Abstract 543: 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.

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Background: A phase 1b study of pembro (anti–PD-1) plus axi (VEGFR-TKI) showed promising antitumor activity and manageable safety in patients (pts) with previously untreated mRCC. The global, open-label, phase 3 KEYNOTE-426 study assessed the efficacy and safety of pembro + axi vs sunitinib as first-line therapy for mRCC (NCT02853331).

Methods: Eligible pts with clear-cell mRCC, no previous systemic therapy for mRCC, and KPS ≥70% were randomized 1:1 to pembro 200 mg IV Q3W for a maximum of 35 cycles plus axi 5 mg orally BID or sunitinib 50 mg orally QD (4-wk on/2-wk off schedule). Treatment was given until PD, intolerable toxicity, or pt/investigator decision. Randomization was stratified by IMDC risk group and geographic region. Primary endpoints were OS and PFS (RECIST v1.1 by blinded, independent central review [BICR]). ORR was the key secondary endpoint. At the protocol-specified first interim analysis, the superiority thresholds were P = 0.0001 for OS, 0.0013 for PFS, and 0.025 for ORR (if OS and PFS were significant). Results: 861 pts were randomized: 432 to pembro + axi, 429 to sunitinib. After a 12.8-mo median follow-up, 59.0% of pts in the pembro + axi arm and 43.1% in the sunitinib arm remained on treatment. Pembrol + axi significantly improved OS (HR 0.53 [95% CI 0.38-0.74]; P < 0.0001; 12-mo rate 89.9% vs 78.3%), PFS (HR 0.69 [95% CI 0.57-0.84]; P = 0.0001; median 15.1 vs 11.1 mo), and ORR (59.3% vs 35.7%; P < 0.0001). Duration of response was prolonged with pembro + axi (median not reached vs 15.2 mo). The pembro + axi benefit was observed in all subgroups tested, including all IMDC risk and PD-L1 expression subgroups. Treatment-related AEs were grade 3-5 in 62.9% of pts in the pembro + axi arm vs 58.1% in the sunitinib arm and led to regimen discontinuation in 6.3% vs 10.1%. Conclusions: Pembrolizumab + axitinib provided superior OS, PFS, and ORR compared with sunitinib and had manageable safety in pts with previously untreated, advanced or metastatic clear-cell RCC. These data suggest that pembrolizumab + axitinib should be a new standard of care for this population.
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