

ORIGINAL ARTICLE

## Final analysis of nivolumab plus cabozantinib for advanced renal cell carcinoma from the randomized phase III CheckMate 9ER trial<sup>☆</sup>

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**Background:** Nivolumab plus cabozantinib (NIVO+CABO) showed significant benefits over sunitinib (SUN) in progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) for previously untreated advanced renal cell carcinoma (RCC) in the phase III CheckMate 9ER trial (NCT03141177). We report final, updated efficacy and safety results with median follow-up of 5.6 years.

**Patients and methods:** Patients with advanced RCC were randomized to first-line NIVO 240 mg intravenously every 2 weeks plus CABO 40 mg p.o. o.d. or SUN 50 mg p.o. o.d. (4 weeks each 6-week cycle) until disease progression or unacceptable toxicity (maximum 2 years of NIVO). The primary endpoint was PFS per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints included OS, ORR per RECIST v1.1 by BICR, and safety.

**Results:** Median (range) follow-up was 5.6 years [67.6 (60.2-80.2) months]. In intent-to-treat patients (NIVO+CABO,  $n = 323$ ; SUN,  $n = 328$ ), PFS favored NIVO+CABO versus SUN [hazard ratio (HR) 0.58, 95% confidence interval (CI) 0.49-0.70]. Median PFS was 16.4 versus 8.3 months, respectively; 60-month PFS rates were 13.6% versus 3.6%. OS favored NIVO+CABO versus SUN (HR 0.79, 95% CI 0.65-0.96). Median OS was 46.5 versus 35.5 months, respectively; 60-month OS rates were 40.9% versus 35.4%. ORR was greater with NIVO+CABO versus SUN (55.7% versus 27.4%; complete response 13.9% versus 4.6%). The probability of remaining in response through 60 months with NIVO+CABO versus SUN was 22.0% versus 10.0%. In all treated patients ( $n = 320$  each arm), any-grade (grade 3-4) treatment-related adverse events occurred in 97.5% (67.8%) versus 93.1% (55.0%) with NIVO+CABO versus SUN, respectively. No new deaths due to study drug toxicity occurred since the 32.9-month median follow-up.

**Conclusions:** Long-term efficacy benefit was observed with NIVO+CABO over SUN in this final follow-up from CheckMate 9ER and safety was consistent with previous reports. These results reaffirm NIVO+CABO as a standard of care for previously untreated advanced RCC.

**Key words:** cabozantinib, immunotherapy, nivolumab, phase III, previously untreated advanced renal cell carcinoma

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## INTRODUCTION

First-line treatment options for patients with advanced renal cell carcinoma (RCC) have been expanded with the combination of an immune checkpoint inhibitor (ICI) and vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI).<sup>1-3</sup> Nivolumab (NIVO; a programmed death 1 [PD-1] inhibitor) combined with cabozantinib (CABO; a multitargeted TKI of VEGFRs, MET, and AXL, among others) is an approved standard of care for first-line treatment of previously untreated advanced RCC, based on results from the phase III CheckMate 9ER trial.<sup>1-6</sup>

In the primary analysis of the CheckMate 9ER trial (median follow-up, 18.1 months), NIVO+CABO showed superior efficacy versus sunitinib (SUN) for patients with previously untreated advanced or metastatic RCC.<sup>6</sup> NIVO+CABO showed significant benefits in progression-free survival (PFS) per blinded independent central review [BICR; median 16.6 versus 8.3 months; hazard ratio (HR) 0.51, 95% confidence interval (CI) 0.41-0.64,  $P < 0.001$ ], overall survival (OS; medians not reached; HR 0.60, 98.89% CI 0.40-0.89,  $P = 0.001$ ); and objective response rate (ORR) per BICR 55.7% versus 27.1%,  $P < 0.001$ .<sup>6</sup> The safety profile was consistent with the previous studies of NIVO and CABO as monotherapies and in combination.<sup>6,7</sup> With extended follow-ups, NIVO+CABO maintained survival and response benefits versus SUN, supporting the primary efficacy and safety results.<sup>8,9</sup>

We report the final efficacy and safety results of the CheckMate 9ER trial with a long-term median follow-up of 67.6 months (5.6 years). We also report exploratory subgroup analyses of efficacy by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk category and by baseline organ site of metastases.

## METHODS

### Study design and patients

Details of the study design, eligibility criteria, randomization, endpoints, and statistical analysis have been published in detail previously, along with the CheckMate 9ER protocol and statistical analysis plan.<sup>6,8,9</sup> Briefly, CheckMate 9ER was an open-label, randomized, phase III trial conducted at 125 hospitals and cancer centers in 18 countries. Eligible patients were  $\geq 18$  years old with histologically confirmed advanced/metastatic RCC with a clear cell component, no prior systemic therapy for RCC (one prior adjuvant or neoadjuvant therapy for completely resectable RCC was allowed), measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST; investigator-assessed), Karnofsky performance status of  $\geq 70\%$ , and any IMDC prognostic risk category.<sup>6,8,9</sup>

Patients were randomized 1 : 1 to receive either NIVO 240 mg administered intravenously every 2 weeks plus CABO 40 mg administered orally once daily, or SUN 50 mg administered orally once daily for 4 weeks of every 6-week cycle. Treatment continued until disease progression or

unacceptable toxicity, with a maximum 2 years of NIVO treatment. Patients were stratified by IMDC prognostic risk score (0 versus 1-2 versus 3-6), geographic region (Canada, Europe, and the USA versus the rest of the world), and tumor programmed death-ligand 1 (PD-L1) expression ( $\geq 1\%$  versus  $< 1\%$  or indeterminate).<sup>6,8,9</sup>

Dose reductions were permitted for CABO and SUN, but not for NIVO. Dose delays due to adverse events (AEs) were permitted for all study drugs.<sup>6,8,9</sup>

CheckMate 9ER was conducted by health care professionals and researchers without direct input from patient or public representatives regarding the design, conduct, or reporting of the study.

