Editorial Commentary

Optimal choice of first-line treatment for advanced renal cell carcinoma based on the results of extended follow-up data

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Immuno-oncology (IO) has been utilized in the treatment of renal cell carcinoma since the approval of nivolumab monotherapy as a second-line therapy. Results of randomized controlled trials involving untreated locally advanced and metastatic renal cell carcinoma patients have demonstrated efficacy, establishing IO-IO combinations and IO-TKI (tyrosine kinase inhibitor) combinations as standard treatments (1-5). Despite the expansion of treatment options, there are currently no biomarkers available for IO combination therapy, and the interpretation of existing data and toxicity profiles will be crucial determining factors. *Figure 1* shows the overall survival (OS) and progression-free survival (PFS) for each drug over time, with the most recent data added (2-19).

In the CheckMate 214 study (2), the IO-IO combination of ipilimumab and nivolumab demonstrated a significant prolongation in OS compared to the sunitinib group in the intention-to-treat (ITT) population [hazard ratio (HR): 0.68, 95% confidence interval (CI): 0.49–0.95]. Furthermore, when patients were stratified according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk classification (20), there was no significant OS prolongation in the Favorable risk group. However, the IMDC Intermediate/Poor risk group exhibited significant OS and PFS prolongation (OS: HR, 0.63, 95% CI: 0.44–0.89; PFS: HR, 0.82, 95% CI: 0.64–1.05). The combination of ipilimumab and nivolumab is characterized by a higher rate of progressive disease (PD) (17.6%) and a lower overall response rate (ORR) (39%) than IO-TKI (9). Nonetheless, it presents a more sustained response. In the ITT group, the PFS did not significantly differ from that of the sunitinib group. However, the Kaplan-Meier curve reached a plateau after 24 months, remaining at 30% for 60 months. Moreover, the OS consistently ranged between HR of 0.68–0.72 throughout the long-term course of the study, with no observed progression over time.

In the JAVELIN Renal 101 study (1), among the IO-TKI combinations, avelumab and axitinib demonstrated significant PFS (HR, 0.67, 95% CI: 0.57–0.79) compared to the sunitinib group in the ITT population. However, OS was not reached in the interim analysis, and follow-up was ongoing until the final analysis. In the recently published final analysis, OS was prolonged but not significantly different in the sunitinib group (OS: HR, 0.86, 95% CI: 0.70–01.06) (21). Other IO-TKI combinations, namely pembrolizumab and axitinib, nivolumab and cabozantinib, and pembrolizumab and lenvatinib, have already significantly prolonged OS compared to the sunitinib group in the ITT population. The respective trials reported the following results: KEYNOTE-426 (HR, 0.53, 95% CI: 0.38–0.74) (3), CheckMate9ER (HR, 0.60, 95% CI: 0.40–0.89) (4), and CLEAR (HR, 0.66, 95% CI: 0.49–0.88) (5). Notably, in the KEYNOTE-426 study, the OS HR values at 13, 31, 43, and 67 months were 0.53, 0.68, 0.73, and 0.84, respectively (3,11-13). Similarly, in the CheckMate9ER

