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Brief Correspondence

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

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Abstract

Previous analyses of KEYNOTE-426, an open-label, phase 3 randomized study, showed superior efficacy of first-line pembrolizumab plus axitinib to sunitinib in advanced clear cell renal cell carcinoma (ccRCC). We report results of the final protocol-prespecified analysis of KEYNOTE-426. Patients received pembrolizumab 200 mg intravenously every 3 wk plus axitinib 5 mg orally twice daily or sunitinib 50 mg orally once daily (4 wk per 6-wk cycle). The dual primary endpoints were overall survival (OS) and progression-free survival (PFS) as per RECIST v1.1 by a blinded independent central review. The secondary endpoints included objective response rate (ORR) and duration of response (DOR). The median study follow-up was 43 (range, 36–51) mo. Benefit with pembrolizumab plus axitinib versus sunitinib was maintained for OS (hazard ratio [HR], 0.73 [95% confidence interval {CI}, 0.60–0.88]), PFS (HR, 0.68 [95% CI, 0.58–0.80]), and ORR (60% vs 40%). The median DOR was 24 (range, 1.4+ to 43+) versus 15 (range, 2.3–43+) mo in the pembrolizumab plus axitinib versus the sunitinib arm. No new safety signals emerged. These results support pembrolizumab plus axitinib as a standard of care for patients with previously untreated advanced ccRCC.

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Patient summary: Extended results of KEYNOTE-426 support pembrolizumab plus axitinib as the standard of care for advanced clear cell renal cell carcinoma.

Combination treatment with a programmed death 1 (PD-1) inhibitor and a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor is recommended as first-line treatment for patients with advanced clear cell renal cell carcinoma (ccRCC) [1–3]. Pembrolizumab plus axitinib is a standard-of-care option for advanced ccRCC based on the results from the phase 3 KEYNOTE-426 study [1–5]. At the first interim analysis, KEYNOTE-426 met all the primary and key secondary endpoints, with pembrolizumab plus axitinib demonstrating superior overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) to sunitinib [4].

To determine whether the benefit of pembrolizumab plus axitinib is durable, an assessment of long-term clinical outcomes is critically important, particularly following the completion of immunotherapy. A prespecified analysis of the KEYNOTE-426 study was planned when a target of 404 OS events occurred. Herein, we report the efficacy and safety of the final prespecified analysis based on the number of OS events with a median follow-up of 43 mo.

The detailed methodology of KEYNOTE-426 has been published elsewhere [4]. Enrolled patients were randomly assigned 1:1 to receive pembrolizumab 200 mg intravenously every 3 wk for up to 35 cycles plus axitinib 5 mg orally twice daily continuously or sunitinib 50 mg orally once daily for 4 wk on and 2 wk off, continuously. This study was done in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki, and the study protocol was approved by the institutional review boards or ethics committees of all participating sites. All patients provided written informed consent to participate.

The dual primary endpoints were OS and PFS. The secondary endpoints were ORR and duration of response (DOR). A post hoc exploratory analysis of PFS2 was also performed. As per the regulatory guidelines, PFS2 was defined as the time from randomization to progression after the first subsequent therapy or any-cause death, whichever comes first, regardless of subsequent therapy use [6]. For PFS2, patients who had not died and who had not experienced disease progression after subsequent therapy were censored at the time they were last known to be alive or at the initiation of the second subsequent anticancer therapy. Additional post hoc exploratory analyses are described in the Supplementary material. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0.

Per protocol, the current analysis was conducted when the target number of OS events (404 deaths) was reached, which was projected to occur at 43 mo after the start of the study. The statistical analysis methodology is reported in the Supplementary material.

Of 861 enrolled patients, 432 were randomly assigned to pembrolizumab plus axitinib and 429 randomly assigned to sunitinib (Supplementary Fig. 1). As of the data cutoff date of January 11, 2021, the median follow-up, defined as the time from randomization to database cutoff date, was 43 (range, 36–51) mo. Patients' baseline characteristics were generally balanced across treatments (Supplementary Table 1). Most patients in both the combination arm (n = 315; 73%) and the sunitinib arm (n = 331; 77%) had two or more sites of metastases. The most common sites of metastasis in both arms were the lung (combination arm, n = 312 [72%]; sunitinib arm, n = 309 [72%]) and lymph node (combination arm, n = 199 [46%]; sunitinib arm, n = 197 [46%]).