The CheckMate 9ER trial was approved by an institutional review board or independent ethics committee at each site. The study was conducted in accordance with Good Clinical Practice guidelines as defined by the International Council on Harmonisation and in accordance with the ethical principles underlying European Union Directive 2001/20/EC, the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50), and the ethical principles based on the Declaration of Helsinki. All patients provided written informed consent. An independent data monitoring committee provided oversight of efficacy, safety, and study conduct.<sup>6,8,9</sup> The study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03141177; <https://clinicaltrials.gov/study/NCT03141177>) on 3 May 2017.

### Endpoints and assessments

The primary endpoint was PFS per RECIST version 1.1 by BICR (defined as the time between the randomization date and the first date of documented disease progression, or death due to any cause, whichever occurred first). Secondary endpoints included OS (defined as the time between the randomization date and the date of death due to any cause), ORR per RECIST version 1.1 by BICR [defined as the proportion of randomized patients who had a best response of confirmed complete response (CR) or confirmed partial response (PR); including time to and duration of response (DOR)]. Time to response was defined as the time from randomization to the date of the first confirmed documented response (CR or PR) by BICR. DOR was defined as the time between the date of first confirmed documented response (CR or PR) to the date of the first documented tumor progression per RECIST version 1.1 by BICR, or death due to any cause, whichever occurred first. Safety and tolerability were other secondary endpoints.<sup>6,8,9</sup>

AEs were assessed according to the Medical Dictionary for Regulatory Activities (version 27.0; to assign the system organ classification and preferred term) and the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0; to assign the grade of severity) and are reported between first dose and 30 days after the last dose of study therapy.<sup>6,8,9</sup>

Immune-mediated AEs were events occurring within 100 days of the last dose of study drug regardless of causality, with no clear alternate etiology (per investigator assessment) or had an immune-mediated component and was treated with immune-modulating medication. The use of corticosteroids ( $\geq 40$  mg prednisone daily or equivalent) to manage immune-mediated AEs was also reported.<sup>6,8,9</sup>

An exploratory analysis of depth of response categories based on confirmed objective response per BICR over the course of the study was evaluated post hoc. PRs were categorized as being either PR with  $\geq 60\%$  tumor reduction (i.e. best percentage reduction in the sum of diameters for target lesions by  $\geq 60\%$  up to  $< 100\%$ ), or PR with  $< 60\%$  tumor reduction (i.e. PR with best percentage reduction in the sum of diameters for target lesions by  $\geq 30\%$  and  $< 60\%$ ). Additional analyses of efficacy outcomes by baseline IMDC prognostic risk group (prespecified) and by baseline organ sites of metastases (prespecified for bone; post hoc for liver and lung) were conducted in the intent-to-treat (ITT) population. Within each organ sites of metastases subgroup, all patients had metastasis within the specified site but may have had lesions in more than one site. We also conducted a post hoc exploratory analysis of the occurrence over time of grade 3-4 treatment-related AEs of clinical interest by system organ class in treated patients.

Additional details are provided in the [Supplementary Methods](https://doi.org/10.1016/j.annonc.2025.09.006), available at <https://doi.org/10.1016/j.annonc.2025.09.006>.

### Statistical analysis

Full details of protocol-prespecified statistical analyses and hierarchical testing for the primary and secondary endpoints have been reported previously.<sup>6,8</sup> All analyses are descriptive and exploratory in this report. PFS, OS, DOR, and time to treatment discontinuation were estimated using Kaplan–Meier methods.<sup>10</sup> PFS, OS, and DOR rates at fixed timepoints are presented. A stratified Cox proportional hazards model, using randomization stratification factors, was used for between-treatment arm comparisons of PFS and OS in the ITT population, along with two-sided 95% CIs. An unstratified Cox proportional hazards model was used for between-treatment arm comparisons of PFS and OS in IMDC risk groups and subgroups based on organ site of metastases at baseline, along with two-sided 95% CIs. For ORR, the exact two-sided 95% CIs were computed using the Clopper–Pearson method.<sup>11</sup>

Efficacy endpoints were assessed in the ITT population (all randomized patients), by IMDC risk group, and in subgroups based on organ site of metastases at baseline. Exposure, safety, and tolerability were assessed in all treated patients (patients who received at least one dose of any study drug). Subsequent systemic anticancer therapy was assessed in all treated patients who discontinued study therapy.

A post hoc analysis of time to subsequent systemic therapy (defined as the time from the last dose of study

treatment to the start of subsequent systemic therapy or death) in patients treated with NIVO+CABO and SUN, and in patients who completed the per-protocol 2 years of NIVO treatment, was also carried out using Kaplan–Meier methods.