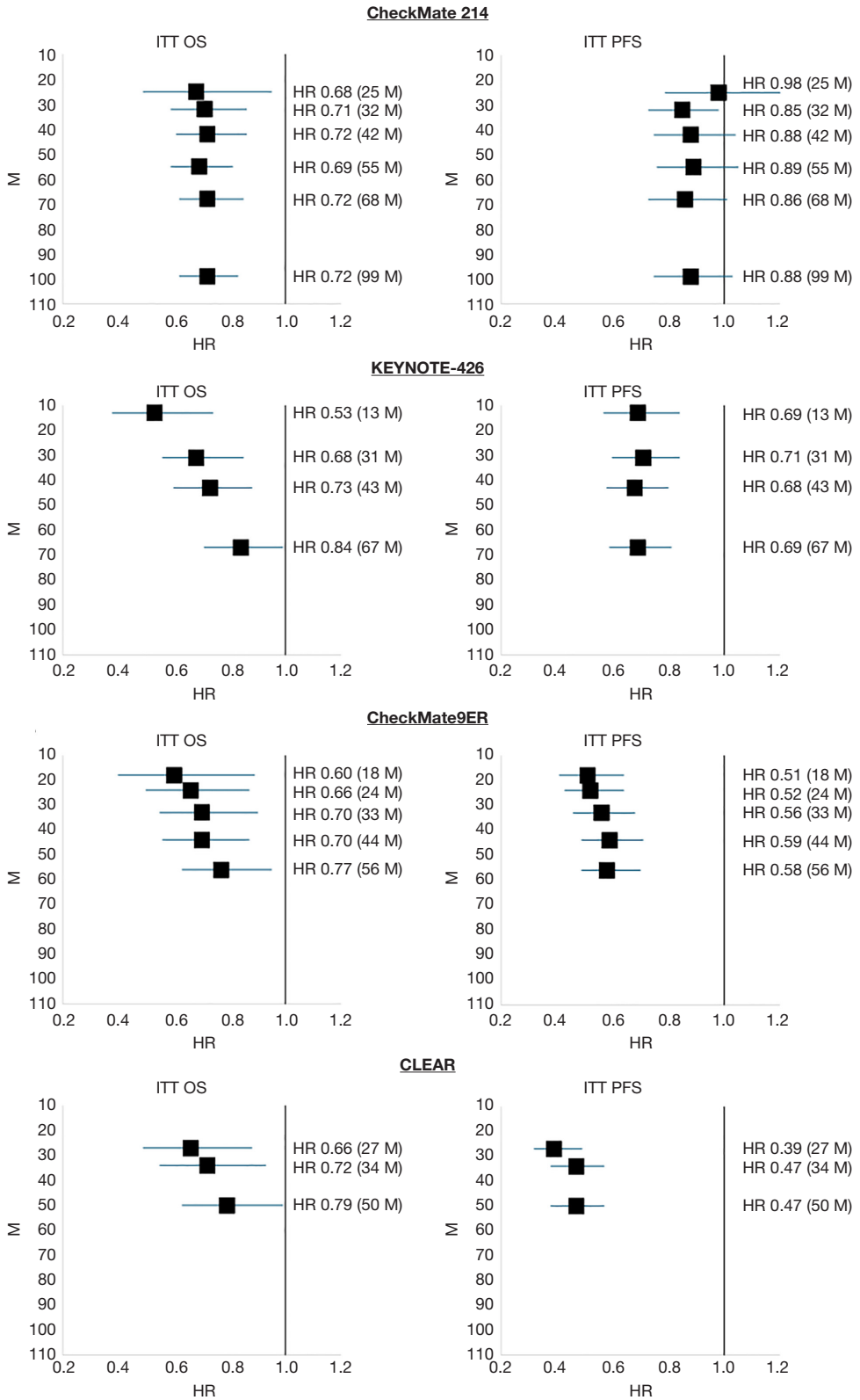

Figure 1 HR for OS and PFS for each clinical trial over time. HR, hazard ratio; M, months of median follow-up; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

study, the OS HR values at 18, 24, 33, 44, and 56 months were 0.60, 0.66, 0.70, 0.70, and 0.77 (4,14-17), respectively, and in the CLEAR study, the OS HR values at 27, 34, and 50 months were 0.66, 0.72 and 0.79, respectively (5,18,19). OS HR values stratified into IMDC Intermediate/Poor risk group also increases over time. These results suggest a stable OS over long-term use of IO-IO combinations, as indicated by consistently favorable OS HR values. Conversely, IO-TKI combinations exhibited worsening OS HR values over time. However, despite this trend, significant OS prolongation was consistently observed with HR values in the latest analysis of each trial. In the decision-making process between IO-IO and IO-TKI, it is anticipated that IO-IO combinations will offer durable responses, albeit with inferior ORR and rates of PD compared to IO-TKI. Additionally, the lack of long-term data on IO-TKI has been a limitation until now. However, the 43-month data from the KEYNOTE-426 study (12) we are evaluating here showed maintenance of PFS, and similar results were reported with longer-term data of 5 years (13). This is the longest data of any IO-TKI, and the combination of pembrolizumab and axitinib is increasingly supported as a standard treatment option.

Another important aspect of treatment selection involves understanding adverse events (AEs). It is essential to note that direct comparisons between trials may not be appropriate due to differing patient backgrounds. Although less overall AEs were observed with IO-IO combinations compared to IO-TKI combinations, the rate of high-dose steroid use for immune-related adverse events (irAE) was 29% higher in IO-IO combinations compared to 11–27% in IO-TKI combinations (1,3,4,6).

Among IO-TKI combinations, pembrolizumab and lenvatinib had the highest incidence of Grade 3 or higher AEs (82.4%), whereas avelumab and axitinib had the lowest incidence (71.2%). When comparing AEs by category, the combination of nivolumab and cabozantinib was associated with higher rates of diarrhea (63.8%) and palmar-plantar erythrodysesthesia syndrome (40%), while pembrolizumab and lenvatinib showed higher rates of hypertension (52.3%), but lower rates of liver injury [aspartate aminotransferase (AST)/alanine aminotransferase (ALT): 9.4%/9.7%]. In contrast, the combination pembrolizumab and axitinib had higher rates of Grade 3 or higher AEs related to liver injury (AST/ALT: 6.8%/12.1%). Excluding serious irAE, it is important to determine the tolerability of AEs attributed to TKIs. Axitinib advantages over other TKIs are a potent vascular endothelial growth factor receptor (VEGFR) inhibition, little off VEGFR targeted effect (22). Furthermore, AEs related to axitinib are relatively manageable due to its short half-life among TKIs. Additionally, familiarity of clinicians with axitinib, because of its extensive use, is advantageous.

