# CLINICAL UPDATE

Translating Scientific Advances into Clinical Practice

## mTOR Inhibitors in Sarcoma

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**H&O** What is the current treatment landscape in sarcoma?

**GD** Over the last decade, pathology and diagnostics have assumed a new importance in sarcoma. In the past, the belief was that all sarcomas were alike: some were bone sarcomas and some were soft-tissue sarcomas, but it did not matter because the only treatment available if surgery and radiotherapy failed was chemotherapy, and this was only rarely directed at specific subtypes of sarcomas. Some sarcomas were curable with expert multidisciplinary management with judicious consideration of surgery, radiotherapy, and chemotherapy. However, for many other sarcomas—outside of the advances in cure rates for sarcomas such as Ewing sarcoma, osteosarcoma, and rhabdomyosarcomas, which disproportionately affect children and young adults—it was less clear whether advances in management were being made towards the end of the last millennium. In 2000, the treatment paradigm for sarcomas changed with the discovery of a critical molecular target in gastrointestinal stromal tumor (GIST) and the revolutionary development of imatinib (Gleevec, Novartis) for this previously untreatable malignancy. Since this breakthrough, we have been collaborating with scientists to uncover other types of sarcomas that might be dependent upon a targetable molecular defect unique to the tumor. Following GIST, the next most common sarcoma is liposarcoma, for which some good molecular targets have also been found. The third most common sarcoma subset is leiomyosarcoma, which represents the most complex biology of this group. There are hundreds of other forms of sarcomas, many of which are exceedingly rare.

In a targetable, molecularly-identified disease like GIST, advanced dermatofibrosarcoma protuberans (DFSP) or ALK-mutated inflammatory myofibroblastic tumor, it makes sense to give a targeted therapy. Otherwise, it is most reasonable to be on the lookout for new leads coming from research and to obtain the best multidisciplinary care from a cancer center with dedicated expertise in sarcomas. The current treatment landscape for routine management of sarcoma is still, even in the eyes of the most restrictive managed care organization, to go to a team that is experienced in sarcoma diagnosis and treatment, because the surgical options may differ, the consideration for systemic therapy may be controversial, and any radiation therapy may offer technical challenges to get the best possible outcomes.

Sarcomas have been recognized since antiquity, but only now are people recognizing how complicated this heterogeneous group of cancers truly are. Drugs were rarely developed for sarcomas until the past decade mainly because there was not much interest in these rare "orphan diseases." Sarcoma was perceived as a small market size for pharmaceutical companies, yet the discovery of imatinib and sunitinib (Sutent, Pfizer) proved that drugs could be developed rapidly (and be commercially viable) in this field if a good target was present.

**H&O** What spurred investigation into the mTOR pathway in sarcoma?

**GD** The mammalian target of rapamycin (mTOR) is an intracellular signaling pathway that is extensively shared among multiple receptors. It functions as the central component in the downstream signaling pathway involved in the control of angiogenesis and cell growth, survival, and metabolism. The mTOR pathway is a very well-trodden path for a variety of cell signals, and research has identified mTOR as a "target" that is often activated in multiple different kinds of sarcomas. The mechanisms by which the mTOR pathway is "turned on" in different sarcomas appear to be as diverse as the sarcomas themselves. A number of other forms of cancers have this pathway activated, so it is not unique to sarcomas. However, one of the reasons it is now being actively investigated is the result of a phase I study that evaluated ridaforolimus (then known as AP23573) in various cancer indications. The study found that a number of sarcoma patients in the study responded very well to treatment. Those data prompted a phase II trial, which presented a challenge to drug development: although only very few tumors actually shrank in the phase II study, a sizeable percentage remained stable for a reasonably long period of time relative to what was expected for metastatic sarcomas. This was an uncon-

trolled study, so it is not known whether the disease stability was really attributable to the mTOR inhibition or whether the patients selected for the trial just happened to have slow-growing tumors due to selection bias.