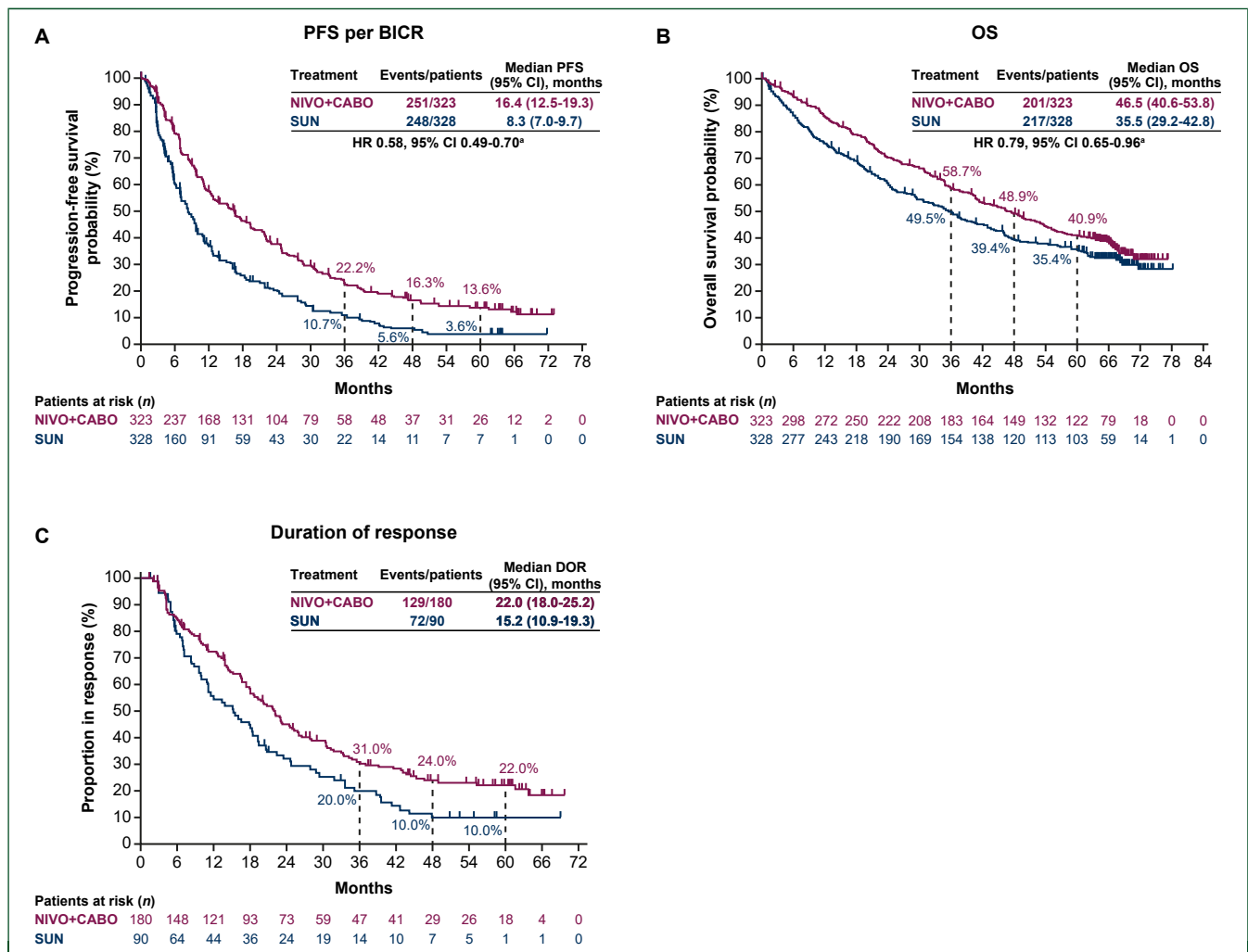
## RESULTS

### Patients

Between 11 September 2017, and 14 May 2019, 323 patients were randomized to NIVO+CABO and 328 patients to SUN. Overall, 320 patients in each arm received the study treatment. Of all treated patients (NIVO+CABO,  $n = 320$ ; SUN,  $n = 320$ ), 21 (6.6%) patients remained on treatment in the NIVO+CABO arm and 15 (4.7%) patients remained on treatment in the SUN arm ([Supplementary Figure S1](https://doi.org/10.1016/j.annonc.2025.09.006), available at <https://doi.org/10.1016/j.annonc.2025.09.006>). The most common reasons for study treatment discontinuation from the NIVO+CABO and SUN arms were disease progression [176 (55.0%) versus 212 (66.3%) patients, respectively], study drug toxicity [38 (11.9%) versus 39 (12.2%) patients, respectively], and AEs unrelated to study drug [28 (8.8%) versus 25 (7.8%), respectively]. Baseline demographic and clinical characteristics of the ITT population and IMDC risk groups have been reported previously.<sup>6,8,9</sup> A summary of baseline characteristics of the ITT population (NIVO+CABO,  $N = 323$ ; SUN,  $N = 328$ ) is provided in the [Supplementary Appendix](https://doi.org/10.1016/j.annonc.2025.09.006), available at <https://doi.org/10.1016/j.annonc.2025.09.006>. Baseline characteristics of each IMDC risk group were generally balanced between treatment arms. At the time of the clinical data cut-off date (17 May 2024), the median (range) follow-up was 67.6 months (60.2–80.2 months) in the ITT population. The date of database lock was 21 June 2024.

In the ITT population, PFS per BICR was improved with NIVO+CABO versus SUN (HR 0.58, 95% CI 0.49–0.70) ([Figure 1A](#)). The median PFS was 16.4 months (95% CI 12.5–19.3 months) with NIVO+CABO versus 8.3 months (95% CI 7.0–9.7 months) with SUN, with 60-month PFS probabilities of 13.6% versus 3.6%, respectively. OS also favored NIVO+CABO versus SUN in the ITT population (HR 0.79, 95% CI 0.65–0.96) ([Figure 1B](#)). The median OS was 46.5 months (95% CI 40.6–53.8 months) with NIVO+CABO versus 35.5 months (95% CI 29.2–42.8 months) with SUN, with 60-month OS probabilities of 40.9% versus 35.4%, respectively.

