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A Matching-adjusted Indirect Comparison of Nivolumab Plus Cabozantinib Versus Pembrolizumab Plus Axitinib in Patients with Advanced Renal Cell Carcinoma

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Abstract

Background: The comparative efficacy and health-related quality of life (HRQoL) outcomes of nivolumab plus cabozantinib versus pembrolizumab plus axitinib as first-line treatments for advanced renal cell carcinoma (aRCC) have not been assessed in head-to-head trials.
Objective: To assess the efficacy and HRQoL outcomes of nivolumab plus cabozantinib versus pembrolizumab plus axitinib.
Design, setting, and participants: Patient-level data for nivolumab plus cabozantinib from the CheckMate 9ER trial and published data for pembrolizumab plus axitinib from the KEYNOTE-426 trial were used. CheckMate 9ER data were reweighted to match the key baseline characteristics as reported in KEYNOTE-426.
Intervention: Nivolumab (240 mg every 2 wk) plus cabozantinib (40 mg once daily) and pembrolizumab (200 mg every 3 wk) plus axitinib (5 mg twice daily, initially).
Outcome measurements and statistical analysis: Hazard ratios (HRs) for progression-free survival (PFS), duration of response, overall survival (OS), and deterioration in HRQoL were

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comparison
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Cabozantinib
Pembrolizumab
Axitinib
Advanced renal cell carcinoma
Progression-free survival
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Health-related quality of life

assessed using weighted Cox proportional-hazard models, with sunitinib as a common anchor. Objective response rates (ORRs) and changes in HRQoL scores from baseline were assessed as difference-in-differences for the two treatments relative to sunitinib.

Results and limitations: After balancing patient characteristics between the trials, nivolumab plus cabozantinib was associated with significantly improved PFS (HR [95% confidence interval {CI}] 0.70 [0.53–0.93]; $p = 0.01$) and a significantly decreased risk of confirmed deterioration in HRQoL (Functional Assessment of Cancer Therapy—Kidney Symptom Index—Disease-related Symptoms: HR [95% CI] 0.48 [0.34–0.69]) versus pembrolizumab plus axitinib. OS was similar between treatments (HR [95% CI] 0.99 [0.67–1.44]; $p = 0.94$). Nivolumab plus cabozantinib was associated with numerically greater ORRs (difference-in-difference [95% CI] 8.4% [−1.7 to 18.4]; $p = 0.10$) and longer duration of response (HR [95% CI] 0.79 [0.47–1.31]; $p = 0.36$) than pembrolizumab plus axitinib. Comparative studies using data with a longer duration of follow-up are warranted.

Conclusions: Nivolumab plus cabozantinib significantly improved PFS and HRQoL compared with pembrolizumab plus axitinib as first-line treatment for aRCC.

Patient summary: This study was conducted to indirectly compare the results of two immunotherapy-based combinations—nivolumab plus cabozantinib versus pembrolizumab plus axitinib—for patients who have not received any treatment for advanced renal cell carcinoma. Patients who received nivolumab plus cabozantinib had a significant improvement in the length of time without worsening of their disease and in their perceived physical and mental health compared with pembrolizumab plus axitinib; patients remained alive for a similar length of time from the start of either treatment. This analysis further adds to our current knowledge of the relative benefits of these two treatment regimens and will help with physician and patient treatment decisions.

1. Introduction

Renal cell carcinoma (RCC) is the most prevalent type of kidney cancer, accounting for approximately 80% of all cases [1] and is often diagnosed at an advanced stage [2]. Previously, sunitinib, a multitarget tyrosine kinase inhibitor (TKI), was one of the most commonly used first-line treatments for advanced RCC (aRCC) [3,4]. However, the efficacy of sunitinib is limited, with a reported objective response rate (ORR) of 25%, median progression-free survival (PFS) of 9.5 mo, and median overall survival (OS) of 29.3 mo [5].

Over the past decade, combination regimens that contain programmed death 1/programmed death ligand 1 immune checkpoint inhibitors (PD-1/PD-L1 ICIs; eg, pembrolizumab, nivolumab, or avelumab) and a TKI (eg, axitinib, cabozantinib, or lenvatinib) have emerged as effective first-line therapies for aRCC across risk groups [6–9]. In 2019, the US Food and Drug Administration (FDA) approved pembrolizumab plus axitinib for patients with untreated aRCC based on the results of the pivotal KEYNOTE-426 trial (NCT02853331), whereby the combination showed significant improvements over sunitinib in OS, PFS, and ORR [10,11]. In 2021, the FDA approved nivolumab plus cabozantinib as first-line treatment for aRCC based on the pivotal CheckMate 9ER trial (NCT03141177), whereby the combination showed significant improvements in OS, PFS, and ORR, as well as a longer duration of response (DoR) versus sunitinib [8].

In addition to clinical efficacy, patients' health-related quality of life (HRQoL) is an important consideration in oncology treatment selection and optimization [12]. In aRCC, HRQoL is often measured using instruments such as the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy—Kidney Cancer Symptom Index (FKSI) [13,14] and the EuroQol Group's EQ-5D [15–18]. In CheckMate 9ER, patients treated with nivolumab plus cabozantinib had a decreased risk of deterioration in FKSI and greater scores for the FKSI disease-related symptom (DRS) subscale at all times than those treated with sunitinib [8]. In KEYNOTE-426, no significant differences were reported in changes from baseline to 30 wk for FKSI-DRS and the three-level version of the EQ-5D (EQ-5D-3L), and in the risk of deterioration for FKSI-DRS and EQ-5D-3L visual analog scale (VAS) among patients treated with pembrolizumab plus axitinib relative to sunitinib [19].

