KIDNEY CANCER UPDATE

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Highlights in Kidney Cancer

From the Eighteenth International Kidney Cancer Symposium
November 15-16, 2019 • Miami, Florida

Lenvatinib Plus Pembrolizumab Shrinks Metastatic Kidney Cancer After Previous Checkpoint Inhibitor

A combination of lenvatinib (Lenvima, Eisai) and pembrolizumab (Keytruda, Merck) is effective at shrinking tumors in patients with metastatic renal cell carcinoma (mRCC) whose disease has progressed despite treatment with a previous checkpoint inhibitor, according to interim results from a phase 2 trial. The results were presented by Dr Chung-Han Lee of Memorial Sloan Kettering Cancer Center (MSKCC) in New York, New York.

The trial included 33 patients with mRCC who had measurable disease by the immune-related Response Evaluation Criteria In Solid Tumors (irRECIST), had previously received no more than 2 systemic therapies, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and had a life expectancy of at least 12 weeks. Participants received 20 mg of oral lenvatinib per day and 200 mg of intravenous pembrolizumab every 3 weeks.

"The baseline characteristics of this cohort were very similar to what we would expect to see for RCC in this context," said Dr Lee. The median age was 64 years, the proportions of men and women were 73% and 27%, respectively, and the numbers of patients with an ECOG performance status of 0 or 1 were nearly even. Thirty-nine percent of the patients were considered "favorable risk" by both the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model and MSKCC risk stratification. Programmed death ligand 1 (PD-L1) status was available for two-thirds of the patients, and the numbers of PD-L1–positive and PD-L1–negative patients were approximately even.

At week 24, the objective response rate for lenvatinib/pembrolizumab was 64%, and the median progression-free survival by irRECIST was 11.3 months (95% CI, 7.3 to not evaluable). The best objective response was a partial response in 64% of patients and stable disease in 30%. The median duration of response was 9.1 months, and the median time to response was 1.6 months. The median duration of treatment was 6.9 months for lenvatinib, with a mean daily dose of 16.4 mg (82% of the intended dose), and 6.7 months for pembrolizumab, with a median of 10 doses. Of the 21 patients who exhibited an objective response, 16 (76%) continued treatment.

Dr Lee said that the adverse events (AEs) were "fairly characteristic" of patients treated with the combination of a vascular endothelial growth factor receptor (VEGFR) inhibitor and a checkpoint inhibitor, with 55% of patients experiencing grade 3 or 4 AEs such as fatigue, proteinuria, and hypertension. One death, which was caused by an upper gastrointestinal hemorrhage, was potentially treatment-related. A total of 27% of patients required a reduction in the dose of lenvatinib and 18% required a reduction in the dose of pembrolizumab because of AEs. Pembrolizumab caused AEs of special interest in 39% of patients, which included hypothyroidism in 18% of patients. "Overall, the adverse events were manageable, and no safety signals were identified," he said.

Lee CH, Shah AY, Makker V, et al. Phase 2 study of lenvatinib plus pembrolizumab for disease progression after PD-1/PD-L1 immune checkpoint inhibitor (ICI) in metastatic clear cell (MCC) renal cell carcinoma (RCC): results of an interim analysis.

Combination Immunotherapy Improves Treatment-Free Survival Without Toxicity vs Sunitinib

Combination immunotherapy with nivolumab (Opdivo, Bristol-Myers Squibb) plus ipilimumab (Yervoy, Bristol-Myers Squibb) improves treatment-free survival (TFS) without toxicity compared with sunitinib in patients who have advanced RCC, according to a new analysis of a phase 3 trial. CheckMate 214 (Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma) had previously shown that combination immunotherapy improved overall survival (OS) compared with sunitinib in these patients.

Dr Meredith Regan of the Dana-Farber Cancer Institute and Harvard Medical School in Boston, Massachusetts, who presented the results, explained that conventional measures—such as progression-free survival and OS—may not accurately characterize the full effect of immunotherapy agents vs other systemic therapies, including inhibitors of VEGFR. For example, patients who discontinue immunotherapy agents "may experience periods of disease control without needing subsequent systemic anticancer therapy." She also pointed to the possibility of persistent or new-onset toxicity even after therapy discontinuation. In response, she and her colleagues proposed a novel outcome measure, TFS.