Objective response outcomes were better with NIVO+CABO versus SUN in the ITT population ([Table 1](#)). ORR was 55.7% (95% CI 50.1% to 61.2%) with NIVO+CABO versus 27.4% (95% CI 22.7% to 32.6%) with SUN. The CR rate was higher (13.9% versus 4.6%), and progressive disease rate was lower (6.5% versus 14.3%) with NIVO+CABO versus SUN, respectively. More patients had deep PRs with NIVO+CABO versus SUN. Overall, 20.1% of patients had a PR with  $\geq 60\%$  tumor reduction and 21.7% had a PR with  $< 60\%$  tumor reduction in the NIVO+CABO arm, whereas in the SUN arm 8.5% and 14.3% of patients had a PR with either  $\geq 60\%$  or  $< 60\%$  tumor reduction, respectively.

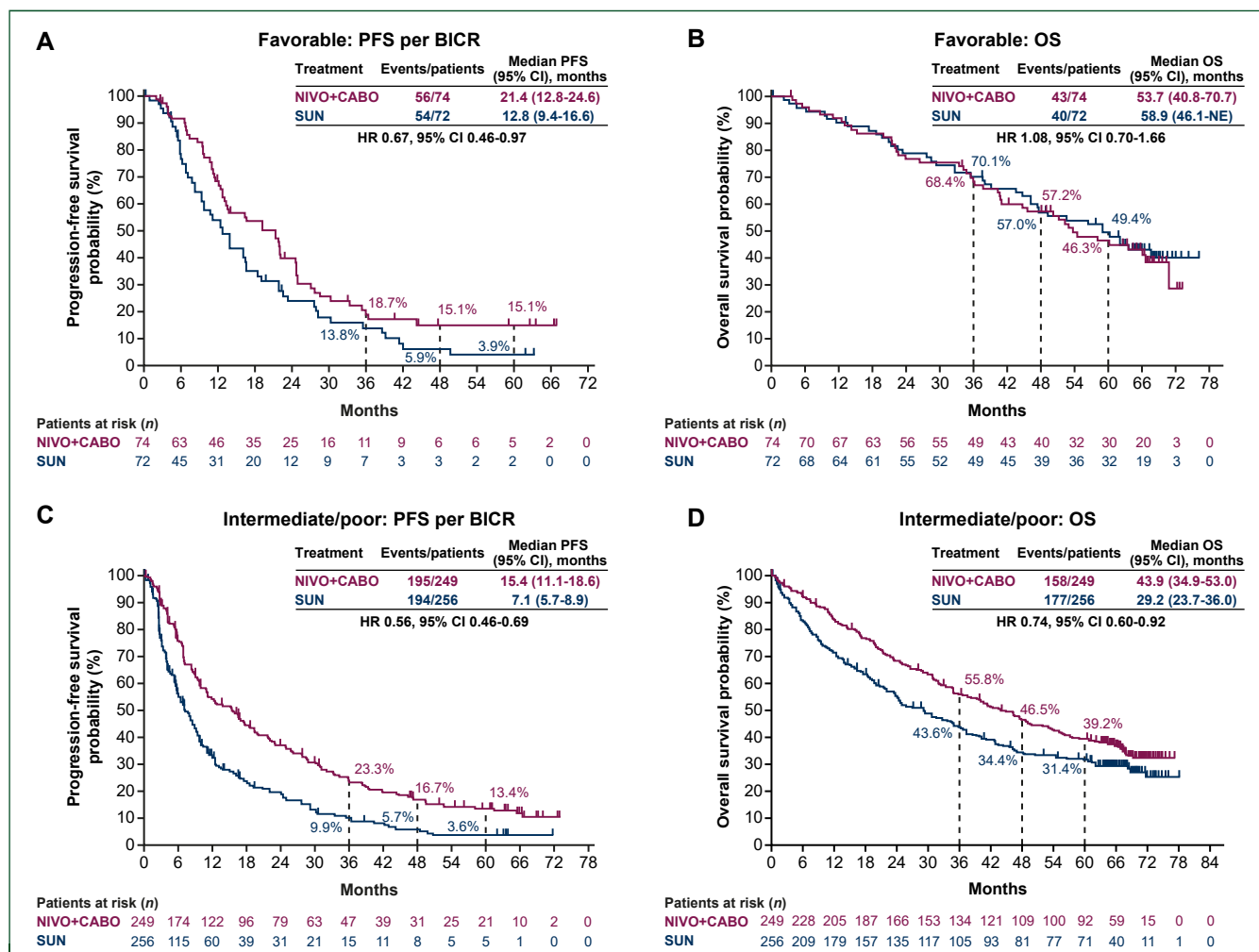


**Figure 1.** Kaplan–Meier analysis of efficacy outcomes in the ITT population. PFS per BICR (A), OS (B), and duration of response (C) in the ITT population. BICR, blinded independent central review; CI, confidence interval; DOR, duration of response; HR, hazard ratio; ITT, intent-to-treat; NIVO+CABO, nivolumab plus cabozantinib; OS, overall survival; PFS, progression-free survival; SUN, sunitinib.  
\*Stratified Cox proportional hazards model used for hazard ratio.

