

# KIDNEY CANCER UPDATE

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## Highlights in Kidney Cancer From the 2017 American Society of Clinical Oncology Annual Meeting

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### Adjuvant Pazopanib Does Not Extend Disease-Free Survival in Locally Advanced Renal Cell Carcinoma

Adjuvant pazopanib (Votrient, Novartis) at a daily dose of 600 mg does not improve disease-free survival (DFS) in locally advanced renal cell carcinoma (RCC), according to a new phase 3 study. A reduction in recurrence or death was observed in patients who received a starting dose of 800 mg of pazopanib, but this was one of the study's secondary objectives.

For the PROTECT study, conducted by Dr Robert J. Motzer of the Memorial Sloan Kettering Cancer Center in New York, New York, and colleagues, 1538 patients with high-risk, locally advanced RCC who had undergone nephrectomy were randomly assigned in a ratio of 1:1 to receive either pazopanib or a placebo for 52 weeks. Participants were required to have a high-grade pT2 tumor, a pT3 or pT4 tumor of any grade, or any N1 tumor; most patients had a pT3 tumor (82%-83%). Although the initial dose of pazopanib was 800 mg (403 patients; median age, 56-60 years), this was changed to 600 mg (1135 patients; median age, 58 years) in response to a high rate of treatment discontinuation owing to adverse events.

The study did not meet its primary endpoint of DFS with 600 mg of daily pazopanib (hazard ratio [HR], 0.86; 95% CI, 0.70-1.06;  $P=.16$ ). It did, however, show an improvement in DFS with 800 mg of daily pazopanib (HR, 0.69; 95% CI, 0.51-0.94;  $P=.02$ ).

Adverse events (AEs) with pazopanib included diarrhea, hypertension, hair color changes, nausea, fatigue, increased levels of alanine aminotransferase (ALT), dysgeusia, increased levels of aspartate aminotransferase (AST), headache, and decreased appetite. The safety profiles were similar for the 600-mg and 800-mg doses, with similar percentages of patients experiencing AEs

leading to dose reduction (48% and 53%) or discontinuing treatment because of AEs (4% and 53%).

Dr Motzer and his colleagues concluded that “pazopanib is not recommended for adjuvant therapy following resection of locally advanced RCC.”

Motzer RJ, Haas NB, Donskov F, et al. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with locally advanced renal cell carcinoma (RCC) (PROTECT) [ASCO abstract 4507]. *J Clin Oncol*. 2017;35(15)(suppl).

### Gene Assay Identifies Patients With RCC at High Risk for Recurrence

A prognostic 16-gene assay is able to identify which patients who had undergone nephrectomy for RCC were at high risk for recurrence, according to a new study. However, the assay was unable to predict which patients would respond to sunitinib (Sutent, Pfizer).

The study, presented by Dr Bernard Escudier of the Gustave Roussy Institute of Oncology in Villejuif, France, examined records from 193 patients with stage III clear cell RCC in the S-TRAC trial. The mean age of the patients was 56 to 59 years.

The researchers found that for every 25-unit increase in the recurrence score based on the gene assay, the risk for recurrence more than quadrupled among the 90 patients in the placebo group (HR, 4.24; 95% CI, 2.31-7.80;  $P<.0001$ ) and more than doubled among the 103 patients in the sunitinib group (HR, 2.53; 95% CI, 1.29-4.97;  $P=.008$ ). Regarding the secondary objectives of the study, the recurrence score was found to predict DFS and renal cancer-specific survival (RCSS), but not to predict which patients would respond to sunitinib treatment.

Dr Escudier concluded that using the gene assay to determine a recurrence score could “help identify which

patients with clear cell, stage III RCC could benefit from adjuvant treatment, especially sunitinib.”

Escudier BJ, Rini BI, Martini JF, et al. Phase III trial of adjuvant sunitinib in patients with high-risk renal cell carcinoma (RCC): validation of the 16-gene recurrence score in stage III patients [ASCO abstract 4508]. *J Clin Oncol*. 2017;35(15)(suppl).

## Checkpoint Inhibitors Plus Tyrosine Kinase Inhibitors Produce Mixed Early Results

Several early-phase trials of various checkpoint inhibitors—pembrolizumab (Keytruda, Merck), avelumab (Bavencio, EMD Serono/Pfizer), and atezolizumab (Tecentriq, Genentech)—in combination with vascular endothelial growth factor (VEGF) inhibitors for the treatment of RCC have produced mixed results.

