

KIDNEY CANCER UPDATE

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Highlights in Kidney Cancer

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Nivolumab Plus Ipilimumab Continues to Improve Survival in Renal Cell Carcinoma

Nivolumab (Opdivo, Bristol-Myers Squibb) plus ipilimumab (Yervoy, Bristol-Myers Squibb) improved overall survival (OS) compared with sunitinib (Sutent, Pfizer) in advanced renal cell carcinoma (RCC) after follow-up lasting at least 30 months, according to updated results from an open-label phase 3 study. Earlier results, which led to US Food and Drug Administration approval of the combination in these patients, were based on follow-up lasting at least 17.5 months.

For the CheckMate 214 study (Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma), Dr Nizar M. Tannir of the MD Anderson Cancer Center and coinvestigators randomly assigned 1096 patients (847 intermediate- or poor-risk, 249 favorable-risk) with previously untreated advanced or metastatic RCC in a 1:1 ratio to nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg every 3 weeks for 4 cycles, followed by nivolumab at 3 mg/kg every 2 weeks, or to sunitinib at 50 mg daily for 4 weeks on, 2 weeks off.

After follow-up lasting a median of 32.4 months, median OS was significantly better in the nivolumab/ipilimumab group than in the control group in both the intention-to-treat (ITT) population (not reached vs 37.9 months; hazard ratio [HR], 0.71; 95% CI, 0.59-0.86; $P=.0003$) and the intermediate- or poor-risk group (not reached vs 26.6 months; HR, 0.66; 95% CI, 0.54-0.80; $P=.0001$), which was consistent with the previous results. In the favorable-risk population, OS was similar between the 2 groups. Progression-free survival (PFS) and the objective response rate (ORR) also were significantly better in the nivolumab/ipilimumab group than in the control group in both the ITT population and the intermediate- or poor-risk group, but were similar between the 2 groups in the favorable-risk population.

The extended follow-up did not reveal any new safety concerns with nivolumab/ipilimumab. Treatment-related adverse events (TRAEs) occurred in 94% of the nivolumab/ipilimumab-treated patients and in 97% of the sunitinib-treated patients; the most common TRAEs with nivolumab/ipilimumab were fatigue, pruritis, diarrhea, rash, and nausea. Patients who received nivolumab/ipilimumab also were less likely than those who received sunitinib to experience grade 3 or 4 TRAEs (47% vs 64%). TRAEs leading to discontinuation occurred in 22% of patients receiving nivolumab/ipilimumab and 12% of patients receiving sunitinib, and treatment-related deaths occurred in 1.5% and 0.7% of patients, respectively.

The investigators concluded that improvements in OS, PFS, and ORR with nivolumab/ipilimumab in the ITT and intermediate- or poor-risk populations that were seen at 17.5 months persisted at 30 months, whereas no statistically significant differences in OS, PFS, or ORR were seen among patients in the favorable-risk subgroup. They also noted that nivolumab/ipilimumab produced impressive complete response rates, and that responses were deeper and more durable than with sunitinib.

Tannir NM, Frontera OA, Hammers HJ, et al. Thirty-month follow-up of the phase III CheckMate 214 trial of first-line nivolumab + ipilimumab (N+I) or sunitinib (S) in patients (pts) with advanced renal cell carcinoma (aRCC) [ASCO GU abstract 547]. *J Clin Oncol*. 2019;37(suppl 7).

Pembrolizumab Plus Axitinib Improves Survival in Renal Cell Carcinoma

Pembrolizumab (Keytruda, Merck) plus axitinib (Inlyta, Pfizer) improved OS, PFS, and ORR compared with sunitinib in patients with previously untreated, advanced or metastatic clear cell RCC, according to the first interim

results from a global phase 3 study. The combination also had a manageable safety profile.

The open-label KEYNOTE-426 study (Study to Evaluate the Efficacy and Safety of Pembrolizumab in Combination With Axitinib Versus Sunitinib Monotherapy in Participants With Renal Cell Carcinoma) enrolled patients with metastatic clear cell RCC who had not received previous systemic therapy for metastatic RCC. Dr Thomas Powles of the Barts Cancer Institute in London, the United Kingdom, and coinvestigators randomly assigned 861 patients in a 1:1 ratio to pembrolizumab at 200 mg intravenously every 3 weeks for a maximum of 35 cycles plus axitinib at 5 mg orally twice a day, or to sunitinib at 50 mg orally per day on a 4-week-on, 2-week-off schedule. Treatment continued until disease progression, intolerable toxicity, or the patient or investigator decided to halt treatment.