Despite the demonstrated efficacy of nivolumab plus cabozantinib and pembrolizumab plus axitinib relative to sunitinib in their respective trials [8,20], their comparative efficacy and impact on HRQoL have not been evaluated in a head-to-head trial. Matching-adjusted indirect comparison (MAIC) is a method that evaluates the comparative effectiveness of different treatment options while controlling for differences in their trial population, which may help inform treatment decisions [21]. To that end, this study used MAIC with sunitinib as a common anchor point to compare nivolumab plus cabozantinib versus pembrolizumab plus axitinib in terms of clinical efficacy outcomes (PFS, OS, ORR, and DoR) and HRQoL measures (time to deterioration and mean changes from baseline in EQ-5D-3L and FKSI-19 scores) among patients with previously untreated aRCC.

2. Patients and methods

2.1. Data sources

Individual patient data for nivolumab plus cabozantinib and sunitinib from CheckMate 9ER were used in this analysis. To match the timeframe of data reported from KEYNOTE-426, the September 2020 data cut (minimum follow-up, 16 mo; median, 23.5 mo) was used for the MAIC of clinical outcomes, while the earlier March 2020 data cut (minimum follow-up, 10.6 mo; median, 18.1 mo) was used for HRQoL outcomes. Published aggregate data for pembrolizumab plus axitinib and sunitinib were obtained from KEYNOTE-426, using the January 2020 data cut for efficacy outcomes (minimum follow-up, 23.4 mo, median, 30.6 mo) [11] and the August 2018 data cut for HRQoL (median follow-up, 12.8 mo), which are the only available HRQoL data from the trial publication [10] at this time (see the Supplementary material).

2.2. Study outcomes

PFS, ORR, and DoR in both trials were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (v1.1) with evaluations conducted via a blinded independent central review [8,11]. PFS, OS, and ORR were assessed in the intent-to-treat populations; DoR was assessed only among patients achieving an objective response. Survival data for PFS, OS, and DoR in KEYNOTE-426 [11] were reconstructed based on published survival curves using the method of Guyot et al [22] .

Since only the subscales EQ-5D-3L VAS and FKSI-DRS were reported in KEYNOTE-426, these HRQoL measures from comparable time points of week 31 for CheckMate 9ER and week 30 for KEYNOTE-426 were analyzed in this study. In both trials, a deterioration event was defined as a 7-point decrease from baseline in the EQ-5D-3L VAS score and a 3-point decrease from baseline in the FKSI-DRS score [14,23]. Time to first deterioration (TTFD) was defined as the time from the date of randomization to the date of the first deterioration event. Time to confirmed deterioration (TTCD) was defined as the time from the date of randomization to the date of the first deterioration event, which was also subsequently confirmed at the next consecutive visit [8,19]. TTFD for EQ-5D-3L VAS scores, TTCD for EQ-5D-3L VAS, TTCD for FKSI-DRS, and changes in EQ-5D-3L VAS and FKSI-DRS scores from baseline to week 30/31 were evaluated. TTFD for FKSI-DRS was not reported in KEYNOTE-426 and therefore not assessed (see the Supplementary material).

2.3. Statistical analysis

Baseline characteristics that were adjusted in the MAIC were selected based on the common baseline characteristics and evidence for potential treatment effect modifiers [24]. Treatment effect modifiers were evaluated and selected separately for efficacy outcomes and for different HRQoL measures, as the modification status may differ by outcome type (see the Supplementary material).

After weighting, baseline characteristics and outcomes were compared between trial populations using weighted Wald tests [25,26] for continuous and categorical variables. The Nelson-Aalen estimator was used to derive PFS, OS, and DoR curves. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) and p values of PFS, OS, and DoR for nivolumab plus cabozantinib versus sunitinib and pembrolizumab plus axitinib versus sunitinib were estimated using weighted Cox proportional-hazard models. To derive the relative effect between nivolumab plus cabozantinib and pembrolizumab plus axitinib, HRs of PFS, OS, and DoR were examined using the method of Bucher et al [27] as the ratio of the weighted HR of nivolumab plus cabozantinib versus sunitinib to the reported HR of pembrolizumab plus axitinib versus sunitinib. ORR was evaluated as the difference in the weighted risk difference between nivolumab plus cabozantinib and sunitinib, and the risk difference between pembrolizumab plus axitinib and sunitinib.

TTCD for EQ-5D-3L VAS and FKSI-DRS and TTFD for EQ-5D-3L VAS were modeled using weighted Cox proportional-hazard models. Average changes from baseline to week 30/31 in EQ-5D-3L VAS and FKSI-DRS scores were estimated using least-square mean difference (LSMD) obtained from a mixed model for repeated measures in the weighted trial population. Similar to the efficacy outcomes, HRs and LSMDs were compared between nivolumab plus cabozantinib and pembrolizumab plus axitinib based on the method of Bucher et al [27] using sunitinib as a common anchor point. All statistical assessments were two tailed; $p < 0.05$ was considered statistically significant. No adjustments were made for multiple comparisons.

