Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma (ccRCC): Results from 42-month follow-up of KEYNOTE-426.

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Background: In the first interim analysis of the randomized, multicenter, open-label, phase 3 KEYNOTE-426 study (NCT02853331), treatment with pembro + axi significantly improved OS, PFS, and ORR vs sunitinib monotherapy in treatment-naive advanced ccRCC. Extended follow-up (median, 30.6 mo) continued to demonstrate the superior efficacy of pembro + axi vs sunitinib monotherapy in this patient population. Here, we present the results of the prespecified final analysis with 42.8-mo median follow-up. **Methods:** Treatment-naive patients (pts) with advanced ccRCC, KPS ≥70%, and measurable disease (RECIST v1.1) were randomly assigned 1:1 to receive pembro 200 mg IV Q3W for up to 35 doses + axi 5 mg orally BID or sunitinib 50 mg orally QD on a 4-wk on/2-wk off schedule until progression, intolerable toxicity, or withdrawal. Randomization was stratified by IMDC risk (favorable vs intermediate vs poor) and geographic region (North America vs Western Europe vs Rest of World). Dual primary endpoints were OS and PFS. Secondary endpoints were ORR, DOR, and safety. The protocol-specified final analysis was based on a target of 404 OS events. No formal hypothesis testing was performed because all efficacy endpoints were met previously at the first interim analysis; nominal *P* values are reported. **Results:** Overall, 861 pts were randomly assigned to receive pembro + axi (n=432) or sunitinib (n=429). Median duration of follow-up, defined as time from randomization to the database cutoff date, was 42.8 mo (range, 35.6-50.6). At data cutoff, 418 pts had died: 193 (44.7%) of 432 pts in the pembro + axi arm vs 225 (52.4%) of 429 pts in the sunitinib arm. Compared with sunitinib, pembro + axi improved OS (median: 45.7 vs 40.1 mo; HR, 0.73 [95% CI, 0.60-0.88]; *P*<0.001) and PFS (median: 15.7 vs 11.1 mo; HR, 0.68 [95% CI, 0.58-0.80]; *P*<0.0001). The 42-mo OS rate was 57.5% with pembro + axi vs 48.5% with sunitinib; the 42-mo PFS rate was 25.1% with pembro + axi vs 10.6% with sunitinib. For pembro + axi vs sunitinib, ORR was 60.4% vs 39.6% (*P*<0.0001); CR rate was 10.0% vs 3.5%; median DOR was 23.6 mo (range 1.4+ to 43.4+) vs 15.3 mo (range, 2.3-42.8+). Subsequent anticancer therapy was administered to 47.2% of pts in pembro + axi arm vs 65.5% of pts in sunitinib arm. Although a similar proportion of pts in each arm received VEGF/VEGFR inhibitors, only 10.2% of pts in the pembro + axi arm received subsequent treatment with a PD-1/L1 inhibitor compared to 48.7% of pts in the sunitinib arm. No new safety signals were observed. **Conclusions:** With a median follow-up of 42.8 mo, this is the longest follow-up of an anti-PD–1/L1 immunotherapy combined with a VEGF/VEGFR inhibitor for first-line RCC. These results show that pembro + axi continues to demonstrate superior efficacy over sunitinib with respect to OS, PFS, and ORR, with no new safety signals. Clinical trial information: NCT02853331.

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