**Table 1. Objective response in the intent-to-treat (ITT) population (including depth of response) and by IMDC favorable- and intermediate/poor combined-risk groups**

Outcome	ITT population		IMDC risk group			
			Favorable		Intermediate/poor	
	NIVO+CABO (N = 323)	SUN (N = 328)	NIVO+CABO (n = 74)	SUN (n = 72)	NIVO+CABO (n = 249)	SUN (n = 256)
ORR (95% CI), %	55.7 (50.1-61.2)	27.4 (22.7-32.6)	66.2 (54.3-76.8)	43.1 (31.4-55.3)	52.6 (46.2-58.9)	23.0 (18.0-28.7)
Complete response, n (%)	45 (13.9)	15 (4.6)	12 (16.2)	5 (6.9)	33 (13.3)	10 (3.9)
Partial response, n (%)	135 (41.8)	75 (22.9)	37 (50.0)	26 (36.1)	98 (39.4)	49 (19.1)
≥60% tumor reduction <sup>a</sup>	65 (20.1)	28 (8.5)	—	—	—	—
<60% tumor reduction <sup>a</sup>	70 (21.7)	47 (14.3)	—	—	—	—
Stable disease, n (%)	104 (32.2)	136 (41.5)	23 (31.1)	28 (38.9)	81 (32.5)	108 (42.2)
Progressive disease, n (%)	21 (6.5)	47 (14.3)	2 (2.7)	4 (5.6)	19 (7.6)	43 (16.8)
Unable to determine/not reported, n (%)	18 (5.6)	55 (16.8)	0	9 (12.5)	18 (7.2)	46 (18.0)
Median time to response (range), months <sup>b</sup>	2.8 (1.0-22.2)	4.3 (1.7-22.0)	2.8 (1.5-19.8)	4.2 (1.7-22.0)	2.8 (1.0-22.2)	4.4 (1.7-18.1)
Median duration of response (95% CI), months <sup>b,c</sup>	22.0 (18.0-25.2)	15.2 (10.9-19.3)	18.7 (13.9-22.2)	17.0 (11.1-19.4)	23.1 (17.3-30.5)	13.8 (7.1-23.5)

Per RECIST version 1.1, confirmation of response required. IMDC prognostic risk score was recorded at screening by interactive response technology. CI, confidence interval; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ITT, intent-to-treat; NIVO+CABO, nivolumab plus cabozantinib; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; SUN, sunitinib.  
<sup>a</sup>Depth of response categories were based on confirmed objective response per BICR assessed over the course of the study.  
<sup>b</sup>Calculated only for patients with a complete response or partial response.  
<sup>c</sup>Median computed using the Kaplan–Meier method.



**Figure 2. Kaplan—Meier analysis of efficacy outcomes by IMDC risk group.** PFS per BICR and OS in patients with IMDC favorable risk (A, B) and with combined IMDC intermediate/poor risk (C, D). IMDC prognostic risk score was recorded at screening by interactive response technology. Unstratified Cox proportional hazards model used for HR. BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ITT, intent-to-treat; NE, not estimable; NIVO+CABO, nivolumab plus cabozantinib; OS, overall survival; PFS, progression-free survival; SUN, sunitinib.

The median (range) time to response was shorter with NIVO+CABO [2.8 months (1.0-22.2 months)] versus SUN [4.3 months (1.7-22.0 months)]. Responses were also more durable with NIVO+CABO versus SUN. The median DOR was 22.0 months (95% CI 18.0-25.2 months) with NIVO+CABO versus 15.2 months (95% CI 10.9-19.3 months) with SUN; the probability of remaining in response through 60 months was 22.0% versus 10.0%, respectively (Figure 1C).

In the IMDC favorable-risk group, an improvement was observed in PFS per BICR with NIVO+CABO versus SUN (HR 0.67, 95% CI 0.46-0.97), with 60-month PFS probabilities of 15.1% versus 3.9%, respectively (Figure 2A). However, no benefit with NIVO+CABO versus SUN was observed in OS (HR 1.08, 95% CI 0.70-1.66), with 60-month OS probabilities of 46.3% versus 49.4% (Figure 2B). ORR was 66.2% (95% CI 54.3% to 76.8%) with NIVO+CABO versus 43.1% (95% CI 31.4% to 55.3%) with SUN; median time to response and median DOR outcomes were numerically improved with NIVO+CABO versus SUN (Table 1).

In the IMDC intermediate/poor combined-risk group, PFS per BICR favored NIVO+CABO versus SUN (HR 0.56, 95% CI

0.46-0.69), with 60-month PFS probabilities of 13.4% versus 3.6%, respectively (Figure 2C). OS favored NIVO+CABO versus SUN (HR 0.74, 95% CI 0.60-0.92), with 60-month OS probabilities of 39.2% versus 31.4%, respectively (Figure 2D). ORR was 52.6% (95% CI 46.2% to 58.9%) with NIVO+CABO versus 23.0% (95% CI 18.0% to 28.7%) with SUN (Table 1).

PFS and ORR outcomes also favored NIVO+CABO versus SUN among IMDC intermediate and poor separate-risk groups (Supplementary Figure S2A and C, Table S1, available at <https://doi.org/10.1016/j.annonc.2025.09.006>). Although a clear OS benefit with NIVO+CABO versus SUN was seen in patients with IMDC poor risk (HR 0.49, 95% CI 0.33-0.74), the HR for OS trended toward an improvement with NIVO+CABO in patients with IMDC intermediate risk (HR 0.86, 95% CI 0.67-1.11) (Supplementary Figure S2B and D, available at <https://doi.org/10.1016/j.annonc.2025.09.006>). This trend was not observed in patients with IMDC favorable risk.