3. Results

3.1. Patient characteristics

The trials included patients with similar distributions in age, sex, and metastasis in the lung and bone. The nivolumab plus cabozantinib arm had a significantly lower proportion of patients with previous nephrectomy and favorable International Metastatic Renal Cell Carcinoma Database Consortium risk scores, and a significantly higher proportion with metastasis in liver versus the pembrolizumab plus axitinib arm. After weighting, patient characteristics were well matched between trials. The effective sample size [24,28] of the reweighted CheckMate 9ER population was 529 (269 for nivolumab plus cabozantinib and 260 for sunitinib) for clinical efficacy outcomes and ranged from 557 to 582 for HRQoL outcomes (Supplementary Tables 2 and 3).

3.2. Progression-free survival

The before-weighting PFS results are shown in Figure 1A. In the weighted population, the median (95% CI) PFS for nivolumab plus cabozantinib (19.3 [15.2–22.4] mo) was numerically longer than for pembrolizumab plus axitinib (15.7 [13.7–20.6] mo). Using sunitinib as an anchor (median [95% CI] PFS: CheckMate 9ER, 8.9 [7.1–10.4] mo; KEYNOTE-426, 11.0 [9.4–12.7] mo), nivolumab plus cabozantinib was associated with a significantly lower risk of progression or death versus pembrolizumab plus axitinib (HR [95% CI] 0.70 [0.53–0.93]; $p = 0.01$; Fig. 1B).

3.3. Overall survival

The median OS was not reached for either nivolumab plus cabozantinib or pembrolizumab plus axitinib, regardless of weighting (Fig. 2). After weighting, the observed OS was similar in the anchor-based comparison between nivolumab plus cabozantinib and pembrolizumab plus axitinib (HR [95% CI] 0.99 [0.67–1.44]; $p = 0.94$).

3.4. Objective response rate

The before-weighting ORR results are shown in Figure 3A. After weighting, the difference in ORR between nivolumab plus cabozantinib and sunitinib (ORR [95% CI] 28.7% [21.0–36.4]; $p < 0.01$) was larger than that between pem-

