

# IN FOCUS: RENAL CELL CARCINOMA

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## mTOR as a Target for Therapy of Renal Cancer

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### **H&O** Why is mTOR a useful target in renal cancer?

**GH** A combination of factors make mammalian target of rapamycin (mTOR) a relevant target for kidney cancer: clinical trial experience with mTOR inhibitors, the importance of angiogenesis and dysregulation of cell cycle control in the biology of solid tumors, particularly in renal cell carcinoma (RCC), and the discovery that mTOR is a central player in the control of cell growth and angiogenesis. These factors apply broadly to the treatment of many types of cancer, but perhaps more so to kidney cancer because of the importance of angiogenesis in kidney cancer development and progression. We know that unregulated angiogenesis is a key driver of renal cell carcinogenesis and tumor progression, which relates to the molecular pathology of RCC. This carcinoma is the best example of a solid tumor with a well-defined molecular lesion, ie, loss of function of the von Hippel-Lindau protein, underlying increased angiogenesis. Though angiogenesis is a target for solid tumor oncology in general, its importance seems to be greater in RCC.

### **H&O** Do all patients with kidney cancer express mTOR?

**GH** mTOR protein is expressed and functional in all solid tumors. Interestingly, there are no known examples in which the *mTOR* gene is amplified, overexpressed, or mutated. mTOR kinase is activated by upstream signaling, so what drives mTOR is likely the key in RCC and other cancers. mTOR is one component of the phosphoinositide-3 kinase (PI3K)/Akt pathway, a critical module involved in cell growth, proliferation, and survival as well as angiogenesis. Any change that activates Akt, such as loss of the tumor suppressor gene *PTEN*, will in

turn lead to activation of mTOR. Tumors with activating mutations of PI3K also have abnormal activation of Akt, and consequently, of mTOR. Thus, mTOR function is regulated by the more proximal signaling proteins, and alterations in those proteins can lead to an activation of mTOR. Researchers at Fox Chase Cancer Center found evidence of mTOR activation in approximately 60% of primary RCC cases. This finding has been confirmed by other researchers. We are currently evaluating the rate of activation of mTOR in metastatic lesions from patients with RCC.

### **H&O** Is activation of mTOR linked to prognosis?

**GH** Whether activation of mTOR is linked to prognosis is an important area for research. Drs. Allan Pantuck and Robert Figlin and colleagues from the University of California Los Angeles authored an article suggesting that activation of the mTOR pathway does seem to affect prognosis for patients with localized and metastatic kidney cancer. In their tissue microarray-based immunohistochemical study, mTOR pathway activation occurred most significantly in clear-cell carcinomas, high-grade tumors, and tumors with poor prognostic features. An important question that has not been definitively answered is whether tumors that have greater activation of mTOR would be more susceptible to treatment with an mTOR inhibitor. A small, preliminary study by Dr. Daniel Cho and colleagues suggests that this may be the case. A larger clinical trial of mTOR inhibitor therapy that correlates treatment outcomes with tissue studies of mTOR pathway activation could provide a more definitive answer to this question.

## H&O What have been the findings with mTOR inhibitors in RCC?

**GH** There are three inhibitors of mTOR currently in the clinic, but only two have been used for treatment of RCC. Temsirolimus (Torisel, Wyeth) is approved for treatment of advanced renal carcinoma, and is being evaluated in other tumors. RAD001 (Novartis), an orally administered mTOR inhibitor, is being further studied in renal cancer following a preliminary report of antitumor activity in patients with renal carcinoma. This evaluation includes a randomized study of RAD001 as second-line treatment for patients who have progressive disease after sunitinib or sorafenib therapy. The activity of temsirolimus against renal cancer and other tumors was first observed during phase I evaluations. Subsequently, a randomized phase II study of temsirolimus administered at high, low, or intermediate doses in 110 patients with metastatic RCC was published in 2004 by Dr. Michael B. Atkins and colleagues. Their study showed that the median time to progression was almost 6 months for a previously treated, cytokine-refractory population. The objective response rate was only 7%, but 51% of patients had clinical benefit, defined as either objective response or stable disease for at least 6 months. Approximately 50% of the patients in the study had three or more factors predictive of short survival, but these poor-prognosis patients survived longer than expected. The results of the randomized phase II study sparked interest in a larger, definitive study to determine if mTOR inhibition with temsirolimus could improve survival of patients with poor-prognosis RCC.

