UROLOGICAL CANCER

Axitinib–ICIs boost the RCC armamentarium

The FDA is conducting a Priority Review of both combinations

Sunitinib, a VEGF receptor-directed tyrosine-kinase inhibitor (VEGFR-TKI), is a standard-of-care frontline therapy for patients with advanced-stage renal cell carcinoma (RCC). Several ongoing trials are based on the rationale of combining VEGFR-TKIs with immune-checkpoint inhibitors (ICIs) to improve clinical outcomes. Promising results of two of these studies, JAVELIN Renal 101 and KEYNOTE-426, were presented at the ASCO 2019 Genitourinary Cancers Symposium and simultaneously published in the *New England Journal of Medicine*.

Owing to a previously reported lower incidence of hepatic toxicities compared with sunitinib, axitinib was the VEGFR-TKI used in the combination regimen tested in these trials. The anti-programmed cell death 1 ligand 1 (PD-L1)

antibody avelumab was tested in JAVELIN Renal 101, whereas the anti-programmed cell death 1 (PD-1) antibody pembrolizumab was used in KEYNOTE-426.

Both trials involved patients with advanced-stage clear cell RCC who had not previously received systemic therapy for advanced-stage disease ($n=886$ in JAVELIN Renal 101 and $n=861$ in KEYNOTE-426).

In addition to their similar size, both cohorts had comparable demographics and baseline disease characteristics, with the exception of the

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)-defined risk score. The percentage of patients with favourable-risk and intermediate-risk disease was 22% and 65%, respectively, in JAVELIN Renal 101, and 31% and 56% in KEYNOTE-426.

Median progression-free survival (PFS) duration was longer in patients receiving combination therapy than in those receiving sunitinib: 13.8 months with avelumab plus axitinib versus 8.4 months, and 15.1 months for pembrolizumab plus axitinib versus 11.1 months (HR 0.69; $P<0.001$ for both comparisons). The longer PFS of patients receiving sunitinib in KEYNOTE-426 probably reflects the higher proportion of patients with favourable-risk disease in this trial.

A PFS benefit with combination therapy was observed across all patient subgroups of both trials, although seemingly with more variable levels of benefit in patients with favourable-risk disease.

In JAVELIN Renal 101, the median PFS of patients with PD-L1⁺ tumours ($\geq 1\%$ immune cells in the tumour area; 63% of patients) was 13.8 months with avelumab plus axitinib and 7.2 months with sunitinib (HR 0.61; $P<0.001$).

In KEYNOTE-426, overall survival (OS) was higher with the combination therapy than with sunitinib: 12-month OS 89.9% versus 78.3% and 18-month OS 82.3% versus 72.1% (overall HR 0.53, $P<0.0001$). “This is an unprecedented OS benefit,” comments Brian Rini, lead investigator of this trial. The OS data in JAVELIN Renal 101 are not mature yet. “We hope to have OS results in 2019,” indicates co-lead investigator Toni Choueiri.

Objective response rates (ORRs) were also higher in both trials with combination therapy than with sunitinib: 59.3% with pembrolizumab plus axitinib versus 35.7% ($P<0.001$) and 51.4% with avelumab plus axitinib versus 25.7% (OR 3.10). In KEYNOTE-426, 5.8% of patients had a complete response to combination therapy versus 1.9% with sunitinib, with similar rates of 3.4% and 1.8%, respectively, in JAVELIN Renal 101.

Virtually all patients in all treatment groups had at least one adverse event (AE) of any grade. The rates of grade ≥ 3 AEs were 75.8% with pembrolizumab plus axitinib, 71.2% with avelumab plus axitinib and 70.6–71.5% with sunitinib.

“The FDA is conducting a Priority Review of both combinations,” explains Choueiri. “Pembrolizumab plus axitinib will become the standard of care for patients with advanced-stage clear cell RCC,” Rini opines.

“A similar PFS benefit was observed in both trials but, at the current analysis cut-off, only axitinib plus pembrolizumab was associated with a significant increase in OS,” summarizes Rini. Comparative trials of different ICI plus TKI combinations and further analyses of the role of several biomarkers in guiding treatment decisions will enable the best use of these regimens in RCC.

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ORIGINAL ARTICLES Motzer, R. J. et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N. Engl. J. Med.* <https://doi.org/10.1056/NEJMoa1816047> (2019) | Rini, B. I. et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N. Engl. J. Med.* <https://doi.org/10.1056/NEJMoa1816714> (2019)