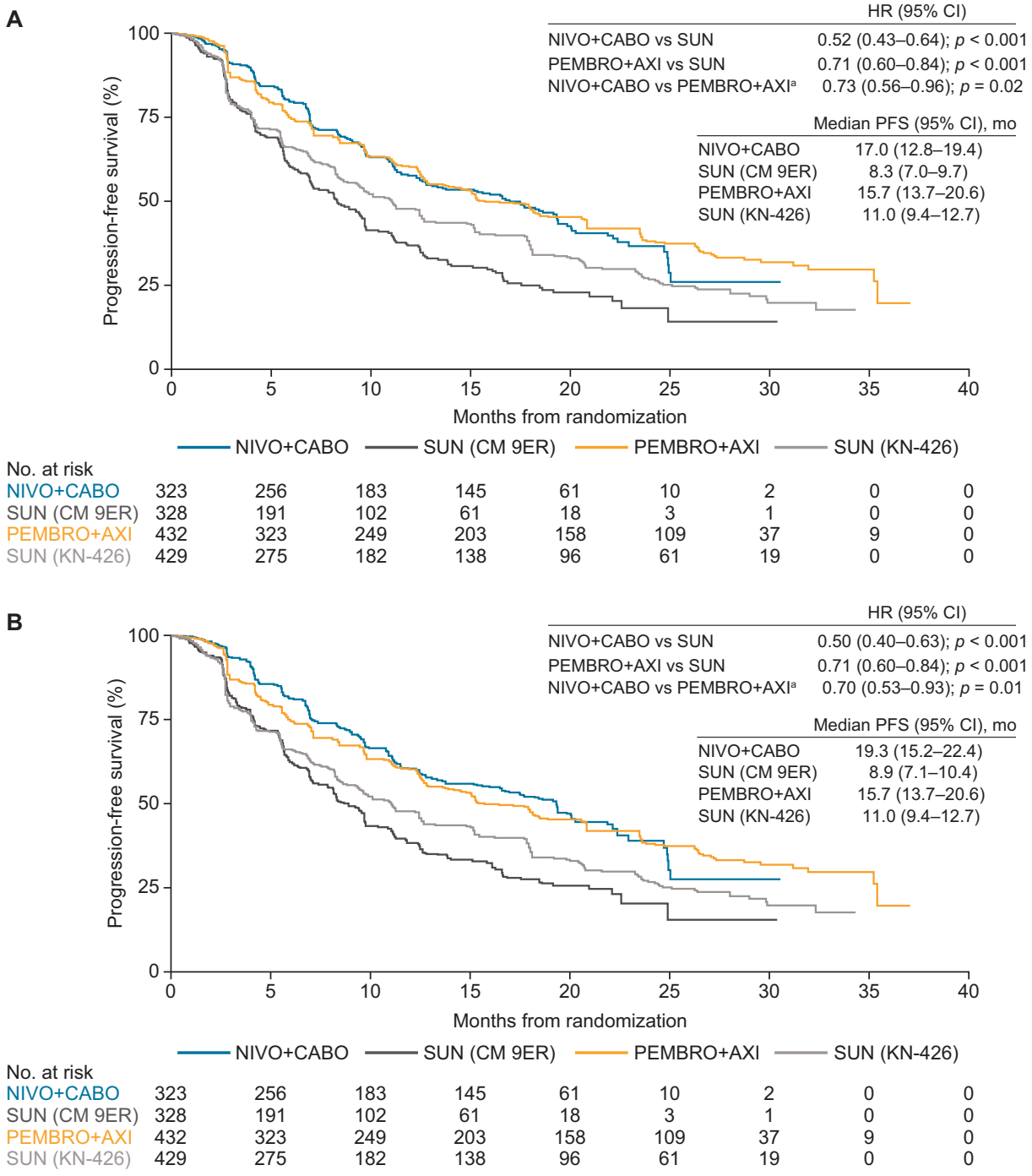

Fig. 1 – PFS for nivolumab plus cabozantinib versus pembrolizumab plus axitinib (A) before and (B) after weighting using an anchor-based MAIC. CI = confidence interval; CM = CheckMate; HR = hazard ratio; KN = KEYNOTE; MAIC = matching-adjusted indirect comparison; NIVO + CABO = nivolumab plus cabozantinib; PEMBRO + AXI = pembrolizumab plus axitinib; PFS = progression-free survival; SUN = sunitinib. [a] The HR of NIVO + CABO versus PEMBRO + AXI was estimated using an anchor-based comparison and was calculated as the HR of NIVO + CABO versus SUN (CheckMate 9ER) divided by the HR of PEMBRO + AXI versus SUN (KEYNOTE-426).

brolizumab plus axitinib and sunitinib (20.3% [13.8–26.9]; $p < 0.01$), driven by a relatively higher ORR rate for sunitinib in KEYNOTE-426 (39.9%) than in CheckMate 9ER (30.6%). Using sunitinib as an anchor, nivolumab plus cabozantinib was associated with a numerically larger improvement in ORR than pembrolizumab plus axitinib (difference-in-difference [95% CI], 8.4% [−1.7 to 18.4]; $p = 0.10$; Fig. 3B).

3.5. *Duration of response*

The before-weighting DoR results are shown in Figure 4A. After weighting, the median DoR (95% CI) was 22.0 (20.2–not reached) mo for nivolumab plus cabozantinib and 13.3 (11.1–not reached) mo for sunitinib (HR [95% CI] 0.55 [0.35–0.85]; $p < 0.01$). In KEYNOTE-426, the median DoR