To further characterize patients with long-term efficacy benefit with NIVO+CABO, an exploratory analysis was conducted in subgroups of ITT patients by baseline organ sites of metastases. PFS per BICR and ORR per BICR each

avored NIVO+CABO versus SUN in patients with liver, bone, or lung metastases at baseline (Supplementary Table S2 and Supplementary Figure S3, available at <https://doi.org/10.1016/j.annonc.2025.09.006>). OS also favored NIVO+CABO versus SUN in patients with liver metastases (HR 0.65, 95% CI 0.43-0.97), in patients with bone metastases (HR 0.66, 95% CI 0.45-0.95), and in patients with lung metastases (HR 0.75, 95% CI 0.60-0.94) at baseline (Supplementary Table S2 and Supplementary Figure S4, available at <https://doi.org/10.1016/j.annonc.2025.09.006>).

### Exposure and subsequent therapy

The median time to treatment discontinuation in all treated patients ( $n = 320$  each arm) was 21.8 months (95% CI 18.0-23.7 months) in the NIVO+CABO arm versus 8.4 months (95% CI 7.0-10.5 months) in the SUN arm.

Among all treated patients ( $n = 320$  each arm), dose delays occurred in 238 (74.4%) patients receiving NIVO, 274 (85.6%) patients receiving CABO, and 239 (74.7%) patients receiving SUN. Dose reductions occurred in 199 (62.2%) patients receiving CABO and in 175 (54.7%) patients receiving SUN. The median time to first dose reduction was 4.11 months (range 0.3-50.4 months, Q1-Q3 2.3-7.4 months) with CABO ( $n = 199$ ) and 2.0 (range 0.2-50.1 months, Q1-Q3 1.4-6.0 months) with SUN ( $n = 175$ ).

In those who discontinued study treatment, subsequent systemic therapy was received by 129 (43.1%) of 299 patients in the NIVO+CABO arm and 168 (55.1%) of 305 patients in the SUN arm (Table 2; Supplementary Table S3, available at <https://doi.org/10.1016/j.annonc.2025.09.006>). Among those patients, the most common class of subsequent systemic therapy received was a VEGF(R)-targeted agent in the NIVO+CABO arm [102/129 (79.1%); most commonly axitinib, 36/129 (27.9%)] and a PD-(L)1 inhibitor in the SUN arm [136/168 (81.0%); most commonly nivolumab, 126/168 (75.0%)]. Additionally, belzutifan, a hypoxia-inducible factor-2 alpha inhibitor, was received by 8 (6.2%) patients in the NIVO+CABO arm and 1 (0.6%) in the SUN arm. The median time to subsequent systemic therapy (post hoc exploratory analysis) was 3.0 months (95% CI 2.0-4.6 months) in 317 NIVO+CABO-treated patients (irrespective of the completion of NIVO treatment; Figure 3A), 1.5 months (95% CI 1.2-2.1 months) in 270 SUN-treated patients (Figure 3B), and 35.0 months (95% CI 24.9-43.9 months) in 115 patients in the NIVO+CABO arm who completed per-protocol 2 years of NIVO treatment (irrespective of continuing or completing CABO treatment; Figure 3C).

### Safety

Treatment-related AEs of any grade and grade 3-4 occurred in 312 (97.5%) and 217 (67.8%) of 320 treated patients in the NIVO+CABO arm, and in 298 (93.1%) and 176 (55.0%) of 320 treated patients in the SUN arm (Table 3). The most common grade 3-4 treatment-related AEs in the NIVO+CABO arm were hypertension [42 (13.1%)], palmar-plantar erythrodysesthesia [25 (7.8%)], and diarrhea [23

**Table 2. Summary of subsequent systemic anticancer therapy in all treated patients who discontinued study treatment**

	NIVO + CABO ( $n = 299$ )	SUN ( $n = 305$ )
Received subsequent systemic therapy, $n$ (%) <sup>a</sup>	129 (43.1)	168 (55.1)
	$n^b = 129$	$n^b = 168$
Any PD-(L)1 inhibitor, $n$ (%) <sup>c</sup>	46 (35.7)	136 (81.0)
NIVO	36 (27.9)	126 (75.0)
	$n^b = 129$	$n^b = 168$
Any VEGF(R) inhibitor, $n$ (%) <sup>c</sup>	102 (79.1)	86 (51.2)
Axitinib	36 (27.9)	28 (16.7)
Sunitinib	25 (19.4)	12 (7.1)
Lenvatinib	24 (18.6)	8 (4.8)
Cabozantinib	16 (12.4)	50 (29.8)
	$n^b = 129$	$n^b = 168$
Any CTLA-4 inhibitor, $n$ (%) <sup>c</sup>	13 (10.1)	25 (14.9)
Ipilimumab	13 (10.1)	24 (14.3)
	$n^b = 129$	$n^b = 168$
Other, $n$ (%) <sup>c</sup>	48 (37.2)	24 (14.3)
Everolimus	29 (22.5)	15 (8.9)

CABO, cabozantinib; CTLA-4, cytotoxic T-lymphocyte associated protein 4; NIVO, nivolumab; PD-(L)1, programmed death (ligand) 1; SUN, sunitinib; VEGF(R), vascular endothelial growth factor (receptor).

<sup>a</sup>Patients may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if the patient was never treated).

<sup>b</sup>Number of patients listed ( $n = 129$  and  $n = 168$ ) are the denominators for 'patient number (%)' reported below.

