KIDNEY CANCER

CheckMate 214 — a winning combination?

This combination represents a change in the first-line treatment paradigm for advanced-stage RCC

The standard-of-care treatment for patients with advanced-stage renal cell carcinoma (RCC) is sunitinib, a multi-target tyrosine kinase inhibitor (TKI) with activity against VEGFR. One of the FDA-approved options for patients with disease recurrence after treatment with a VEGFR TKI is the anti-PD-1 antibody nivolumab. In patients with melanoma or non-small-cell lung cancer, the efficacy of nivolumab can be improved by combining this agent with the anti-CTLA-4 antibody ipilimumab. This combination, already deemed safe in patients with advanced-stage RCC, has now been demonstrated to be associated with better outcomes than sunitinib in the CheckMate 214 trial.

In this randomized phase III trial, 547 and 535 patients with previously untreated advanced-stage RCC received nivolumab plus ipilimumab or sunitinib, respectively; 423 and 416 patients in these cohorts, respectively, had intermediate-risk or poor-risk disease according to the International Metastatic Renal Cell Carcinoma Database Consortium criteria and the primary end points of the trial were all focused on this population. Notably, a limited number of studies have

been conducted in patients with intermediate-risk or poor-risk RCC.

At a median follow-up duration of 25.2 months in the intermediate-risk and poor-risk group, overall survival was higher for patients who received the combination than for those treated with sunitinib at both 12 months (80% versus 72%) and 18 months (75% versus 60%). The median overall survival was not reached with combination immunotherapy versus 26 months with sunitinib (HR 0.63; $P < 0.001$); the median progression-free survival (PFS) was 11.6 months versus 8.4 months (HR 0.82; $P = 0.03$). The objective response rate (ORR) was 42% with the combination versus 27% with sunitinib ($P < 0.001$); complete responses were observed in 40 patients (9%) versus 5 patients (1%). Moreover, 81% of patients treated with immunotherapy versus 70% of those receiving sunitinib had response durations ≥ 1 year (median duration of response not reached and 18.2 months, respectively).

“Our study confirms the emerging role of immunotherapy in the management of patients with advanced-stage RCC. This combination represents a change in the first-line treatment paradigm for advanced-stage RCC, away from sunitinib. The benefits include a higher response rate, higher frequency of complete responses and, most notably, improved overall survival,” explains Robert Motzer, the lead investigator of this trial.

In exploratory biomarker analyses, 776 patients with intermediate-risk or poor-risk disease had quantifiable tumour PD-L1 expression. The ORRs were 37% with the immunotherapy combination and 28% with sunitinib among patients with $\leq 1\%$ PD-L1 expression ($P = 0.03$), and 58% and

22%, respectively, among patients with $\geq 1\%$ PD-L1 expression ($P < 0.001$). In those with PD-L1 levels $\leq 1\%$, 12-month overall survival was 80% with the combination and 75% with sunitinib, and 18-month overall survival was 74% versus 64%; the median overall survival durations were not reached in either treatment arm. In those with PD-L1 levels $\geq 1\%$, 12-month overall survival was 86% versus 66%, and 18-month overall survival was 81% versus 53%; the median overall survival durations in this group were not reached and 19.6 months with the combination and sunitinib, respectively.

In the intention-to-treat population, combination immunotherapy provided an overall survival benefit (HR 0.68; $P < 0.001$), but no statistically significant ORR or PFS benefit. In the favourable-risk subgroup, no clear benefit of immunotherapy was observed (although the complete response rate was higher); however, the data are immature.

“Of note, the toxicity of this combination needs to be recognized and managed, but overall the benefit outweighs the risk,” states Motzer. Treatment-related adverse events (AEs) of any grade occurred in 93% and 97% of patients receiving the combination and sunitinib, respectively, which were grade 3–4 in 46% and 63% of patients. AEs leading to treatment discontinuation occurred in 22% versus 12% of patients.

Motzer believes that nivolumab plus ipilimumab “will become a new standard of care in patients with intermediate-risk or poor-risk advanced-stage RCC.” In addition, Motzer and his collaborators are now conducting a large phase III trial comparing adjuvant nivolumab plus ipilimumab to placebo in patients with localized kidney cancer.

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