KEYNOTE-564: Adjuvant immunotherapy for renal cell carcinoma

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SUMMARY
Renal cell carcinoma (RCC) accounts for 3% of all the cancers and has a 2% reported annual rise in the incidence over the past two decades.† Despite extensive research, no form of adjuvant therapy has shown a meaningful survival advantage or is practiced widely for this malignancy.

KEYNOTE-564 was an international, phase three, randomized, double-blind trial involving patients with clear cell RCC at high risk for recurrence post nephrectomy.‡ The protocol defined the high-risk criteria as T2 tumors with nuclear grade four or sarcomatoid morphology, T3–4 tumors, regional lymph node metastasis, metastatic disease post nephrectomy, and metastasectomy without evidence of disease.

Patients were randomly assigned to receive either adjuvant pembrolizumab or a placebo in a 1:1 ratio for a period of 1 year (maximum 17 cycles). The primary end-point was disease-free survival and was defined as the time to first local or distant recurrence or death from any cause. The critical secondary end-point was overall survival and efficacy was evaluated in the intention-to-treat population.

The trial randomized 994 patients either to adjuvant pembrolizumab (n = 496) or to placebo (n = 498) arms. At the time of reporting of this preplanned interim analysis, performed at a median period of 24 months post randomization, 260 events of recurrence or death had occurred (pembrolizumab (n = 109); placebo (n = 151)). Adjuvant pembrolizumab therapy was associated with significantly higher disease-free events (77% versus 68%) with a hazard ratio of 0.68 (95% confidence interval 0.53–0.87; P = 0.002) for recurrence or death. In the pembrolizumab arm, 61% of the patients received all the 17 planned treatment cycles and 21% discontinued the treatment due to adverse events and 10% discontinued as they developed recurrence. Grade three to five adverse events were reported in 32% and 18% of the patients who received pembrolizumab and placebo, respectively, and no treatment-related deaths were recorded.

The authors concluded that adjuvant pembrolizumab therapy significantly improved the disease-free survival as compared to a placebo in patients with RCC who were at high risk of recurrence post nephrectomy.

COMMENTS
Nephrectomy is the current standard of care for locally advanced RCC, although more than half of these patients develop recurrence, primarily as distant metastases, significantly compromising survival. Despite the proven benefit of targeted agents in patients with metastatic RCC, trials reported till date have failed to demonstrate a meaningful survival advantage for these agents when used in the adjuvant setting for non-metastatic disease.

A recent meta-analysis included four, phase-three, randomized controlled trials (ASSURE, S-TRAC, PROTECT, ATLAS) evaluating adjuvant tyrosine kinase inhibitors (TKIs) in patients with clear cell RCC to assess the overall survival benefit, poor tolerability resulting in dose reductions, and poor quality of life led the authors to conclude a lack of clinical benefit.

Recent reports demonstrating the survival benefit of immune checkpoint inhibitors (ICIs) in patients with metastatic RCC has revived interest in adjuvant therapy for RCC. Extrapolating from the benefit of pembrolizumab in metastatic RCC as seen in KEYNOTE-426 and CLEAR trials to the current trial evaluated pembrolizumab in an adjuvant setting. The improvement in the disease-free survival was primarily driven by reduced distant recurrences in the pembrolizumab group, and the overall incidence of distant recurrence, local recurrence, and all-cause death events was 20%, 5%, and 5%, respectively. The adverse effect profile was also superior to that reported with TKIs, with no need for dose reduction and only around 20% of the treatment discontinuation were attributed to adverse events. However, the reported survival benefit may actually be inflated as the study included higher-risk patients than those in the TKI trials, with 89% T3 tumors, 66% grade three or four, and the inclusion of metastatic cancers.
A growing matter of concern is the lack of a proper definition of high-risk group who are likely to benefit from the adjuvant therapy. In this study, patients with wide range of high risk factors were included, and the majority were positive for programmed death ligand-1 (PDL-1), a known target for pembrolizumab. Long-term data, with subgroup analyses for individual risk factors, may help better define the patient sub-group with an appropriate risk-benefit profile. The benefit of adjuvant therapy in patients with nonclear-cell RCC also remains questionable.

Currently, pembrolizumab is approved only in combination with a TKI in patients with metastatic RCC, based on the KEYNOTE-426 and CLEAR trials, and the optimum adjuvant regimen is yet to be defined. If the long-term follow-up data confirms an overall survival advantage, the dilemma of neoadjuvant versus adjuvant therapy and the optimum management of recurrences after adjuvant treatment will also need evaluation.

The study’s primary limitation was the lack of long-term follow-up, with only 26% of the deaths required for the overall survival evaluation. With the long-term outcomes awaited, the trial indicates that adjuvant therapy for high-risk RCC may be useful and the ongoing trials evaluating other ICIs including nivolumab (PROSPER; NCT03055013), atezolizumab (IMmotion010; NCT03024996), and durvalumab (RAMPART; NCT03288532), will further shed light on the matter.

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