Editorial Commentary

The final report of KEYNOTE-426 showed the efficacy and safety as a treatment for advanced renal cell carcinoma

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Combinations of immune checkpoint inhibitors (ICIs), such as nivolumab plus ipilimumab (1), and ICIs plus tyrosine-kinase inhibitors (TKIs), such as pembrolizumab plus axitinib (2), avelumab plus axitinib (3), nivolumab plus cabozantinib (4) and pembrolizumab plus lenvatinib (5), have achieved better outcomes than sunitinib monotherapy in patients with advanced/metastatic renal cell carcinoma (RCC). The combination of pembrolizumab plus axitinib is one such combination. In addition, the difference between the combination of avelumab plus axitinib and the combination of pembrolizumab plus axitinib was the type of ICI, but both showed similar efficacy. Herein, we have assessed the report of the KEYNOTE-426 study as treatment of clear cell RCC, in which the minimum duration of follow-up was 36 months (6).

The Society for Immunotherapy of Cancer Immunotherapy Guidelines – Advanced Renal Cell Carcinoma Subcommittee ranked endpoints of published studies and selected landmark overall survival (OS) as the most important and relevant endpoint, most of the subcommittee agreeing that the 3-year landmark OS was the most relevant (7). This final report of the KEYNOTE-426 study complied with this recommendation and deserves evaluation. In this study, the 3-year landmark OS remained superior at 63% in the combination arm compared with 54% in the sunitinib arm. However, the hazard ratio (HR), which was for the median OS, increased to 0.73 in the latest analysis compared with 0.53 at the time of first analysis, indicating that the difference between the two groups had decreased.

In addition, the following points should be noted: (I) the median progression-free survival (PFS) was 16 months in the combination arm compared with 11 months in the sunitinib arm (HR =0.68; 95% confidence interval, 0.58–0.80), and the objective response rate was 60%, remaining so even with long-term follow-up; (II) of the 43 patients in the combination arm with complete responses, 12 developed progressive disease and two died; (III) the median duration of response was 24 months and only 45% of patients in the combination arm were still responding after 30 or more months. Thus, although this combination seems to significantly improve the efficacy of early treatment, looking at the survival curve, the Kaplan-Meier curve made a downward slope to the right. So, it has not been demonstrated that the responses are durable.

This final analysis also revealed International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) data on risk groups obtained by analyzing subgroups. The median OS in patients in the IMDC favorable-risk group was 47 months in the combination arm with a HR of 1.2 compared with the sunitinib arm; however, the HR was 0.64 in the first interim. The median PFS was 21 months (HR =0.76 compared with the sunitinib arm), however, the advantage in the combination arm

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disappeared with subsequent therapies. Given that IMDC risk classification is an index for predicting the efficacy of TKIs, it is possible that the results were better in both the combination and sunitinib arms in the favorable-risk group, which was, therefore, less distinguishable from the combination arm.

In contrast, the HR for OS in patients in the IMDC intermediate/poor-risk group was 0.64 in the combination arm compared with the sunitinib arm. Furthermore, the HRs of PFS and PFS2 were 0.67 and 0.62, respectively. In the patients in the IMDC intermediate/poor-risk groups, the combination arm was always superior to the sunitinib arm, indicating that it is beneficial to administer a combination of ICIs as first-line treatment.

This final analysis did not examine efficacy separately for the IMDC poor-risk group. Given that patients classified by IMDC as poor risk seem to have a poor prognosis when treated with TKIs, it would be interesting to determine the outcomes after a combination of ICIs. Further data on poor-risk patients are needed.

Regarding adverse events (AEs), 14% of patients in the combination arm were treated with systemic high-dose corticosteroids for immune-related AEs. Because the frequency of AEs increases with increasing duration of follow-up, late-onset AEs associated with this combination therapy need more attention.

With the combination of an ICI plus TKI therapy, it seems that the characteristics of the TKI used greatly affect the efficacy and safety of the combination. We believe that axitinib generally has fewer severe AEs than other TKIs and is easier to manage. The efficacy and safety of this combination regimen reflect the characteristics of axitinib. The characteristics of other combinations of an ICI and TKI, such as nivolumab plus cabozantinib and pembrolizumab plus lenvatinib, also depend on the TKI used. We speculate that pembrolizumab plus axitinib has fewer AEs and a milder therapeutic effect than the other two regimens named above.

To summarize, because this final report showed that pembrolizumab plus axitinib is effective in the early stages of treatment, we recommend the ICI plus TKI therapy that include this when patients need an early response to treatment. Furthermore, a useful characteristic of this regimen may be ease of control of AEs.

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