR and eight SD ≥4 months after a median 14 weeks’ treatment. Preclinical data support the combination of ridaforolimus and doxorubicin, carboplatin or paclitaxel in four sarcoma cell lines and three endometrial cancer cell lines [67].

The use of mTOR inhibitors to overcome acquired immunity to targeted therapies has been repeatedly demonstrated in vitro. For instance, breast cancer cells have demonstrated increased sensitivity to both endocrine treatment with tamoxifen [68, 69], letrozole and fulvestrant [70] and cytotoxic therapy with doxorubicin [69], carboplatin [71] and paclitaxel [71] when co-administered with an mTOR inhibitor. In patients with breast cancer, the addition of an mTOR inhibitor to neoadjuvant letrozole was found to significantly increase the response rate to treatment [72]. The use of an mTOR inhibitor to overcome resistance to chemotherapy has also been investigated with other tumour types, including lung cancer [61] and gastric carcinoma [73]. The PI3K–Akt–mTOR pathway is particularly significant in the development of resistance to TKIs [74], and the combination of mTOR inhibition with an EGFR inhibitor has shown in vitro efficacy in a range of tumour types, including lung cancer [75], renal cell carcinoma [76] and colorectal cancer [77]. This approach has also been investigated in patients with GIST and primary resistance to imatinib [66] and in two patients with chemotherapeteresistant pancreatic cancer [78]. Currently, there are several clinical trials investigating combinations of mTOR inhibitors with TKIs and monoclonal antibodies in the treatment of breast, renal, pancreatic and neuroendocrine tumours, among other malignancies.

The early detection of clinical efficacy for new therapies is crucial. However, traditional response criteria alone, which are based on anatomical measurements of target lesions, may not be adequate for the assessment of sarcoma therapies. It is often difficult to determine which lesions are ‘target’, and the morphology of sarcomas combined with nonmalignant tissue changes around tumours may make it difficult to define the edges of individual lesions. The cytostatic nature of many new therapies (e.g. antiangiogenic agents and mTOR inhibitors) may cause early effects in tumours that may not involve changes in tumour size and may consequently be missed by anatomical measurements [18]. Furthermore, a responding sarcoma may initially increase in physical size as a result of intratumoural haemorrhage or myxoid degeneration [79]. In addition, prolonged disease stabilisation may provide as much clinical benefit to the patient as a RECIST-defined response in patients with advanced sarcomas [80].

Computerised tomography scanning is the cornerstone of anatomical measurement to assess the response of solid tumours to chemotherapy, although this technology may not be widely available [18]. Several other imaging approaches have been taken to assess the response of tumours to targeted and antiangiogenic therapies experimentally and in clinical development. Such imaging techniques include dynamic contrast-enhanced (DCE) magnetic resonance imaging [81, 82] and DCE ultrasonography [83] offer the possibility to assess tumour vascularity, while [18F]2-fluoro-2-deoxy-D-glucose PET has the potential to assess the metabolic activity of tumours as a surrogate for their activity [84, 85].

As new techniques are developed, it is, of course, crucial that they are also validated, to ensure that the surrogate markers that they detect are representative of clinical changes and can also be correlated with changes in survival [86]. Currently, such techniques are largely employed investigationally, alongside more traditional measures of response.
Sarcoma presents a different therapeutic challenge compared with other solid tumours both because of the limited success of traditional treatment approaches and because monitoring the response of sarcoma lesions to therapy is not straightforward. The PI3K–Akt–mTOR pathway is an exciting target for therapy in many types of solid malignancy and its blockade represents an opportunity to improve outcomes in poor prognosis sarcoma. Activation of the PI3K–Akt–mTOR pathway is implicated both in the establishment of tumours and as an alternative signalling pathway in the development of resistance to antineoplastic therapy via PI3K–Akt or PTEN. Promising results have been observed with mTOR inhibitors both as monotherapy and in combination with cytotoxic and targeted therapies, where mTOR blockade has been shown to circumvent the development of resistance.

The varying degrees of therapeutic success in different tumour types with the available synthetic rapamycin analogues indicate that they are not therapeutically equivalent, and consequently, more research is necessary to define where each agent fits into the treatment strategy for different cancers. Currently, encouraging prolongation of survival in soft tissue sarcoma has been observed with ridaforolimus, and phase III data are eagerly anticipated for this drug. Clinical benefit from mTOR inhibition in sarcoma appears to be focused on SD or PR. The rarity of complete responses in patients indicates a cytostatic, rather than cytotoxic, effect for mTOR inhibition, although it must be noted that such trials enrolled heavily pretreated patients who would be considered difficult to treat. Areas of further exploration include combination therapy and selection of disease types for mTOR inhibitor-based treatment [17] to further define the role of mTOR inhibitors in sarcoma therapy. It is likely that more well-defined patient selection criteria according to specific mutations in the PI3K–Akt pathway will be necessary to improve the efficacy of mTOR inhibitors, either alone or in combination, and such research is essential to define our use of these agents.

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