

KIDNEY CANCER UPDATE

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Highlights in Kidney Cancer

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Commentary by Robert A. Figlin, MD

Atezolizumab Plus Bevacizumab Improves Progression-Free Survival in Metastatic Renal Cell Carcinoma

First-line treatment with atezolizumab (Tecentriq, Genentech) plus bevacizumab (Avastin, Genentech) improves progression-free survival (PFS) compared with sunitinib (Sutent, Pfizer) in patients who have metastatic renal cell carcinoma (RCC), according to early results of a phase 3 trial.

“Atezolizumab’s T-cell-mediated cancer cell killing may be enhanced through bevacizumab’s reversal of VEGF [vascular endothelial growth factor]-mediated immunosuppression via promotion of T-cell priming, normalization of tumor vasculature, and establishment of an immune-permissive tumor microenvironment,” said study author Robert Motzer, MD, of Weill Cornell Medical College in New York, New York, during his presentation. This was the first phase 3 trial to look at the combination of a programmed death ligand 1 (PD-L1) inhibitor and an anti-VEGF agent in these patients.

The IMmotion151 study (A Study of Atezolizumab in Combination With Bevacizumab Versus Sunitinib in Participants With Untreated Advanced Renal Cell Carcinoma) included 915 treatment-naïve patients with advanced or metastatic RCC. Patients were stratified according to Memorial Sloan Kettering Cancer Center (MSKCC) risk category, the presence or absence of liver metastases, and PD-L1 status, with PD-L1 positivity defined as PD-L1 expression of 1% or higher on tumor-infiltrating immune cells. They were then randomly assigned in a 1:1 ratio to receive atezolizumab at 1200 mg intravenously every 3 weeks plus bevacizumab at 15 mg/kg intravenously every 3 weeks, or sunitinib at 50 mg orally every day on a 4-week-on, 2-weeks-off schedule. A total of 40% of patients were PD-L1-positive.

After a median follow-up of 15 months, PFS per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 was significantly longer in the atezolizumab/bevacizumab group than in the sunitinib group in both the PD-L1-positive patients (11.2 vs 7.7 months; hazard ratio [HR]; 0.74; 95% CI, 0.57-0.96; $P=.02$) and the intent-to-treat patients (11.2 vs 8.4 months; HR, 0.83; 95% CI, 0.70-0.97). This improvement in PFS was consistent across the analyzed subgroups. Among the PD-L1-positive patients, the objective response rates (ORRs) were 43% and 35%. The duration of response was not reached for the atezolizumab/bevacizumab group vs 12.9 months for the sunitinib group. Overall survival (OS) data were immature at this first interim analysis, but Dr Motzer described the results so far as “encouraging” in favor of atezolizumab/bevacizumab.

Grade 3 or 4 treatment-related adverse events occurred in 40% of the atezolizumab/bevacizumab-treated patients and 54% of the sunitinib-treated patients. Adverse events of any grade led to treatment discontinuation in 8% of the atezolizumab/bevacizumab-treated patients and 12% of the sunitinib-treated patients. “The safety profile of atezolizumab plus bevacizumab is one of its strongest attributes,” said Dr Motzer. Adverse effects such as diarrhea, hand-foot reactions, fatigue, nausea, and stomatitis were more common with sunitinib, he added; only proteinuria was more common in the atezolizumab/bevacizumab group. Corticosteroids were required for 16% of the patients taking atezolizumab/bevacizumab.

“These results support atezolizumab plus bevacizumab as a first-line treatment option in patients with PD-L1-positive advanced RCC,” concluded Dr Motzer.

Motzer RJ, Powles T, Atkins MB, et al. IMmotion151: a randomized phase III study of atezolizumab plus bevacizumab vs sunitinib in untreated metastatic renal cell carcinoma (mRCC) [ASCO GU 578]. *J Clin Oncol*. 2018;36(suppl 6).

Pembrolizumab Plus Axitinib Tolerable, Promising in Advanced RCC

The combination of pembrolizumab (Keytruda, Merck) and axitinib (Inlyta, Pfizer) is tolerable and shows promising antitumor activity in treatment-naïve patients with advanced RCC, according to an ongoing open-label phase 1b study. “Prior studies combining PD-1 [programmed death 1] checkpoint inhibitors with VEGFR TKIs [vascular endothelial growth factor receptor tyrosine kinase inhibitors] demonstrated clinical benefit, but excessive toxicity precluded further development,” said presenter Michael B. Atkins, MD, of the Georgetown Lombardi Comprehensive Cancer Center, Washington, DC.