As outlined above, the consideration of IO-TKI combinations becomes pertinent when an early response is expected, and the selection should be driven by comprehensive data analysis, including the evaluation of AEs. The combination of pembrolizumab and axitinib has apparent strengths reaching the final analysis, and the ease of use associated with axitinib compared to other IO-TKIs enhances its appeal. As a standard treatment, the accumulation of real-world clinical data and the identification of biomarkers represent crucial future endeavors.

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References

1. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2019;380:1103-15.
2. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med 2018;378:1277-90.
3. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2019;380:1116-27.
4. Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2021;384:829-41.
5. Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med 2021;384:1289-300.
6. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol 2019;20:1370-85.
7. Motzer RJ, Escudier B, McDermott DF, et al. Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial. J Immunother Cancer 2020;8:e000891.
8. Albiges L, Tannir NM, Burotto M, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. ESMO Open 2020;5:e001079.
9. Motzer RJ, McDermott DF, Escudier B, et al. Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma. Cancer 2022;128:2085-97.
10. Motzer RJ, Tannir NM, McDermott DF, et al. ASCO GU 2024: Nivolumab plus Ipilimumab vs Sunitinib for First-Line Treatment of Advanced RCC: Long-Term Follow-up Data from the Phase 3 CheckMate 214 Trial. Proceedings of the American Society of Clinical Oncology Genitourinary Cancers Symposium; 2024 Feb 8-10; San Francisco, CA.
11. Powles T, Plimack ER, Soulières D, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. Lancet Oncol 2020;21:1563-73.
12. Plimack ER, Powles T, Stus V, et al. Pembrolizumab Plus Axitinib Versus Sunitinib as First-line Treatment of Advanced Renal Cell Carcinoma: 43-month Follow-up of the Phase 3 KEYNOTE-426 Study. Eur Urol 2023;84:449-54.
13. Rini BI, Plimack ER, Stus V, et al. ASCO 2023: Pembrolizumab + Axitinib Versus Sunitinib as First-Line Therapy for Advanced Clear Cell RCC: 5-Year Analysis of KEYNOTE-426. Proceedings of the American Society of Clinical Oncology Annual Meeting; 2023 Jun 2-6; Chicago, IL.
14. Cella D, Motzer RJ, Suarez C, et al. Patient-reported outcomes with first-line nivolumab plus cabozantinib versus sunitinib in patients with advanced renal cell carcinoma treated in CheckMate 9ER: an open-label, randomised, phase 3 trial. Lancet Oncol 2022;23:292-303.
15. Choueiri TK, Powles T, Burotto M, et al. Final overall survival analysis and organ-specific target lesion assessments with two-year follow-up in CheckMate 9ER: Nivolumab plus cabozantinib versus sunitinib for patients with advanced renal cell carcinoma. J Clin Oncol 2022;40:abstr 350.
16. Burotto M, Powles T, Escudier B, et al. Nivolumab plus cabozantinib vs sunitinib for first-line treatment of advanced renal cell carcinoma (aRCC): 3-year follow-up from the phase 3 CheckMate 9ER trial. J Clin Oncol 2023;41:abstr 603.
17. Choueiri TK, Powles T, Burotto M, et al. ASCO GU 2024: Nivolumab plus Cabozantinib vs Sunitinib for Previously Untreated Advanced RCC: Results from 55-Month Follow-up of the CheckMate 9ER Trial. Proceedings of the American Society of Clinical Oncology Genitourinary Cancers Symposium; 2024 Feb 8-10; San Francisco, CA.
18. Choueiri TK, Eto M, Motzer R, et al. Lenvatinib plus pembrolizumab versus sunitinib as first-line treatment of patients with advanced renal cell carcinoma (CLEAR): extended follow-up from the phase 3, randomised, open-label study. Lancet Oncol 2023;24:228-38.
19. Motzer RJ, Porta C, Eto M, et al. Lenvatinib Plus Pembrolizumab Versus Sunitinib in First-Line Treatment

of Advanced Renal Cell Carcinoma: Final Prespecified Overall Survival Analysis of CLEAR, a Phase III Study. J Clin Oncol 2024;42:1222-8.
20. Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol 2013;14:141-8.
21. Motzer RJ, Penkov K, Haanen J, et al. ASCO 2024: Avelumab + Axitinib vs Sunitinib in Patients with Advanced Renal Cell Carcinoma: Final Overall Survival Analysis from the JAVELIN Renal 101 Phase 3 Trial. Proceedings of the American Society of Clinical Oncology Annual Meeting; 2024 Jun 2-6; Chicago, IL.
22. Bellesoeur A, Carton E, Alexandre J, et al. Axitinib in the treatment of renal cell carcinoma: design, development, and place in therapy. Drug Des Devel Ther 2017;11:2801-11.

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