



## FEATURE STORY

# Reining in Renal Cancer

BY KAREN PATTERSON

*As new therapies stack up, controlling advanced kidney cancer is becoming a reality.*

Tattooed in Chinese lettering over the former location of Marc Benner's right kidney are the words "Kidney Cancer Survivor"—emblems of his year-and-a-half-long journey battling stage 4 renal cell carcinoma.

Benner, of Jackson, New Jersey, was 42 in 2007 when he began feeling excruciating pain in his back and noticed blood in his urine. "Like most guys, back then you couldn't get me to the hospital," he says. "I thought I was just passing a stone, to be honest." In December that year, surgeons at Thomas Jefferson University Hospital in Philadelphia removed his kidney using minimally invasive robotic surgery. At the same time they excised a lung mass. He was back at work 10 days later.

But his battle was only beginning. His first set of scans in early 2008 showed masses in his liver and lung. That's when his doctors prescribed Sutent (sunitinib), one of several relatively new drugs for advanced kidney cancer. Benner took Sutent for about a year, in cycles where he was on the drug for four weeks and off for two. Although he still has nodules in his lung—and a tumor just above his hip—the spots on his liver have disappeared. "I think it helped buy me time," he says of the drug. And the self-described "gym rat" has been lifting more weight than ever in his workouts.

When his cancer progressed on Sutent, he switched to Nexavar (sorafenib). "I've heard a lot of good things about Nexavar," he says, three weeks after beginning the drug. Ultimately, he hopes that this drug, too, will buy him time until other treatments are available. "There's some new stuff out there that might work better," he says.

Benner is typical not just because his cancer is a type known as clear cell, which accounts for the vast majority of the almost 55,000 renal cancers diagnosed in the United States yearly, but also in his mix of hope for the future and anticipation of what's coming next through the pharmaceutical pipeline.



Marc Benner, a self-described "gym rat" who was diagnosed with stage 4 renal cell carcinoma, has had some success with the newer targeted kidney cancer agents. Photo by Ryan Ashby.

Robert Figlin, MD, interim director of City of Hope Comprehensive Cancer Center in Duarte, California, and director of the center's kidney cancer program, says that more treatments are available for metastatic renal cell carcinoma (RCC) than ever. In addition to the current arsenal of Sutent, Nexavar, and Torisel (temsirolimus), and the newly approved Afinitor (everolimus), all green-lighted by the Food and Drug Administration since December 2005, one additional product is likely to receive approval for kidney cancer this year—Avastin (bevacizumab). While they don't promise a cure, collectively the five drugs have the potential to extend patients' lives considerably.

Before the new agents came on the market, "there was no progress and few options," says Robert Motzer, MD, who oversees the clinical trials program for advanced kidney cancer at Memorial Sloan-Kettering Cancer Center in New York City. "Now it's changed dramatically. ... You can see it in the faces of the patients."

"This is a waterfall time for patients," adds Figlin, who is also chair of medical oncology and therapeutics research at City of Hope. "The challenges for both doctors and patients are now how to choose the proper drugs, in what sequence, and whether or not to use them in combination."

These new, so-called targeted, drugs vary in their mechanism of action in the body. Sutent, Nexavar, and Avastin disrupt a process known as angiogenesis—the formation of blood vessels that feed tumors. In a phase III trial to demonstrate Avastin's potential benefit, a combination of the drug and an older treatment, interferon, nearly doubled the window of time in which patients' metastatic RCC failed to progress, compared with placebo plus interferon.

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—Robert Figlin, MD

Torisel and Afinitor are in a class of drugs called mTOR inhibitors, which means they target a cell protein that is part of a biochemical pathway implicated in the growth of tumor cells as well as blood vessels. While phase III trials have shown, for instance, that Sutent versus interferon can more than double the time before progression for many advanced kidney cancers, the mTOR inhibitors might be able to extend that period further.

In addition, Torisel, which is given intravenously weekly, has been studied in the treatment of patients with poor prognosis RCC—"those with the most symptoms, most extensive disease, who would otherwise have a short survival," says Motzer. "It was the first of the targeted agents to show a survival benefit in that very poor prognosis population." That population, he adds, accounts for up to one-quarter of people who are first diagnosed with metastatic kidney cancer.

The eagerly anticipated approval of Afinitor occurred in late March. That drug is

administered orally, and updated results from a phase III trial examining people whose cancers had progressed on Sutent, Nexavar, or both found that Afinitor delayed the cancer's progression by a median period of almost five months, compared with just less than two months in patients receiving a placebo. Afinitor also compared favorably to the other drugs in terms of quality of life and safety profile, with mouth ulcers and anemia among the side effects.

"The sense we have is that if a cancer cell builds up resistance to one medicine with one mechanism of action, switching over to another mechanism is attractive," Motzer says.

## A Chronic Disease?

Figlin says evidence most strongly supports using the new agents in sequence, with the antiangiogenic agents first, followed by an mTOR inhibitor if the cancer progresses. "That's not to say other drugs can't be interwoven, but the data are not as robust."

Research into combinations of the targeted agents has, meanwhile, been disappointing. "Our early studies showed there seemed to be more toxicity in the combinations," Motzer says. "So I'm more firmly behind the sequential use of these agents."

The new drugs also appear beneficial for the approximately 20 percent of RCC patients whose tumors are not clear-cell type. While the benefits might not be as dramatic, "these targeted agents should still be used," Figlin says.