The study consisted of a dose-finding phase to determine the maximum tolerated dose, followed by a dose-expansion phase. Patients with advanced RCC received pembrolizumab at 2 mg/kg intravenously every 3 weeks and axitinib at 5 mg orally twice daily. Tumors were assessed with RECIST v1.1 at baseline, at week 12, and every 6 weeks thereafter. The primary endpoint was dose-limiting toxicity during the first 2 cycles; the study also looked at safety, ORR, PFS, OS, pharmacokinetics, and biomarkers. Treatment continued until disease progression, patient refusal, or unacceptable toxicity.

The researchers saw no unexpected toxicities. Among the 11 patients treated in the dose-finding phase, 3 dose-limiting toxicities were reported: 1 patient had a transient ischemic attack, and 2 patients were unable to complete at least 75% of the planned axitinib dose owing to treatment-related toxicity.

An additional 41 patients were treated in the dose-expansion phase. Among all 52 patients, the most common all-cause grade 3 or higher adverse events were hypertension (23%), diarrhea (10%), and fatigue (10%). The most common grade 3 or higher adverse events that were potentially immune-related were diarrhea (8%), increase in alanine aminotransferase (4%), increase in aspartate aminotransferase (4%), and fatigue (4%).

“This was a highly active regimen,” said Dr Atkins, with an ORR among the 52 patients of 73.1% (95% CI, 59.0%-84.4%) and a median PFS of 20.9 months (95% CI, 15.4 months to not evaluable). The median time to response was 3 months, and the median duration of tumor response was 19 months. OS data were not mature at the minimum follow-up period of 17.6 months. A total of 6 deaths occurred, which were unrelated to treatment.

Dr Atkins concluded that the combination of pembrolizumab and axitinib is tolerable and exhibits promising antitumor activity in treatment-naïve patients with advanced RCC. A randomized phase 3 trial comparing the combination vs sunitinib monotherapy is under way.

Atkins MB, Plimack ER, Puzanov I, et al. Safety and efficacy of axitinib (axi) in combination with pembrolizumab (pembro) in patients (pts) with advanced renal cell cancer (aRCC) [ASCO GU 579]. *J Clin Oncol*. 2018;36(suppl 6).

Cytoreductive Nephrectomy Linked to Improved Survival in Metastatic Papillary RCC

Cytoreductive nephrectomy (CN) in patients with metastatic papillary RCC is associated with improved survival, according to a retrospective analysis that adjusted for prognostic factors. Evidence had already existed that CN is beneficial in metastatic clear cell RCC, but the role of CN in patients with papillary histology has been unclear.

“To our knowledge, this is the largest analysis exploring CN in papillary RCC,” said presenter Jeffrey Graham, MD, of the University of Calgary Cumming School of Medicine in Alberta, Canada.

For the analysis, Dr Graham and colleagues identified 353 patients with metastatic papillary RCC in the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) who had been treated with or without CN (244 and 109 patients, respectively). Of these, 75 patients had tumors with a component of clear cell histology.

The median follow-up time was 57.1 months, and the median OS for the entire cohort from the start of first-line targeted therapy was 13.2 months. Patients who underwent CN were more likely to be younger, have a better Karnofsky performance score, and have bone metastases. Sunitinib was the most commonly used first-line therapy in both groups.

The median PFS was 5.1 months in the patients who underwent CN vs 3.4 months in those who did not ($P=.0344$). In addition, the median OS was 16.3 months in the patients who underwent CN vs 8.6 months in those who did not (95% CI, 6.1-12.2; $P<.0001$), a difference that represented an “almost doubling of the survival.” After adjustment for individual IMDC risk factors, the HR for death with CN was 0.62 (95% CI, 0.45-0.85; $P=.0031$). After further adjustment for age and the presence of bone metastases, the HR decreased to 0.55 (95% CI, 0.39-0.78; $P=.0006$).

Dr Graham concluded that CN in patients with metastatic papillary RCC is associated with improved survival when compared with no CN, even after control for prognostic imbalances. Although a clinical trial in this rare population may not be possible, he said, the data are consistent with the literature on clear cell RCC.