The results of a phase 1/2 trial that examined the use of pembrolizumab plus pazopanib in 25 patients with advanced RCC were presented by Dr Simon Chowdhury of Guy's Hospital in London, United Kingdom. Although the overall response rate (ORR) was as high as 60% in one 10-person cohort, grade 3 AEs occurred in 22 of the patients and led to permanent discontinuation in 14 patients. Dr Chowdhury concluded that despite preliminary signs of efficacy, the combination was too toxic for use.

The phase 1b trial JAVELIN Renal 100, presented by Dr Toni K. Choueiri of the Dana-Farber Cancer Institute in Boston, Massachusetts, examined the first-line use of avelumab plus axitinib (Inlyta, Pfizer) in 55 patients with advanced RCC. After a median follow-up of 52.1 weeks, the objective response rate was an “encouraging” 58.2% (95% CI, 44.1%-71.3%). Although grade 3 or higher AEs occurred in 60% of the patients, including a grade 3 or higher increase in ALT in 7.3% of the patients, the toxicity appeared to be manageable. Dr Choueiri said that the findings support an ongoing phase 3 trial that is comparing avelumab/axitinib vs sunitinib in patients with untreated metastatic clear cell RCC.

The phase 2 IMmotion150 trial looked at atezolizumab/bevacizumab (Avastin, Genentech) vs sunitinib or atezolizumab alone in 305 treatment-naïve patients with locally advanced or metastatic RCC. Patients were allowed to cross over to treatment with atezolizumab/bevacizumab after first-line treatment with sunitinib

or atezolizumab alone. Dr Michael Atkins of the Georgetown Lombardi Comprehensive Cancer Center in Washington, DC, presented the results. Although the combination of atezolizumab/bevacizumab did not improve PFS compared with sunitinib, a trend toward improved PFS was found among patients who had tumor immune cells with at least 1% expression of PD-L1. In addition, the patients who crossed over to combination treatment had an ORR of 26% and a median PFS of 8.8 months. An ongoing phase 3 study, IMmotion151, is further evaluating the clinical benefit of atezolizumab/bevacizumab vs sunitinib.

Dr Hans Hammers of the UT Southwestern Medical Center in Dallas, Texas, who was the discussant for the 3 presentations, concluded that further study of pembrolizumab/pazopanib is unwarranted because of “overwhelming” hepatotoxicity, but that more-selective VEGF inhibitors might yield better results. He said that the results with avelumab plus axitinib “clearly” showed antitumor activity. Although the combination produced hepatotoxicity and immune-related AEs, he agreed with Dr Choueiri that the side effect profile was manageable.

Regarding atezolizumab/bevacizumab, Dr Hammers said that the ORR of 32% with this combination “paled” next to the 58% ORR seen with avelumab/axitinib, and that toxicity was not much higher than what would be expected with single agents. An especially interesting finding of the study was that patients whose tumors had high levels of T-cell infiltration and myeloid inflammation appeared to require the addition of bevacizumab in order for atezolizumab to exhibit clinical activity.

Dr Hammers theorized that checkpoint inhibitors and tyrosine kinase inhibitors (TKIs) might have biological synergy or that they might work better in combination by changing the balance between tumor cell death and growth.

Atkins MB, McDermott DF, Powles T, et al. IMmotion150: A phase II trial in untreated metastatic renal cell carcinoma (mRCC) patients (pts) of atezolizumab (atezo) and bevacizumab (bev) vs and following atezo or sunitinib (sun) [ASCO abstract 4505]. *J Clin Oncol*. 2017;35(15)(suppl).

Choueiri TK, Larkin JM, Oya M, et al. First-line avelumab + axitinib therapy in patients (pts) with advanced renal cell carcinoma (aRCC): results from a phase 1b trial [ASCO abstract 4504]. *J Clin Oncol*. 2017;35(15)(suppl).

Chowdhury S, McDermott DF, Voss MH, et al. A phase I/II study to assess the safety and efficacy of pazopanib (PAZ) and pembrolizumab (PEM) in patients (pts) with advanced renal cell carcinoma (aRCC) [ASCO 4506]. *J Clin Oncol*. 2017;35(15)(suppl).