<sup>c</sup>The most common subsequent systemic therapies for each arm are listed. See Supplementary Table S3, available at <https://doi.org/10.1016/j.annonc.2025.09.006> for full list.

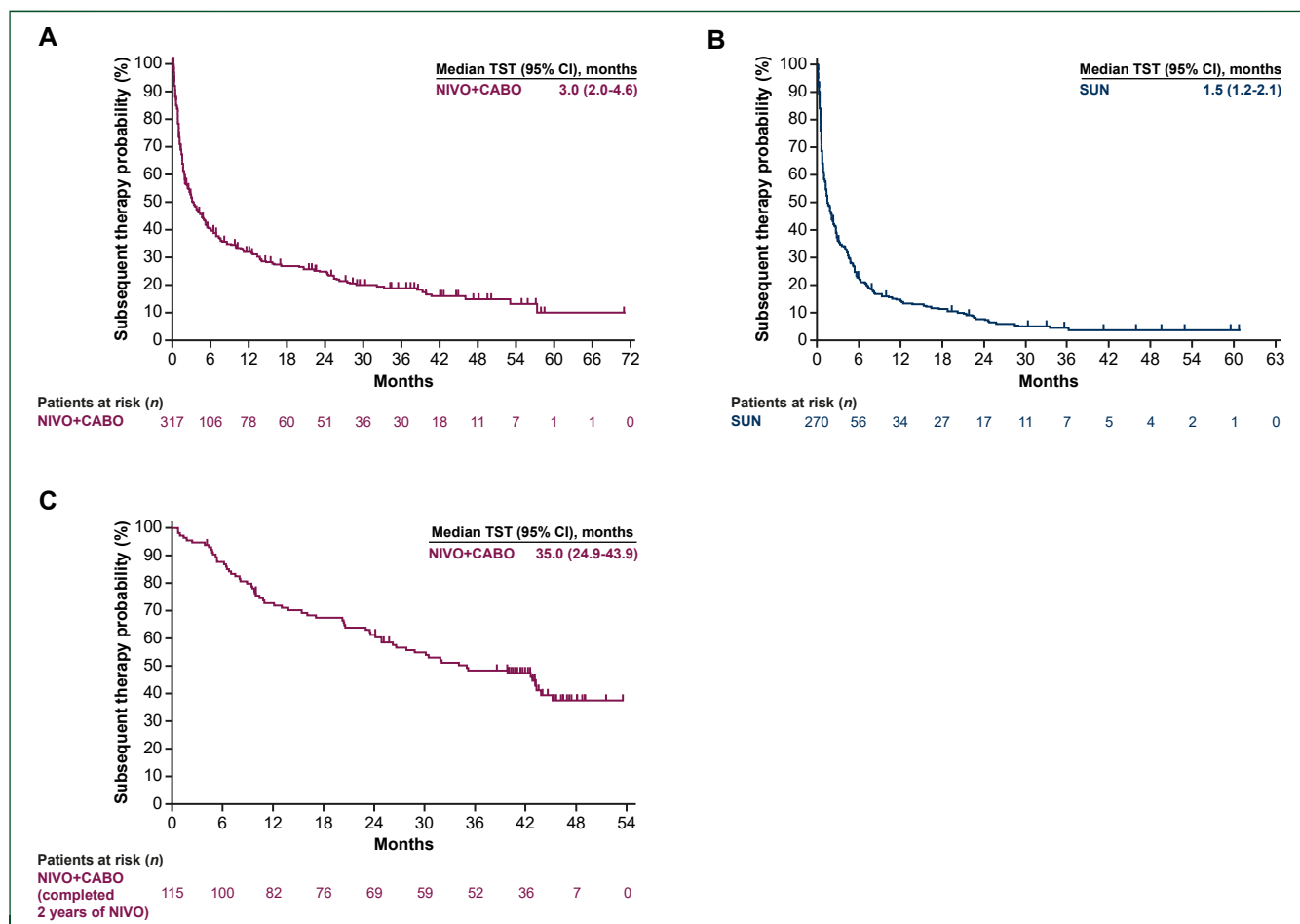
(7.2%); and in the SUN arm were hypertension [40 (12.5%)] and palmar-plantar erythrodysesthesia [26 (8.1%)].

The occurrence of grade 3-4 treatment-related AEs by common system organ class of clinical relevance is shown over time for both treatment arms in Supplementary Figure S5A and B, available at <https://doi.org/10.1016/j.annonc.2025.09.006> (post hoc exploratory analysis). In the NIVO+CABO arm, vascular disorders (e.g. hypertension) were common within the first 60 days but transient, whereas renal and urinary disorders emerged over time. In the SUN arm, vascular disorders (e.g. hypertension) were also common early and persisted after treatment initiation, together with blood and lymphatic system disorders.

Treatment-related AEs of any grade led to the discontinuation of either study drug in 90 (28.1%) of 320 treated patients in the NIVO+CABO arm [NIVO only, 32 (10.0%); CABO only, 34 (10.6%); NIVO+CABO both simultaneously, 20 (6.3%); and NIVO+CABO both sequentially 4 (1.3%)], and in 35 (10.9%) of 320 treated patients in the SUN arm.

No new treatment-related deaths per investigator occurred since the 32.9-month median follow-up. Treatment-related deaths over the entire course of the Check-Mate 9ER trial occurred in one patient in the NIVO+CABO arm (small-intestine perforation) and three patients in the SUN arm (one each of pneumonia, respiratory distress, and sudden death).