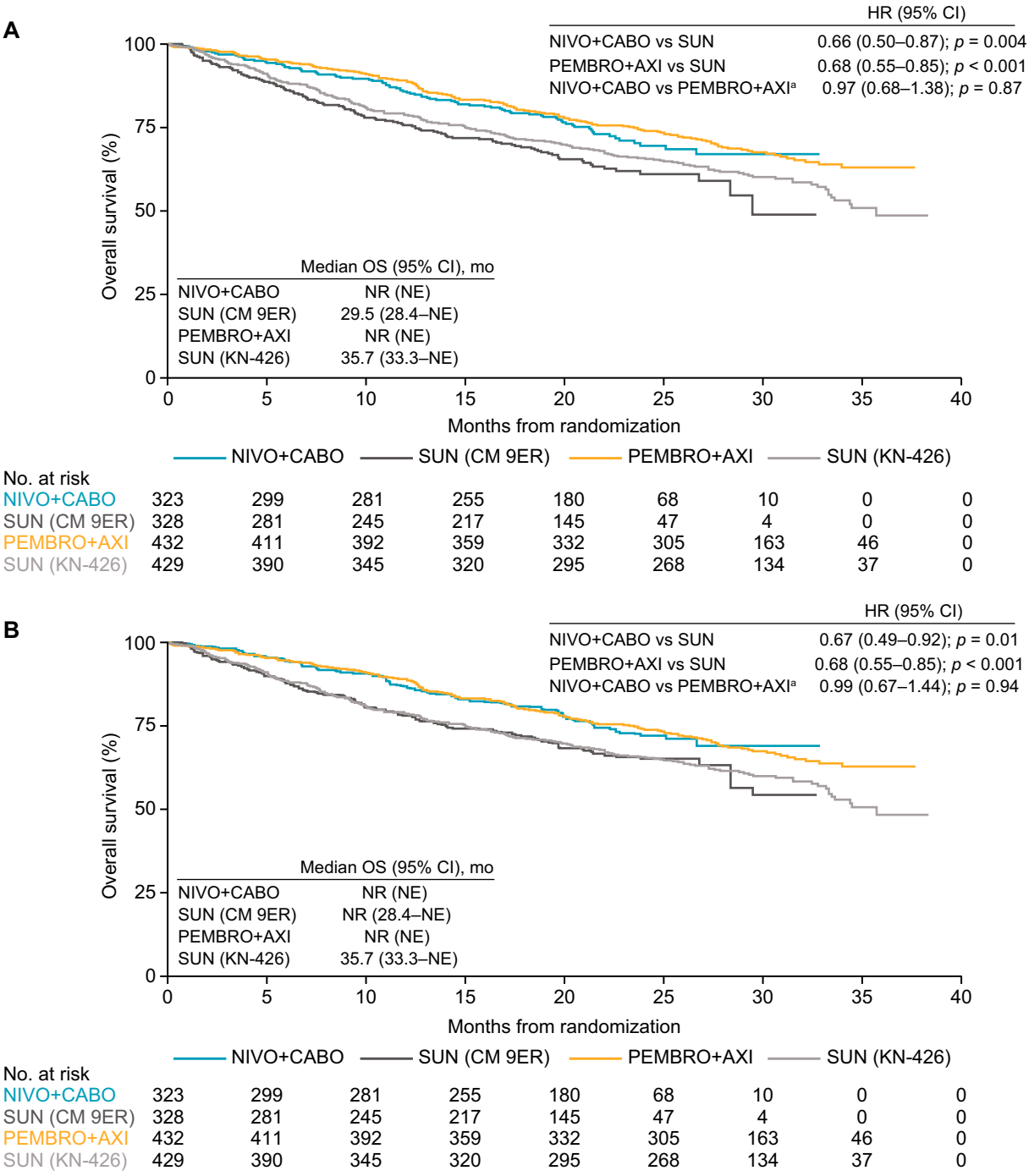

Fig. 2 – OS for nivolumab plus cabozantinib versus pembrolizumab plus axitinib (A) before and (B) after weighting using an anchor-based MAIC. CI = confidence interval; CM = CheckMate; HR = hazard ratio; KN = KEYNOTE; MAIC = matching-adjusted indirect comparison; NE = not estimable; NIVO + CABO = nivolumab plus cabozantinib; NR = not reached; OS = overall survival; PEMBRO + AXI = pembrolizumab plus axitinib; SUN = sunitinib. [a] The HR of NIVO + CABO versus PEMBRO + AXI was estimated using an anchor-based comparison and was calculated as the HR of NIVO + CABO versus SUN (CheckMate 9ER) divided by the HR of PEMBRO + AXI versus SUN (KEYNOTE-426).

(95% CI) was 23.6 (20.6–29.0) mo for pembrolizumab plus axitinib and 16.0 (13.6–19.8) mo for sunitinib, with a HR of 0.70 (95% CI, 0.53–0.92; $p = 0.01$). Using sunitinib as an anchor, nivolumab plus cabozantinib was associated with a numerical, although not statistically significant, improvement in DoR versus pembrolizumab plus axitinib (HR [95% CI] 0.79 [0.47-1.31]; $p = 0.36$; Fig. 4B).

3.6. Time to deterioration in EQ-5D-3L VAS and FKSI-DRS scores

After weighting, the HR (95% CI) for nivolumab plus cabozantinib versus sunitinib was 0.74 (0.59–0.93) for TTFD, 0.81 (0.62–1.05) for TTCD for EQ-5D-3L VAS, and 0.69 (0.53–0.91) for TTCD for FKSI-DRS. Compared with