After a median follow-up of 12.8 months, 59.0% of patients in the pembrolizumab/axitinib arm and 43.1% of those in the sunitinib arm remained on treatment. Patients who received pembrolizumab/axitinib had significantly better OS (HR, 0.53; 95% CI, 0.38-0.74; $P<.0001$; 12-month rate, 89.9% vs 78.3%), PFS (HR, 0.69; 95% CI, 0.57-0.84; $P=.0001$; median, 15.1 vs 11.1 months), and ORR (59.3% vs 35.7%; $P<.0001$) than those who received sunitinib. The duration of response also was longer with pembrolizumab/axitinib than with sunitinib (median, not reached vs 15.2 months). The benefit of pembrolizumab/axitinib was observed in all subgroups tested, regardless of risk category or level of programmed death ligand 1 (PD-L1) expression.

TRAEs were grade 3 to 5 in 62.9% of patients in the pembrolizumab/axitinib group vs 58.1% of patients in the sunitinib group and led to regimen discontinuation in 8.2% vs 10.1% of patients, respectively. Side effects that occurred more often with pembrolizumab/axitinib included dysphonia and transaminitis, whereas those that occurred more often with sunitinib included thrombocytopenia, stomatitis, and mucosal inflammation.

Based on the results of this study, the FDA approved the combination of pembrolizumab and axitinib on April 19, 2019 as first-line treatment in patients with advanced RCC.

Powles T, Plimack ER, Stus V, et al. Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for locally advanced or metastatic renal cell carcinoma (mRCC): phase III KEYNOTE-426 study [ASCO GU abstract 543]. *J Clin Oncol*. 2019;37(suppl 7).

Rini BI, Plimack ER, Stus V, et al; KEYNOTE-426 Investigators. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380(12):1116-1127.

Pembrolizumab Shows Antitumor Activity in Non-Clear Cell RCC

Single-agent pembrolizumab showed encouraging antitumor activity in non-clear cell RCC, especially with papillary or unclassified histology, according to a single-arm phase 2 study. Although this agent has been shown to be effective in clear cell RCC, researchers are just beginning to look at the use of single-agent programmed death 1 (PD-1) inhibition in non-clear cell RCC.

For the KEYNOTE-427 study (Study of Pembrolizumab Monotherapy in Locally Advanced/Metastatic Renal Cell Carcinoma), Dr David F. McDermott of Beth Israel Deaconess Medical Center in Boston, Massachusetts, and colleagues enrolled patients with advanced RCC who had not received prior systemic therapy. Patients received pembrolizumab at 200 mg intravenously every 3 weeks for 35 cycles or until disease progression, unacceptable toxicity, or withdrawal.

A total of 165 patients in the study had non-clear cell RCC, which was papillary in 72% ($n=118$), chromophobe in 13% ($n=21$), and unclassified in 16% ($n=26$). The majority of the patients (68%) fell into the intermediate- or poor-risk category, and 62% were PD-L1-positive.

After a median follow-up of 11.1 months, 49 patients had died and 3 had withdrawn. More than half (56%) of the patients had discontinued pembrolizumab owing to progressive disease or clinical progression. The ORR was 24.8% (95% CI, 18.5%-32.2%) and included 8 (4.8%) complete responses and 33 (20%) partial responses. The median duration of response was not reached. The ORR was 25.4% (95% CI, 17.9%-34.3%) in papillary, 9.5% (95% CI, 1.2%-30.4%) in chromophobe, and 34.6% (95% CI, 17.2%-55.7%) in unclassified non-clear cell RCC. The ORR was not significantly different between favorable-risk (28.3%) and intermediate- or poor-risk (23.2%) RCC, but was significantly higher in PD-L1-positive disease (33.3%) than in PD-L1-negative disease (10.3%).

Grade 3 to 5 TRAEs occurred in 11% of patients, and 6% of patients discontinued owing to TRAEs. A total of 6 patients died owing to AEs, 2 of which were TRAEs (pneumonia and cardiac arrest).

The authors concluded that single-agent pembrolizumab showed encouraging antitumor activity in non-clear cell RCC, especially with papillary or unclassified histology, and that it should be further investigated in these patients.

McDermott DF, Lee J-L, Ziobro M, et al. First-line pembrolizumab (pembro) monotherapy for advanced non-clear cell renal cell carcinoma (nccRCC): results from KEYNOTE-427 cohort B [ASCO GU abstract 546]. *J Clin Oncol*. 2019;37(suppl 7).