In the combination arm, patients received a median of 20 administrations (range, 1–36) of pembrolizumab and received axitinib for a median of 15 (range, 0.03–48) mo. In the sunitinib arm, patients received sunitinib for a median of 10.4 (range, 0.07–49) mo. At the time of data cutoff, 204 patients in the combination arm and 281 in the sunitinib arm received subsequent therapy at any time following study treatment discontinuation (Supplementary Table 2). Of patients who received subsequent therapy, 169 of 204 patients (83%) in the combination arm received a vascular endothelial growth factor (VEGF)/receptor (VEGFR) inhibitor as their first subsequent therapy, and 154 of 281 patients (55%) in the sunitinib arm received a PD-1/programmed death ligand 1 (PD-L1) inhibitor as their first subsequent therapy (Supplementary Fig. 2A and 2B). Most patients in both arms discontinued treatment because of progressive disease (150/204 [74%] in the combination arm and 192/280 [69%] in the sunitinib arm; Supplementary Table 3).

At 36 mo, the OS rate was 63% in the combination arm and 54% in the sunitinib arm (median: 46 vs 40 mo; hazard ratio [HR], 0.73 [95% confidence interval {CI}, 0.60–0.88]; Fig. 1A). OS adjusted for the use of subsequent therapy is shown in Supplementary Table 4. The median PFS was 16 mo (95% CI, 14–20) with pembrolizumab plus axitinib and 11 mo (95% CI, 8.9–13) with sunitinib (HR 0.68; 95% CI, 0.58–0.80; Fig. 1B). At 36 mo, the PFS rate was 29% in the combination arm and 15% in the sunitinib arm. The median PFS2 was 40 mo (95% CI, 35–44) with pembrolizumab plus axitinib and 28 mo (95% CI, 23–30) with sunitinib (HR 0.63; 95% CI, 0.53–0.75; Fig. 1C).

ORR was 60% (95% CI, 56–65) in the combination arm (43 complete responses [CRs; 10%] and 218 partial responses [PRs; 50%]) compared with 40% (95% CI, 35–44) in the sunitinib arm (15 CRs [3.5%] and 155 PRs [36%]). Of 43 patients with a CR in the pembrolizumab plus axitinib arm, 12 developed progressive disease and two died. Of the 15 patients with a CR in the sunitinib arm, five developed progressive disease. The median DOR was 24 mo (range, 1.4+ to 43+) in the combination arm and 15 mo (range, 2.3–43+) in the sunitinib arm. The estimated percentages of patients with an ongoing response lasting at least 30 mo were 45% in the combination arm and 32% in the sunitinib arm.