As reported in the *New England Journal of Medicine* in 2018, CheckMate 214 showed that nivolumab/ipilimumab significantly improved OS compared with sunitinib in intermediate- and poor-risk patients receiving first-line treatment for advanced clear cell RCC. The new analysis was based on 1082 patients who were followed for at least 30 months.

Among patients at intermediate or poor risk, the 36-month mean TFS was nearly twice as long for nivolumab/ipilimumab as for sunitinib: 5.8 vs 3.0 months, respectively (a difference of 2.8 months; 95% CI, 1.7-4.0). Even when the possibility of persistent or new-onset grade 2 or higher treatment-related AEs was considered, the mean duration of TFS without AEs remained longer with nivolumab/ipilimumab than with sunitinib.

Among the patients at favorable risk, those in the nivolumab/ipilimumab group experienced TFS without toxicity that was on average more than 3.5 times as long as that in the sunitinib group: 9.4 vs 2.6 months for TFS without grade 3 treatment-related AEs, and 6.9 vs 1.8 months for TFS without grade 2 treatment-related AEs.

Dr Regan emphasized that treatment with sunitinib entailed not only being on therapy for a substantial period but also experiencing toxicity for a longer period. She said she hoped that looking at the data in this way will allow physicians "to think about the trade-offs with the different treatment regimens" in their discussions with patients.

Regan MM, Atkins MB, Powles T, et al. Treatment-free survival, with and without toxicity, as a novel outcome applied to immune-oncology agents in advanced renal cell carcinoma.

Use of Circulating Tumor DNA Remains Challenging in Advanced Clear Cell RCC

The use of circulating tumor DNA (ctDNA) analysis remains challenging in RCC, according to a study conducted at MSKCC of 110 patients with advanced clear cell RCC.

The study, which was presented by Dr Ritesh Kotecha, examined data from IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets), a next-generation sequencing panel that is used at MSKCC. The researchers identified 110 patients with advanced clear cell RCC who were analyzed with this panel between 2016 and 2019 and compared the results with tissue from their original tumors (tissue obtained from a resected kidney or a metastatic site). Both liberal and stringent criteria were used to conduct bidirectional genotyping of both of these samples. Liberal criteria were defined as 1 or 2 reads in ctDNA, whereas stringent criteria were defined as more than 3 reads in ctDNA.

The patients in the study were predominantly male (74%), and the mean age at diagnosis of advanced RCC was 59 years. The most common IMDC risk category (45% of patients) was intermediate. The primary tumor of nearly all patients (96%) had been removed before ctDNA was obtained. Patients were heavily pretreated, with a mean of 3 total systemic therapies. All patients had clear cell histology, and 16% had sarcomatoid features. The median time from primary tissue biopsy to ctDNA collection was nearly 2 years.

The analysis of primary tissue revealed "what we would expect," said Dr Kotecha. At least one alteration was detected in the primary tissue of all patients, with *VHL* alterations in 88% of patients, *PBRM1* alterations in 48%, *SETD2* alterations in 34%, *KDM5C* alterations in 17%, and *BAP1* alterations in 17%. Alterations also were identified in *MTOR*, *TP53*, *PTEN*, *TERT*, *ARID1A*, and *PIK3CA*.

The ctDNA analysis revealed alterations in 65% of patients when liberal criteria were used and in 22% of patients when stringent criteria were used, with *VHL* alterations the most common in both categories (40% of alterations by liberal criteria and 50% of alterations by stringent criteria).

The researchers found a wide variation in results. *VHL* mutations, for example, were detected in both primary tissue and ctDNA in 31 patients, whereas they were detected in primary tissue but not in ctDNA in 71 patients.

These data highlight "the continued challenges of using ctDNA, particularly in patients with advanced RCC," said Dr Kotecha. Primary tissue sequencing continues to be valuable for evaluating newer assays. He added that although the specificity of mutational profiles from ctDNA remains comparable with that of mutational profiles from primary tissues, the sensitivity of the former is on the low side and also varies according to the specific gene.

Kotecha R, Gedvilaite E, Murray S, et al. Circulating tumor DNA (ctDNA) results in 110 patients with advanced clear cell renal cell carcinoma.