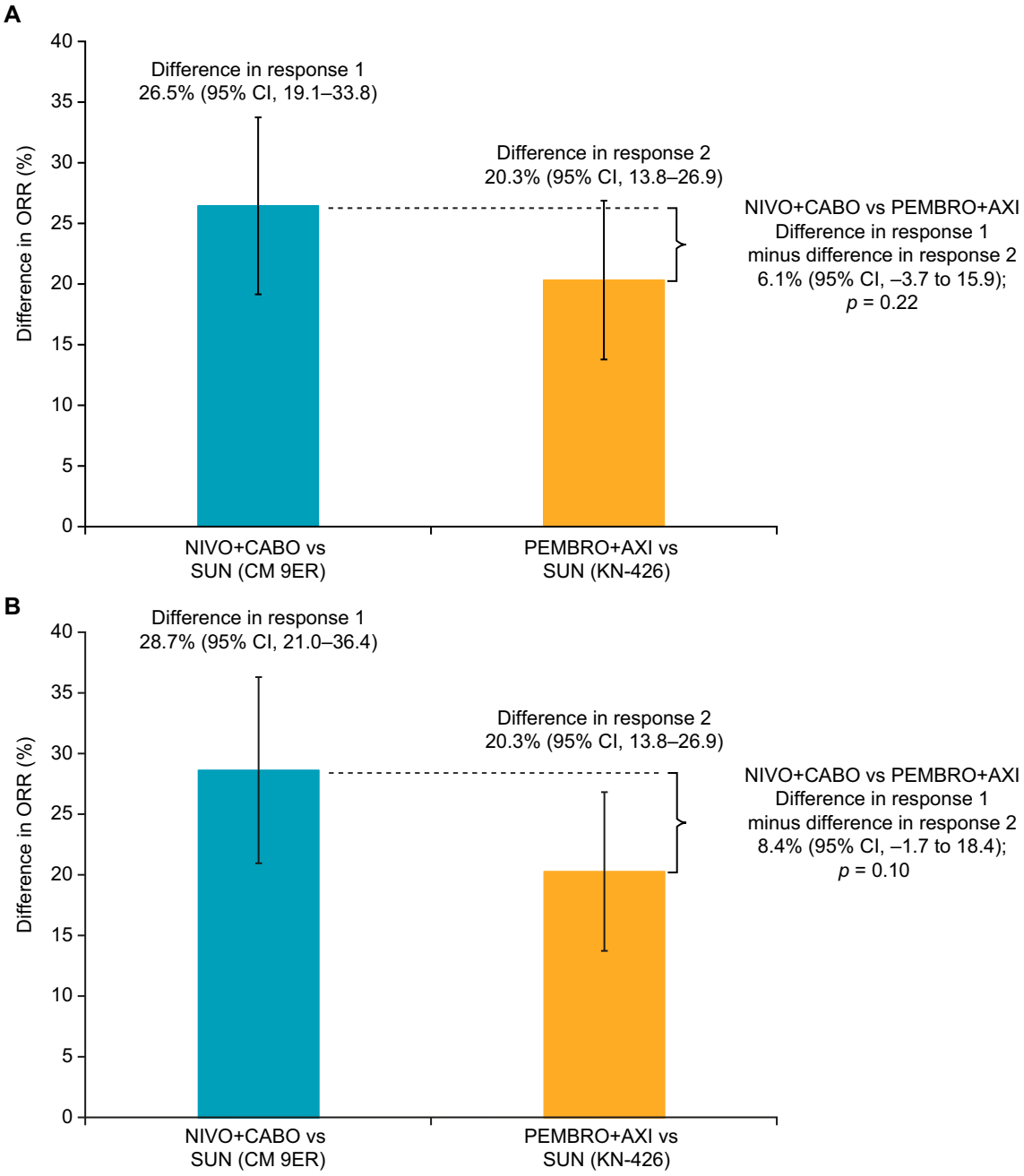

Fig. 3 – ORR for nivolumab plus cabozantinib versus pembrolizumab plus axitinib (A) before and (B) after weighting using an anchor-based MAIC. CI = confidence interval; CM = CheckMate; KN = KEYNOTE; MAIC = matching-adjusted indirect comparison; NIVO + CABO = nivolumab plus cabozantinib; ORR = objective response rate; PEMBRO + AXI = pembrolizumab plus axitinib; SUN = sunitinib.

pembrolizumab plus axitinib, nivolumab plus cabozantinib was associated with a significantly lower risk of first deterioration in EQ-5D-3L VAS (HR [95% CI] 0.73 [0.55–0.96]) and confirmed deterioration in FKSI-DRS (0.48 [0.33–0.69]), and with a numerically, although not statistically significant, lower risk of confirmed deterioration in EQ-5D-3L VAS (0.72 [0.52–1.01]; Table 1).

3.7. Change from baseline to week 30/31 in EQ-5D-3L VAS and FKSI-DRS scores

After weighting, the difference (95% CI) in changes from baseline to week 30/31 for nivolumab plus cabozantinib versus sunitinib was 1.15 (–1.19 to 3.50) for EQ-5D-3L VAS and 1.35 (0.70–2.00) for FKSI-DRS. Compared with pembrolizumab plus axitinib using sunitinib as an anchor, nivolumab plus cabozantinib was associated with a significant improvement in FKSI-DRS score (LSMD [95% CI] 1.85 [0.96–2.74]) and numerically greater changes in EQ-5D-3L VAS score (LSMD [95% CI] 2.55 [–0.88 to 5.98]; Table 1).

4. Discussion

This analysis fills an important knowledge gap by using MAIC to balance the heterogeneities between patients in