A randomized phase III study was designed to compare temsirolimus or temsirolimus plus interferon with interferon alone in patients with poor-prognosis, advanced RCC. The primary efficacy endpoint of that study was overall survival, and the secondary endpoints were progression-free survival, objective response, and clinical benefit (defined as objective response or stable disease for at least 6 months). The safety of temsirolimus was compared to that of interferon, which is associated with significant fatigue, anorexia, and asthenia. The study enrolled 626 patients, and it was designed to have two interim analyses for overall survival. At the second interim analysis, it was determined that overall survival of patients in the temsirolimus-alone arm was significantly longer than that of patients in the interferon-alone arm. The criteria for early stopping were met, and the study was ended in March 2006. The median overall survival was 7.3 months for interferon alone, 10.9 months for temsirolimus alone, and 8.4 months for the combination of temsirolimus and interferon. It is important to note that the patients who received the combination therapy did not have significantly longer survival compared to the

patients who received interferon alone. The doses of each drug in the combination arm were lower than each was in its respective single-agent treatment arm. Patients received temsirolimus alone 25 mg intravenously weekly, but only 15 mg weekly in the combination arm, because a preceding dose-finding phase I study established that this was the maximum dose of temsirolimus that could be safely administered with interferon. Even at reduced doses, treatment with the combination caused severe side effects in a higher proportion of patients than did treatment with either drug alone. Consequently, the combination is not recommended for treatment of RCC. The major side effects associated with temsirolimus were anemia, fatigue, rash, diarrhea, nausea, and peripheral edema. Unlike multitargeted tyrosine kinase inhibitors, temsirolimus and the other mTOR inhibitors are associated with hyperglycemia and hyperlipidemia. These adverse effects usually can be controlled with supportive measures. Temsirolimus has not been associated with hand-foot syndrome or hypertension, as are multitargeted kinase inhibitors.

## H&O Could you discuss research into combining temsirolimus with multitargeted tyrosine kinase inhibitors in this setting?

**GH** Because tyrosine kinase inhibitors and temsirolimus have different mechanisms of action, there is a good deal of interest in combining these agents. A common theme emerging from research on combining mTOR inhibitors with angiogenesis inhibitors is the need for dose reduction. There may be a limit to how much inhibition of angiogenesis is possible without causing toxic effects in normal tissue when these drugs are combined, as well as when a multitargeted tyrosine kinase inhibitor like sorafenib (Nexavar, Bayer/Onyx) is combined with a vascular endothelial growth factor ligand inhibitor like bevacizumab (Avastin, Genentech). Accordingly, determining the tolerable doses of each agent in a new combination is a critical first step in efforts to develop combination therapy. This is illustrated by the preliminary report of a phase I trial of sorafenib and temsirolimus, presented at the annual meeting of the American Society of Clinical Oncology (ASCO) earlier this year. The dose of temsirolimus had to be reduced from 25 mg to 15 mg to be safely combined with the single-agent dose (800 mg per day) of sorafenib. Another interesting preliminary report presented at the 2007 ASCO meeting described the combination of temsirolimus with bevacizumab, which in a very small study was found to have a high objective response rate. Importantly, the combination allowed full doses of each drug to be administered (temsirolimus 25 mg IV weekly + bevacizumab 10 mg/kg every 2 weeks). This combination is thus worthy of further study. Overall,

combinations of angiogenesis inhibitors are a reasonable and logical direction of research in this setting. However, there will be combinations that are not feasible in terms of safety and which, because of required dose reductions, will lose antitumor effectiveness. A possible pitfall of combinations is pharmacokinetic interaction, wherein one drug alters the metabolism of the other. Each combination must be evaluated individually for promising activity with a good deal of careful consideration. It is also important to find out whether combination therapy is better than sequential therapy.

### **H&O** How can risk categories be used to identify which drug is appropriate in a given patient?

**GH** There are good reasons to stratify patients by risk when selecting initial treatment of metastatic RCC. With three approved drugs for kidney cancer, clinicians are left with many questions about which drug is optimal for which patient, and in which order they should be used after first-line therapy. There are no randomized studies comparing sorafenib, temsirolimus, and sunitinib (Sutent, Pfizer), and these agents were studied in different populations of patients with metastatic RCC. The only drug rigorously studied in a poor-prognosis population is temsirolimus. It is also the only drug that has shown an overall survival advantage in patients with metastatic RCC. For these reasons, temsirolimus is the recommended first-line therapy for patients with poor-prognosis metastatic RCC, as defined using a modified Memorial Sloan-Kettering Cancer Center prognostic factor model. For good- and intermediate-prognosis patients, there are no first-line treatment data for temsirolimus. On the other hand, both sunitinib and sorafenib have been evaluated in randomized trials of first-line treatment for predominantly good- and intermediate-prognosis patients. Sunitinib showed a clear advantage in progression-free survival and overall

response rate in this setting, as compared to interferon. A randomized phase II trial comparing first-line sorafenib to interferon did not show a difference in progression-free survival. Accordingly, sunitinib is the drug of choice for the first-line treatment of good- and intermediate-prognosis patients.

### **Suggested Readings**

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