

Three Molecularly Targeted Drugs Tested in Kidney Cancer Clinical Trials

Kidney cancer is difficult to treat; for most patients, only surgery offers the prospect of curing the disease, and chemotherapy and radiation offer only palliative benefit. But early results from three phase I/II studies of three molecularly targeted drugs presented at this year's annual meeting of the American Society of Clinical Oncology (ASCO) suggest that targeting the underlying biology of these tumors is worthy of further study.

Clear-cell renal cancer is the most common form of kidney cancer, and the



Dr. Robert Motzer

tumors in 90% of these patients have lost the Von Hippel-Lindau (VHL) tumor suppressor gene. Loss of this activity stimulates expression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF)—both of which are known to promote angiogenesis and tumor progression.

The drug SU11248 is a kinase inhibitor that targets receptors for VEGF and PDGF, as well as the receptor tyrosine kinases KIT and FLT3. In a phase II study, Robert Motzer, M.D., an attending physician at Memorial Sloan-Kettering Cancer Center in New York, and colleagues tested the overall response rate to SU11248 among 63 patients with metastatic kidney cancer who had been treated with and not responded to cytokine-based therapy. Twenty-one (33%) had a partial response to SU11248 therapy and 23 (37%) had stable disease for longer than 3 months on the therapy. The median duration of treatment was 9 months, with a range of 1 to 16-plus months.

“The trial provides evidence that inhibition of VEGF [receptor]—and

PDGF [receptor]—mediated signaling is an appropriate therapeutic target for renal cell cancer,” Motzer said in his presentation.

In a different trial, Mark J. Ratain, M.D., professor of medicine at the University of Chicago, and colleagues tested the compound BAY 43-9006 in a randomized discontinuation trial in 484 cancer patients, including 106 with kidney cancer. Although BAY 43-9006, now also called sorafenib, was developed as a Raf inhibitor, it has recently been found to inhibit a variety of kinase receptors, including VEGF and PDGF.

In this unusual trial design, all patients were treated for a 12-week induction period with 400 mg of BAY 43-9006 twice daily. At the end of 12 weeks, the patients were reevaluated. If the patients had more than 25% tumor growth during the induction period, they were taken off of the study (23% of the kidney cancer patients were in this group). If patients had a 25% or greater reduction in tumor size, they were allowed to continue taking the drug in the open-label arm of the study until their disease progressed.

Those patients with stable disease—whose tumors stayed within 25% of the original size—were randomly assigned either to continue on BAY 43-9006 or to take a placebo. For these 38 patients, the median progression-free survival was 23 weeks, and 41% of patients remained progression free at 24 weeks. This randomized arm is still blinded, so it is not yet clear what percentage of those on the drug or on placebo are responding. However, Ratain noted during his presentation at the ASCO meeting that, of the patients in the open-label group, 88% of them remained progression free at 24 weeks, and their median time to progression was 48 weeks.

In a third trial, researchers tested a combination of two targeted agents, bevacizumab (Avastin) and erlotinib (Tarceva) in patients with metastatic clear-cell renal carcinoma. Bevacizumab,

which is an antibody that blocks the extracellular domain of the VEGF receptor and is thought to have antiangiogenic effects, had shown limited activity as a single agent in an earlier trial. To try to boost that efficacy, John D. Hainsworth, M.D., from the Sarah Cannon Cancer Center in Nashville, Tenn., and colleagues combined it with erlotinib, a small-molecule inhibitor of EGFR.

Of the 58 of 62 evaluable patients, 12 (21%) had a partial response and 38 (66%) had stable disease or minor responses. Progression-free survival at 6 months was 67% and at 12 months was 50%. The investigators had originally planned to give the drug for only 12 months, but because so many patients were still progression free at 1 year, they extended the trial until patients progressed.

In all three trials, the most common side effects were rash, fatigue, and diarrhea. Most of the toxicities were grades 1 or 2; between 20% and 30% of the toxicities in all three trials were grades 3 or 4. Hypertension was also relatively common, which researchers suggest might be expected with antiangiogenic therapies.

“It behooves us to try to do a systematic analysis of additions of these agents. We don’t know what toxicities will arise or what will be synergistic, additive, or even contradict one another,” said Janice P. Dutcher, M.D., associate director for clinical affairs at Our Lady of Mercy Comprehensive Cancer Center in New York.

Already, researchers have begun a phase III trial of SU11248 in kidney cancer patients, and a similar trial testing BAY 43-9006 is expected to start enrollment later this year. But the question is, said both Dutcher and others, how to put these drugs into combinations in a rational, smart manner and optimize their potential for patients.

Thus, although all of the agents used in these trials have a rational basis for working in kidney cancer, Dutcher and Roy Herbst, M.D., Ph.D., who was a discussant at an ASCO press conference, caution that not all of the agents

are going to behave similarly or even predictably. There is still a large empiric factor in developing therapies, and so combinations need to be tested.

With this in mind, Hainsworth’s team, in collaboration with Vanderbilt-Ingram Cancer Center in Nashville, Tenn., is testing a three-way combination with bevacizumab, erlotinib, and imatinib mesylate (Gleevec), which targets the PDGF receptor. Thus far, they have enrolled five patients, on their way to a total of 60. At the first imatinib dose tested, the combination appears to be well tolerated, although rashes seemed to arise more quickly and be more severe than in previous studies. Hainsworth stressed that little can or should be concluded at this point.

Dutcher’s group has three kidney cancer trials in the works. The team is testing gemcitabine and erlotinib in an

ongoing trial and hopes to have some results by the end of the year. They would also like to set up a trial with these two drugs plus gefitinib (Iressa). Additionally, her team has a trial in the final design stages to test interleukin 2 (IL-2) and bevacizumab. “Remember, IL-2 is the drug that has produced complete responses in renal cell [cancer] that are long lasting, so I think it can’t be counted out in these combinations,” said Dutcher.

Dutcher also pointed out during her ASCO presentation that IL-2 was approved in 1992 for use in metastatic renal-cell carcinoma based on data from 255 patients—only 15% of whom had complete or partial responses to the drug. “So this is the backdrop ... as we either use new agents or perhaps even add new agents [to IL-2],” she said.

—Rabiya S. Tuma