

RENAL CELL CARCINOMA IN FOCUS

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Combination Therapy in Patients With Metastatic Renal Cell Carcinoma

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H&O What have phase I data suggested about the use of temsirolimus and bevacizumab in patients with renal cell carcinoma (RCC)?

BE At the 2007 American Society of Clinical Oncology meeting, Merchan and colleagues presented results from the phase I portion of a trial that aimed to determine the maximum tolerated dose and dose-limiting toxicity of the combination of the mammalian target of rapamycin (mTOR) inhibitor temsirolimus (Torisel, Pfizer) and the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab (Avastin, Genentech). Study inclusion criteria were measurable stage IV clear cell RCC, Eastern Cooperative Oncology Group (ECOG) performance score between 0 and 2, and good organ function. Among the 12 patients in the study, the median age was 66 years [range, 50–77 years]).

The combination of temsirolimus and bevacizumab was excellent, and the preliminary activity was very encouraging (65% response rate). These data provided the encouragement to conduct a phase II trial.

H&O What was the goal of the phase II TORAVA trial?

BE The goal of the TORAVA (Combination of Temsirolimus and Bevacizumab in Patients With Metastatic Renal Cell Carcinoma) trial was to determine whether temsirolimus and bevacizumab could improve outcomes in patients with renal cell carcinoma (RCC) while maintaining an acceptable safety profile.

H&O What were the inclusion criteria of the TORAVA trial?

BE The patients in the TORAVA trial had metastatic RCC. They had received no previous medical treatment for the disease. Patients had an ECOG performance score between 0 and 2. All histologies of RCC were included.

H&O What was the trial design?

BE The primary objective was to measure the nonprogression rate at 48 weeks. For that, we conducted a randomized phase II trial, with 2 control arms—sunitinib (Sutent, Pfizer) and bevacizumab plus interferon alfa—in order to ensure that our results in the experimental arm (temsirolimus plus bevacizumab) would not be biased by patient selection. Secondary endpoints included toxicity, response rate, and survival.

We determined that 80 patients would be necessary to allow an acceptable estimate of a nonprogression rate of less than 50% at 48 weeks in the experimental arm. At the same time, we enrolled 40 patients in each control arm.

H&O What were the main results of the trial?

BE The experimental arm did not provide the expected efficacy. In addition, an unexpectedly high toxicity rate was observed. Nonprogression rates at 48 weeks were 31% for the bevacizumab plus temsirolimus arm, 40.5% for the sunitinib arm, and 66% for the bevacizumab plus interferon arm. Median progression-free survival was 8.2 months, 8.2 months, and 16.8 months, respectively. The best overall response rates, as determined by Response Evaluation Criteria In Solid Tumors (RECIST), were 27% for temsirolimus plus bevacizumab (2% complete responses and 25% partial responses), 24% for sunitinib (partial responses only), and 39% for bevacizumab plus interferon (2% complete responses and 37% partial responses).

H&O What types of toxicities were observed?

BE Toxicities led to discontinuation of treatment in 50% of the patients. Grade 3 events occurred in 26% of patients, and grade 4 events occurred in 12.5%. Three deaths occurred (a rate of 3.4%). A high proportion of patients developed gastrointestinal and colorectal adverse reactions, mainly hemorrhage and perforation. These events had not been anticipated based on previous data.

H&O Are updated results of the TORAVA trial forthcoming?

BE Survival will be provided, and several ancillary studies on biomarkers and imaging will be available.

H&O Do you believe that the results of this study have the potential to change clinical practice?

BE The results of the TORAVA trial strongly caution against the use of combination treatment with an mTOR

inhibitor and bevacizumab. Patients in ongoing phase II and III trials who are receiving this combination should be closely monitored.

This study also underlines the limitation of small, phase II trials. In our study, the progression-free survival rates in the 2 control arms were unexpected; rates were 8.2 months in the sunitinib arm and 16.8 months in the bevacizumab plus interferon alfa arm. No obvious differences in patient characteristics were detected, but these disparate rates were certainly due to variations in the patient population.

Suggested Readings

Merchan JR, Liu G, Fitch T, et al. Phase I/II trial of CCI-779 and bevacizumab in stage IV renal cell carcinoma: phase I safety and activity results. *J Clin Oncol.* 2007;25(18s). Abstract 5034.

Escudier BJ, Negrier S, Gravis G, et al. Can the combination of temsirolimus and bevacizumab improve the treatment of metastatic renal cell carcinoma (mRCC)? Results of the randomized TORAVA phase II trial. *J Clin Oncol.* 2010;28(15s). Abstract 4516.