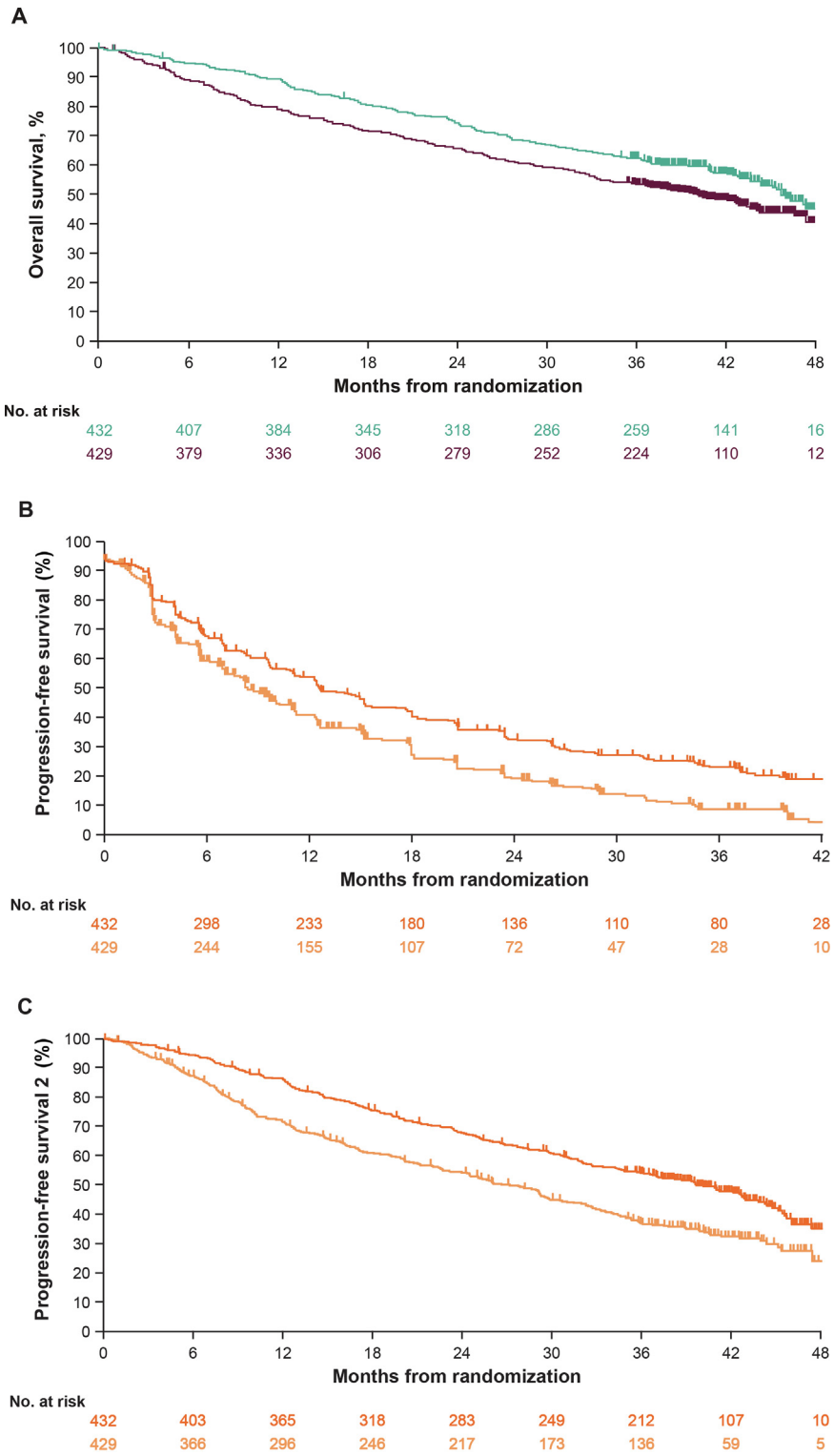

Fig. 1 – Overall survival (OS; primary end point), progression-free survival (PFS; primary end point), and progression-free survival 2 (PFS2; post hoc exploratory endpoint). Kaplan-Meier analysis of (A) OS, (B) PFS, and (C) PFS2 in the ITT population. ITT = intention to treat.

In patients in the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) favorable-risk category (n = 269), the median OS was 47 mo in the combination arm and was not reached in the sunitinib arm (HR, 1.2 [95% CI, 0.76–1.8]; Supplementary Fig. 3A). The median PFS was 21 mo in the combination arm and 18 mo in the sunitinib arm (HR, 0.76 [95% CI, 0.56–1.0]; Supplementary Fig. 3B). The median PFS2 was 46 mo in the combination arm and 39.9 mo in the sunitinib arm (HR, 0.68 [95% CI, 0.47–0.98]; Supplementary Fig. 3C).

In patients in the combined IMDC intermediate/poor-risk category (n = 592), the median OS was 43 mo in the

combination group and 29 mo in the sunitinib group (HR, 0.64 [95% CI, 0.52–0.80]; Supplementary Fig. 4A). The median PFS was 14 mo in the combination arm and 8.2 mo in the sunitinib arm (HR, 0.67 [95% CI, 0.55–0.81]; Supplementary Fig. 4B). The median PFS2 was 32 mo in the combination arm and 20 mo in the sunitinib arm (HR, 0.62 [95% CI, 0.51–0.76]; Supplementary Fig. 4C). Results from other prespecified subgroups were generally consistent with the intention-to-treat population (Supplementary Fig. 5A–C)

The incidence of treatment-related AEs was consistent with that reported in the previous analyses (Supplementary Table 5). Four patients (0.9%) in the combination arm and seven (1.6%) in the sunitinib arm died from treatment-related AEs. No additional treatment-related deaths have been reported in the combination arm since the first interim analysis; one new treatment-related death (grade 5 hepatic failure) was reported in the sunitinib arm. AEs of interest occurred in 246 of 429 treated patients (57%) in the combination arm and in 186 of 425 treated patients (44%) in the sunitinib arm (Supplementary Table 6). Overall, 61 of 429 patients (14%) in the combination arm and four of 425 patients (0.94%) in the sunitinib arm were treated with a high-dose (≥40 mg/d prednisone or equivalent) systemic corticosteroid for AEs of interest.