Graham J, Wells C, Donskov F, et al. Cytoreductive nephrectomy in metastatic papillary renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) [ASCO GU 581]. *J Clin Oncol*. 2018;36(suppl 6).

Cabozantinib Improves PFS in All Subgroups of Advanced RCC

Cabozantinib (Cabometyx, Exelixis) leads to longer PFS and ORR compared with sunitinib in previously untreated patients who have advanced RCC regardless of baseline characteristics, according to an updated analysis of the phase 2 CABOSUN trial (Cabozantinib-s-malate or Sunitinib Malate in Treating Patients With Previously Untreated Locally Advanced or Metastatic Kidney Cancer).

For the trial, Daniel J. George, MD, of Duke University School of Medicine in Durham, North Carolina, and colleagues randomly assigned 157 previously untreated patients with intermediate- or poor-risk RCC in a 1:1 ratio to receive initial systemic therapy with cabozantinib at 60 mg/day or sunitinib at 50 mg/day on a 4-week-on, 2-weeks-off schedule. Patients were stratified by IMDC risk group and the presence or absence of bone metastases. An independent radiology review committee assessed PFS and ORR.

As reported earlier, the researchers found that the median PFS was 8.6 months for cabozantinib vs 5.3 months for sunitinib (HR, 0.48; 95% CI, 0.31-0.74; 2-sided $P=.0008$), and the median ORR was 20% for cabozantinib vs 9% for sunitinib.

The subgroup analysis found that median PFS was longer with cabozantinib than with sunitinib in all subgroups analyzed—intermediate vs poor IMDC risk, presence or absence of bone metastases, older or younger age, sex, baseline European Cooperative Oncology Group (ECOG) performance status of 1 or 2 vs 0, and MET tumor expression status by immunohistochemistry. Cabozantinib performed especially well vs sunitinib among patients who were MET-positive. In these patients, the median PFS was 13.8 months for cabozantinib vs 3.0 months for sunitinib (HR, 0.32; 95% CI, 0.16-0.63). The subgroup analysis of ORR also favored cabozantinib over sunitinib.

Median PFS was reduced in the subgroups of patients who had poor prognostic characteristics (poor IMDC risk, ECOG score of 1 or 2, and presence of bone metastases) with both cabozantinib and sunitinib.

“Cabozantinib demonstrates clear improvement in PFS and ORR compared to sunitinib as initial targeted therapy in patients with metastatic RCC,” Dr George concluded. “These results overall were generally consistent across the baseline characteristics.”

George DJ, Hessel C, Halabi S, et al. Cabozantinib versus sunitinib for previously untreated patients with advanced renal cell carcinoma (RCC) of intermediate or poor risk: subgroup analysis of progression-free survival (PFS) and objective response rate (ORR) in the Alliance A031203 CABOSUN trial [ASCO GU 582]. *J Clin Oncol*. 2018;36(suppl 6).

Commentary

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The presentations at the 2018 American Society of Clinical Oncology Genitourinary Cancers Symposium, including those summarized here, demonstrate the evolving treatment options for patients with renal cancer.

On the heels of the recent US Food and Drug Administration approval of ipilimumab (Yervoy, Bristol-Myers Squibb) in combination with nivolumab (Opdivo, Bristol-Myers Squibb) for patients having an intermediate or poor prognosis, along with the expanded approval of cabozantinib for previously untreated patients on the basis of the results of CABOSUN, we are presented with the future possibility of immuno-oncology approaches in combination with targeted therapy.

How will we assess these evolving data sets? Can we use cross-trial comparisons to make treatment decisions for our patients? Would some subsets of patients benefit from initial therapy with a TKI followed by an immuno-oncology approach, as opposed to the converse?

Unfortunately, we will not get the answers to these questions from the current trials, which are designed primarily to address regulatory approvals. Another question is whether PFS and ORR are the best surrogate markers to use in these trials. For more than a decade, patients have benefited enormously not from a single therapy, but from a series of sequential therapies. The same will be true when we begin using immuno-oncology approaches in treating renal cancer, whether alone or in combination with targeted therapies.

What patients with renal cancer want is a longer life and a good quality of life, which means that side effects must be manageable. Patients also want the possibility of long-term treatment-free intervals. Complete remissions, unmaintained remissions, value-based treatment choices, and improved survival may not yet be seen in renal carcinoma trials, but these are the endpoints that our patients and their families value.