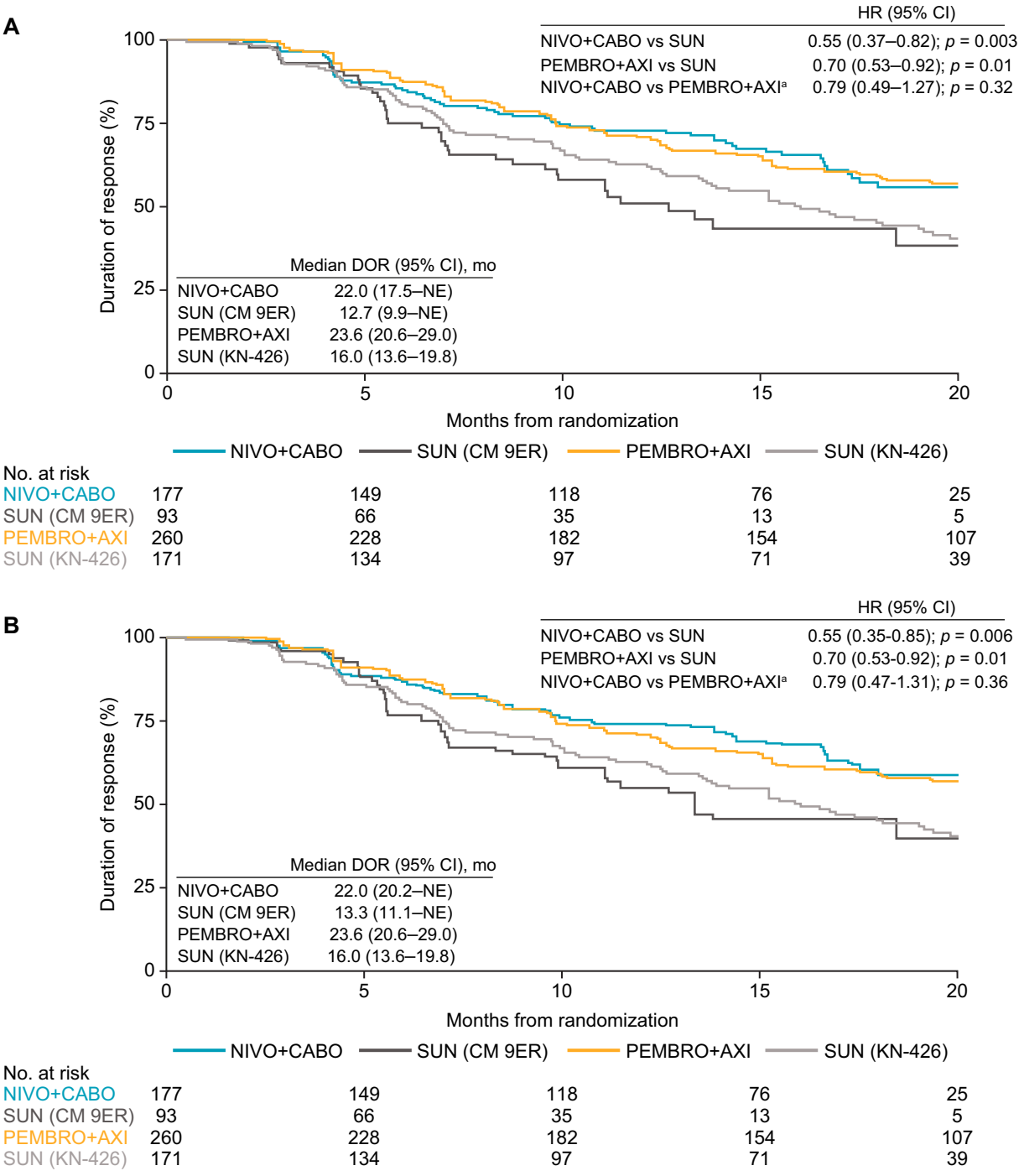

Fig. 4 – DoR for nivolumab plus cabozantinib versus pembrolizumab plus axitinib (A) before and (B) after weighting using an anchor-based MAIC. CI = confidence interval; CM = CheckMate; DoR = duration of response; HR = hazard ratio; KN = KEYNOTE; MAIC = matching-adjusted indirect comparison; NE = not estimable; NIVO + CABO = nivolumab plus cabozantinib; PEMBRO + AXI = pembrolizumab plus axitinib; SUN = sunitinib. [a] The HR of NIVO + CABO versus PEMBRO + AXI was estimated using an anchor-based comparison and was calculated as the HR of NIVO + CABO versus SUN (CheckMate 9ER) divided by the HR of PEMBRO + AXI versus SUN (KEYNOTE-426).

the pivotal CheckMate 9ER and KEYNOTE-426 trials to estimate the comparative efficacy of these regimens as well as their impact on HRQoL. After adjusting for cross-trial differences using sunitinib as an anchor, nivolumab plus cabozantinib was associated with significantly prolonged PFS versus pembrolizumab plus axitinib. Patients treated with nivolumab plus cabozantinib also had a significantly lower risk of confirmed deterioration in FKSI-DRS and first deterioration in EQ-5D-3L VAS scores versus pembrolizumab plus axitinib.

The favorable efficacy profile of nivolumab plus cabozantinib relative to pembrolizumab plus axitinib in terms of significantly prolonged PFS and numerically improved ORR did not translate into OS benefits over the timeframe of the analysis. This may be attributable to OS being confounded by subsequent treatments (eg, crossover patients

Table 1 – HRQoL before and after weighting in the anchor-based MAIC of nivolumab plus cabozantinib versus pembrolizumab plus axitinib

Health-related quality of life	CheckMate 9ER		KEYNOTE-426	NIVO + CABO vs PEMBRO + AXI
	Before weighting	After weighting		
	NIVO + CABO vs SUN	NIVO + CABO vs SUN	PEMBRO + AXI vs SUN	
Time to deterioration				
TTFD EQ-5D-3L VAS, HR (95% CI)	0.71 (0.56–0.89)	0.74 (0.59–0.93)	1.02 (0.86–1.20)	0.73 (0.55–0.96)
TTCD EQ-5D-3L VAS, HR (95% CI)	0.71 (0.55–0.94)	0.81 (0.62–1.05)	1.12 (0.91–1.38)	0.72 (0.52–1.01)
TTCD FKSI-DRS, HR (95% CI)	0.62 (0.46–0.82)	0.69 (0.53–0.91)	1.44 (1.14–1.82)	0.48 (0.33–0.69)
Change from baseline to week 30/31				
EQ-5D-3L VAS, LSMD (95% CI)	1.54 (−0.89 to 3.97)	1.15 (−1.19 to 3.50)	−1.40 (−3.90 to 1.10)	2.55 (−0.88 to 5.98)
FKSI-DRS, LSMD (95% CI)	1.64 (0.98–2.31)	1.35 (0.70–2.00)	−0.50 (−1.10 to 0.10)	1.85 (0.96–2.74)