The results of the current prespecified analysis (based on the number of OS events) of KEYNOTE-426, with a median follow-up of 43 mo, show that the OS, PFS, and ORR benefits of pembrolizumab plus axitinib over sunitinib were maintained in treatment-naive patients with advanced ccRCC. The incidence of treatment-related AEs was similar between the two treatment arms. No new safety signals emerged during this follow-up.

The HR for OS continues to favor pembrolizumab plus axitinib over sunitinib. At the 12-mo follow-up, the HR was 0.53; in the current analysis, the HR was 0.73. The HR in the current analysis was not unexpected and could be related to the use of effective subsequent immunotherapy in the patients treated with sunitinib. Notably, among patients who received subsequent therapy after discontinuing sunitinib, treatment with a checkpoint inhibitor increased from 62% with 14 mo of follow-up to 74% with 43 mo of follow-up [4]. A similar trend was observed in patients with IMDC favorable-risk patients, where the HR increased from 0.64 at 14 mo to 1.2 in this current analysis, which may reflect less precision in the first interim analysis. Patients with favorable risk had a longer time to progression regardless of treatment and were therefore more likely to have access to subsequent checkpoint therapies, as international approvals of immunotherapy occurred later in the course of this study's follow-up period. However, for patients in the combined IMDC intermediate- and poor-risk category, the HR remained at 0.64, suggesting a continued benefit in this subgroup while demonstrating the same reduction from the initial analysis.

PFS remained stable with an HR of 0.69 in the first analysis and 0.68 in the current analysis, suggesting that a relative advantage in disease control in the combination therapy group was maintained over time [4]. As expected, ORR has also remained in favor of pembrolizumab plus axitinib over sunitinib with more CRs and a longer median DOR. The PFS and ORR benefits of the combination continue to be observed across IMDC risk categories, but OS remains similar to sunitinib in the favorable-risk subgroup with extended follow-up. PFS2 was longer for patients in the combination group than for those in the sunitinib group, which is aligned with the OS benefit observed with pembrolizumab plus axitinib.

These results compare favorably with other long-term data from phase 3 trials in advanced renal cell carcinoma treated with immune checkpoint inhibitor–based combinations. Avelumab plus axitinib improved PFS compared with sunitinib (24-mo rate: ∼32% vs ∼25%) in the phase 3 Javelin Renal 101 study, although OS data were immature [7]. The final OS analysis of IMmotion151 for atezolizumab plus bevacizumab showed no difference between atezolizumab plus bevacizumab and sunitinib groups (42-mo rate was ∼40% for both groups) [8]. In the 42-mo update of the phase 3 CheckMate 214 trial, nivolumab plus ipilimumab maintained superior OS over sunitinib (42-mo rate: 52% vs 39%) in patients with intermediate/poor IMDC risk, but not for patients with IMDC favorable risk (42-mo rate: 73% vs 70%) [9].

KEYNOTE-426 was the first study to demonstrate a survival benefit of the combination of a PD-1/PD-L1 checkpoint inhibitor with a VEGF/VEGFR inhibitor in first-line treatment of ccRCC. Other immunotherapy-VEGF inhibitor combinations such as nivolumab plus cabozantinib in the CheckMate 9ER study (PFS HR 0.56 [95% CI 0.46–0.68]; OS HR 0.70 [95% CI 0.55–0.90]) and pembrolizumab plus lenvatinib in the KEYNOTE-581 study (PFS HR 0.39 [95% CI 0.32–0.49]; OS HR 0.66 [95% CI 0.49–0.88]) have also demonstrated clinical benefit in this patient population [2,10,11]. The current analysis of KEYNOTE-426 represents the longest follow-up to date of this combination for first-line ccRCC, and demonstrates sustained and durable clinical benefit.

With a median of 43 mo, durable clinical benefit of pembrolizumab plus axitinib treatment was observed in patients with previously untreated advanced ccRCC. These results further support pembrolizumab plus axitinib as a standard of care for this patient population.

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Data sharing: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants, and as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data-sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be assessed promptly for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved

requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the USA and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor, or construct biomarker covariates and add them to a file with clinical data that are uploaded to an analysis portal so that the requestor can perform the proposed analyses.

Peer Review Summary

Peer Review Summary and Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2023.06.006.

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