**H&O** What other mTOR inhibitors have been studied in sarcoma?

**GD** Other mTOR inhibitors such as temsirolimus (Torisel, Pfizer/Wyeth), everolimus (Afinitor, Novartis), and sirolimus (Rapamune, Pfizer/Wyeth) have also been evaluated in sarcoma. The Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute supported a study using temsirolimus in unselected sarcoma, which was judged to have been "negative" since it found that few patients had reduction in tumor size. This remains a controversial interpretation, since mTOR inhibitors are known to not be cytotoxic per se, and shrinkage of tumors is actually not a logical metric for their evaluation based on the biology of this pathway. Everolimus was tested in combination with imatinib in patients with advanced GIST following failure of imatinib; that trial showed some intriguing activity, but only in a small subset of patients whose disease stabilized. Consequently, the development of everolimus went in the direction of kidney cancer and a brain tumor called subependymal giant cell astrocytoma (SEGA), both of which are approved indications based on prolonged disease stability. SEGA is associated with tuberous sclerosis complex (TSC), which is a rare genetic disorder. This is noteworthy because PEComa, a type of sarcoma, is also associated with TSC gene mutations. PEComas have been reported by Wagner and colleagues to respond to mTOR inhibitors like rapamycin. This type of sarcoma is one of the few in which a genetic mutation can select patients in whom the mTOR pathway is activated, and that can explain the exceptional and targeted activity of the drug in those patients. Unfortunately, no such biomarkers have yet been identified outside of patients with PEComas, so we do not know whether there are other particularly sensitive subsets of sarcoma patients in whom targeting with mTOR inhibitors might lead to major clinical impact.

**H&O** Can you discuss the SUCCEED trial?

**GD** The SUCCEED (Sarcoma Multi-Center Clinical Evaluation of the Efficacy of Ridaforolimus) trial is a global, randomized, double-blind, placebo-controlled, phase III study that was conducted in over 700 patients with metastatic sarcomas of soft tissue or bone who entered the trial with documented benefit from immediate prior chemotherapy (ie, with either objective response or stable disease). Patients were randomized to either placebo or ridaforolimus. The eligibility criterion of selecting patients who had a benefit from chemotherapy was a novel approach, with the rationale that any efficacy seen with ridaforolimus could hopefully prolong the benefit of prior chemotherapy. Recently, the top-line data from the SUCCEED trial have been made public. Detailed results have been submitted for presentation at an upcoming professional meeting. This trial showed that there was a statistically significant benefit in progression-free survival in patients who received ridaforolimus. There was a 28% reduction in the risk of progression in the treatment arm compared to the placebo arm. This benefit in progression-free survival is encouraging, and the trial remains open so that patients can continue to be followed to collect additional information on secondary endpoints like overall survival and safety.

I think it will be interesting to see the kind of discussions the data set generates. Certainly this trial is highly consistent with the aggressive nature of metastatic sarcomas. Although early-stage sarcomas can still often be cured by expert multidisciplinary management, the lack of treatment options in patients with metastatic, life-threatening sarcomas remains an unmet medical need for patients worldwide.

**H&O** What impact will the SUCCEED trial have on sarcoma research?

**GD** The SUCCEED trial is one of the largest controlled trials in sarcoma patients ever to have been conducted. It will be an important data set to analyze, since it will allow us to learn more not only about this particular drug and the mTOR pathway, but also about a population of patients that had never been studied before—patients who have had a benefit from chemotherapy. The inhibition of mTOR signaling as a molecular tool is a fairly new concept in sarcoma, and now that the SUCCEED trial has shown some activity, it provides a lot of other opportunities to think about how to best use ridaforolimus. We can expect to see various studies looking at combinations of other agents with mTOR inhibitors in other clinical settings, such as frontline therapy or even in the adjuvant setting to prevent recurrence. It will also be critical to analyze the results of the SUCCEED trial to determine if there were specific subtypes of sarcomas that might have exhibited more benefit from ridaforolimus than other forms of the disease.

**H&O** Are there any side effects seen with this class of drugs?

**GD** Nearly all of the mTOR inhibitors have a set of known and predictable side effects, ranging from bothersome but manageable toxicities—like mouth sores, cough, nausea, and low blood counts—to more serious complications like hypercholesterolemia or interstitial

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pneumonitis. The latter toxicity is very unusual, but is something that doctors should be aware of when using this class of drugs. A similar spectrum of side effects has been previously seen across the board with virtually all of the available mTOR inhibitors.

**H&O** What is the future for mTOR inhibitors in sarcoma?

**GD** The goal of medical oncology and therapeutic development is to make cancer therapies better. If we are able to intensify the effects of molecular targeting or the effects of chemotherapy or radiation therapy by blocking the mTOR pathway, then we might be able to improve outcomes in sarcoma patients. The current crop of mTOR inhibitors are "first generation," meaning they shut down TOR complex 1 (TORC1). However, the development of new TORC1/TORC2 combination drugs is rapidly moving forward. That being said, we do not know the possible side effects that might be seen with inhibition of both TORC1 and TORC2. Thus, as in all oncology, it will be necessary to find a balance between toxicities and the possible benefits from future mTOR inhibitors, as well as from combinations of mTOR inhibitors with other targeted and nontargeted systemic anticancer therapies.