CI = confidence interval; EQ-5D-3L VAS = EuroQol-5 dimension 3 level visual analog scale; FKSI-DRS = Functional Assessment of Cancer Therapy—Kidney Cancer Symptom Index—Disease-related Symptoms; HR = hazard ratio; HRQoL = health-related quality of life; LSMD = least-square mean difference; MAIC = matching-adjusted indirect comparison; NIVO + CABO = nivolumab plus cabozantinib; PEMBRO + AXI = pembrolizumab plus axitinib; SUN = sunitinib; TTCD = time to confirmed deterioration; TTFD = time to first deterioration.
This study used the same analytical approaches used in the CheckMate 9ER and KEYNOTE-426 trials for HRQoL outcomes. Specifically, longitudinal mean changes from baseline were analyzed using a mixed model for repeated measures, and time to deterioration was analyzed using Kaplan-Meier estimates and a Cox proportional-hazard model to estimate HRs.

from the respective sunitinib control arms). Notably, a higher proportion of patients initiated subsequent treatments in KEYNOTE-426 (pembrolizumab plus axitinib, 39.4%; sunitinib, 56.4%) than in CheckMate 9ER (nivolumab plus cabozantinib, 26.0%; sunitinib, 39.0%) [8,10]. In addition, CheckMate 9ER had less mature OS data with shorter follow-up time than KEYNOTE-426; in both trials, the median OS had not been reached based on the available length of follow-up used in this analysis.

In CheckMate 9ER, patients treated with nivolumab plus cabozantinib also experienced improvements in their well-being as assessed via the FKSI-19 and the EQ-5D-3L instruments compared with sunitinib [8]. By contrast, KEYNOTE-426 demonstrated that patients receiving pembrolizumab plus axitinib only had similar (eg, continuous change in FKSI-DRS scores) or worse (eg, time to deterioration in FKSI-DRS) HRQoL measures versus sunitinib [19,29]. Our MAIC demonstrated that nivolumab plus cabozantinib has an advantage in FKSI-DRS and EQ-5D-3L VAS versus pembrolizumab plus axitinib after weighting for trial differences. The favorable HRQoL associated with nivolumab plus cabozantinib observed in our study may reflect the improved efficacy outcomes, such as PFS. This may also be attributable to an advantageous safety profile, as demonstrated in a study by McGregor et al [30], whereby nivolumab plus cabozantinib was associated with lower all-cause and treatment-related grade 3/4 adverse event rates than pembrolizumab plus axitinib. As the potential risk for toxicity may offset the benefit of improved survival and HRQoL outcomes, the findings should be considered carefully in the clinical management of aRCC [20].

This study is subject to certain limitations that are inherent to indirect comparisons. First, unmeasured or unadjusted cross-trial differences in baseline characteristics may have affected the estimated relative efficacy, and the estimates could have been impacted in both directions. Second, despite the covariate adjustment, the sunitinib arm from CheckMate 9ER had worse PFS and ORR outcomes than the sunitinib arm from KEYNOTE-426, which may be related to uncontrolled or unobserved differences between the two sunitinib arms (eg, PD-L1 level). However, since all known potential treatment effect modifiers were included in the MAIC and the anchor-based comparisons help account for the differences, this is not expected to affect the validity of results. Third, compared with KEYNOTE-426, data from CheckMate 9ER had a shorter follow-up time when this analysis was conducted and therefore might not be mature enough to assess any long-term OS differences between the two treatments. Comparative studies using data with a longer duration of follow-up are warranted. However, the relatively short follow-up time may not affect the results of ORR substantially as the median time to response is 2.8 mo for both treatments. A fourth limitation is that the reduction in the effective sample size after matching may have affected the statistical power to detect significance, specifically in HRQoL outcomes, which was an exploratory endpoint in CheckMate 9ER. Fifth, the collection of HRQoL data after the 2-wk treatment-free period in each sunitinib cycle could have resulted in an underestimation of the impact on HRQoL among patients receiving sunitinib in CheckMate 9ER. Sixth, the generalizability of the results may be limited due to potential differences (eg, different distributions in patient age and disease severity) among patients enrolled in clinical trials relative to patients with aRCC in the real world. Additionally, in this rapidly evolving therapeutic area, novel treatments have continued to emerge during the conduct of this study, including the combination of pembrolizumab and lenvatinib (approved by the FDA in August 2021 as a first-line treatment for aRCC). Future studies, including a separate MAIC comparing nivolumab plus cabozantinib versus pembrolizumab plus lenvatinib and/or a network meta-analysis assessing the comparative efficacy of all novel aRCC treatments, are warranted.

5. Conclusions

This study provided important insights by indirectly comparing clinical outcomes and HRQoL among patients with aRCC treated with nivolumab plus cabozantinib versus pembrolizumab plus axitinib, while adjusting for differences between the trials and their populations. Results from the MAIC using sunitinib as an anchor suggest that nivolumab plus cabozantinib had a more favorable efficacy profile in terms of significantly prolonged PFS and numerically

improved ORR, and a significant advantage in important HRQoL outcomes versus pembrolizumab plus axitinib in patients with previously untreated aRCC.

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Analysis and interpretation of data: McGregor, Geynisman, Burotto, Suárez, Bourlon, Barata, Gulati, Huo, Ejzykowicz, Blum, Del Tejo, Hamilton, May, Du, Wu, Kral, Ivanescu, Chin, Betts, Lee, Choueiri, Cella, Porta.
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Appendix A. Supplementary data

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