For advanced clear-cell RCC, the medicines have made a dramatic difference in physicians' conversations with patients. Figlin says he can tell newly diagnosed patients and their families that there's a high chance of benefit from the treatment, with the potential to improve symptoms and extend life. "Although they are not curative treatments, they can turn this disease into more of a chronic management disease," he says. "We were not able to have that conversation just five years ago."

Coming down the pipeline are other promising new agents currently being tested in large phase III trials. "We are already embarking on next-generation drugs," Figlin says, including the angiogenesis inhibitors pazopanib and axitinib, which have a mechanism of action similar to Sutent and Nexavar. "Both of these may have more activity than our currently available drugs." They might also have a better side effect profile, he says. "That's what we're looking for—better tolerance and more effectiveness."

The AXIS trial, a phase III study still recruiting patients, will test how axitinib measures up to Nexavar as second-line treatment for metastatic RCC. Results of the study are expected in mid-2010. Also going head-to-head in a phase III study are pazopanib and Sutent in locally advanced or metastatic RCC.

Experts agree there's room to improve the targeting of known biochemical pathways related to kidney cancer as well as other pathways that may be important but aren't as clearly understood.

## The Old Kid on the Block

Before the targeted agents arrived on the scene, treatments known as biological or immune therapies, which enlist the body's immune system to fight the cancer, were the standard of care. One such treatment, interferon, available since the 1980s, prompted a response in just a fraction of patients, and most would later see their disease progress. Interferon, Figlin notes, is the agent to which the new drugs have been compared in many of the clinical trials, but it no longer has much of a role as a treatment by itself.

Interleukin-2, or IL-2, an immune therapy on the market since 1992 but rarely used, has had checkered success. Administered to a small, sturdy subset of patients by experienced treatment teams in high (and very toxic) doses, IL-2, also referred to as Proleukin, has the potential to provide a cure in a very small number of patients—5 to 10 percent—with advanced RCC. Researchers, however, are still trying to figure out exactly how it works. “Unfortunately, with decades of experience, we still do not understand why some people benefit tremendously and some don't benefit at all,” Figlin says.

Sue Guenther, 60, of Mesa, Arizona, has experienced high-dose IL-2 firsthand as part of a clinical trial in 2006. “I call it flu in a bag. It makes you sick as a dog,” says Guenther, who is also a survivor of thyroid cancer and sarcoma.

Like many people with kidney cancer, her malignancy was discovered by happenstance—a misstep on some marble stairs, she says, literally saved her life. Guenther stepped down hard, and subsequent pain in her right kidney sent her to the doctor for scans.

That was in 2004, when she underwent a radical nephrectomy at Northwestern Memorial Hospital in Chicago for a large, stage 3 tumor near her liver. By early 2006, doctors found a 9-millimeter metastatic tumor in her lung, reduced to 2 millimeters after combination therapy, including IL-2, in the clinical trial.

Michael Atkins, MD, deputy director of the division of hematology-oncology at Beth Israel Deaconess Medical Center in Boston, believes high-dose IL-2 should remain an important first-line therapy because it is the only one shown to even occasionally cause complete and lasting responses—but it may be rendered less effective and more toxic after treatments such as Sutent. He acknowledges the issue is controversial.

View Illustration : A New Era

“My view is there is a select group of patients and tumors, yet to be completely defined, that are best initially treated with IL-2, with the antiangiogenic or targeted agents reserved for those patients whose disease fails to respond to IL-2,” says Atkins, who is also leader of the Kidney Cancer Program at Dana-Farber/Harvard Cancer Center and a professor of medicine at Harvard Medical School.

Although hard data are pending on factors that can predict responsiveness to IL-2, Atkins notes that researchers do have some idea of the clinical and

biochemical characteristics that may mark patients most likely to benefit. The new therapies are a trade-off, he says. “While the new therapies help the average patient in a major way, without Proleukin, the cure of advanced kidney cancer is likely to become an even rarer event.”

Motzer, on the other hand, sees little role for IL-2, saying the current progress and excitement in the treatment of kidney cancer is based on the discovery and implementation of the targeted agents in the past five years.

## The Ups and Downs

One disadvantage of the new drugs is a variety of toxic side effects. Another is price: They can cost tens of thousands of dollars a year. And the drugs require ongoing outpatient management, including monitoring for cardiovascular side effects in patients who received Sutent and/or Nexavar.

On Sutent, Benner had acid reflex, diarrhea, and fatigue, and had to drop his 50 mg daily dose to 37.5 mg. (Researchers are continuing to evaluate dosing strategies for the drug.) Everything, except chocolate, tasted like metal. On Nexavar, at an 800 mg daily dose, Benner developed a rash starting on his head and face, which moved to his chest and arms. “It almost was like second-degree burns,” he says, noting that his dose was reduced, then re-escalated. He takes special care of his feet, using ointments to avoid blisters that might arise from redness he has there. “I’m a pretty resilient person,” Benner says. “You can’t let a disease beat you.”

Guenther’s treatment odyssey, meanwhile, continued in 2007 and 2008, when she twice underwent cryoablation to treat tumors on her remaining kidney, which is functioning at about 70 percent. She, too, ended up on Sutent.

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—Marc Benner

The first month, starting with a 50 mg daily dose that was later reduced to 37.5 mg, she found the fatigue devastating. The second month she also had a foul taste in her mouth and was living basically on just a few crackers a day. “I thought, ‘At least I’ll lose weight on Sutent,’ ” she says. But her doctor said no, people tend to gain weight on the drug. “It was then that I remembered God had a sense of humor.”

As of her last scans, her two major lung metastases were significantly reduced, and smaller lung spots were gone. “It looked like the Sutent was working,” she says. “This is living with cancer. But you’re living.”