The incidence of immune-mediated AEs (by specific event) of any grade and grade 3-4 occurred in 167 (52.2%)



**Figure 3. Kaplan–Meier analysis of time to subsequent systemic therapy.** Time to subsequent systemic therapy in (A) patients treated with NIVO+CABO<sup>a</sup>, (B) patients treated with SUN, and (C) in patients who completed 2 years of NIVO treatment<sup>b</sup>. Time to subsequent systemic therapy was defined as the time from the last dose of study treatment to the start of subsequent systemic therapy or death, or the last known alive date (for patients who never received subsequent cancer therapy).

CI, confidence interval; NIVO+CABO, nivolumab plus cabozantinib; SUN, sunitinib; TST, time to subsequent systemic therapy.

<sup>a</sup>Irrespective of completion of NIVO treatment.

<sup>b</sup>Irrespective of continuing or completing treatment with CABO.

and 46 (14.4%) of 320 treated patients in the NIVO+CABO arm and 40 (12.5%) and 3 (0.9%) in the SUN arm; no grade 5 events occurred ([Supplementary Table S4](https://doi.org/10.1016/j.annonc.2025.09.006), available at <https://doi.org/10.1016/j.annonc.2025.09.006>). Details on the onset and resolution of immune-mediated AEs (by category) in patients treated with NIVO+CABO are shown in [Supplementary Table S5](https://doi.org/10.1016/j.annonc.2025.09.006), available at <https://doi.org/10.1016/j.annonc.2025.09.006>. Continuous corticosteroids (at least 40 mg prednisone daily or equivalent) to manage any-grade immune-mediated AEs were required by 70 (21.9%) and 9 (2.8%) NIVO+CABO and SUN-treated patients, respectively. In total, 41 (12.8%) and 17 (5.3%) NIVO+CABO-treated patients, and 2 (0.6%) and 2 (0.6%) SUN-treated patients, received corticosteroids continuously for at least 14 days and at least 30 days, respectively.

## DISCUSSION

In these final results from the CheckMate 9ER trial, with a median of 67.6 months (5.6 years) of follow-up, long-term

efficacy benefit was observed with NIVO+CABO over SUN in patients with previously untreated RCC.

The key efficacy measures of PFS, OS, and ORR were improved with NIVO+CABO versus SUN in the ITT population. Median PFS was almost doubled, and an 11.0-month median OS improvement was observed with NIVO+CABO versus SUN. Durable separation of the PFS and OS Kaplan–Meier curves and higher survival probabilities were sustained with NIVO+CABO to least 60 months after randomization. Patients in the ITT population also had a higher CR rate and a lower progressive disease rate with NIVO+CABO versus SUN. Objective responses were also durable with NIVO+CABO, with a 22% probability of remaining in response through 60 months with NIVO+CABO versus 10% with SUN.

Most efficacy outcomes also favored NIVO+CABO across all IMDC risk groups, except for OS benefit in IMDC favorable-risk patients. This subset comprised only 22% of the ITT population, and favorable-risk patients are characterized by a longer survival compared with the other IMDC

**Table 3. Treatment-related adverse events (AEs) in ≥10% of all treated patients in either arm**

Event, n (%)	NIVO + CABO (n = 320)		SUN (n = 320)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Patients with any event	312 (97.5)	217 (67.8)	298 (93.1)	176 (55.0)
Diarrhea	191 (59.7)	23 (7.2)	148 (46.3)	15 (4.7)
PPE	124 (38.8)	25 (7.8)	134 (41.9)	26 (8.1)
Hypothyroidism	118 (36.9)	1 (0.3)	99 (30.9)	1 (0.3)
Hypertension	108 (33.8)	42 (13.1)	111 (34.7)	40 (12.5)
ALT increased	91 (28.4)	20 (6.3)	25 (7.8)	4 (1.3)
Fatigue	88 (27.5)	8 (2.5)	102 (31.9)	15 (4.7)
AST increased	88 (27.5)	13 (4.1)	39 (12.2)	3 (0.9)
Nausea	79 (24.7)	1 (0.3)	88 (27.5)	0
Dysgeusia	69 (21.6)	0	67 (20.9)	0
Decreased appetite	70 (21.9)	4 (1.3)	56 (17.5)	2 (0.6)
Mucosal inflammation	67 (20.9)	3 (0.9)	83 (25.9)	8 (2.5)
Rash	67 (20.9)	6 (1.9)	22 (6.9)	0
Pruritus	62 (19.4)	2 (0.6)	14 (4.4)	0
Asthenia	60 (18.8)	13 (4.1)	48 (15.0)	8 (2.5)
Stomatitis	59 (18.4)	7 (2.2)	78 (24.4)	9 (2.8)
Lipase increased	56 (17.5)	21 (6.6)	41 (12.8)	16 (5.0)
Amylase increased	47 (14.7)	16 (5.0)	30 (9.4)	8 (2.5)
Vomiting	43 (13.4)	4 (1.3)	52 (16.3)	2 (0.6)
Hyponatremia	40 (12.5)	22 (6.9)	19 (5.9)	13 (4.1)
Proteinuria	40 (12.5)	16 (5.0)	32 (10.0)	9 (2.8)
Hypophosphatemia	39 (12.2)	19 (5.9)	16 (5.0)	4 (1.3)
Dysphonia	39 (12.2)	1 (0.3)	9 (2.8)	0
Anemia	38 (11.9)	2 (0.6)	68 (21.3)	13 (4.1)
Hypomagnesemia	38 (11.9)	1 (0.3)	12 (3.8)	0
Arthralgia	36 (11.3)	0	18 (5.6)	0
Hyperthyroidism	32 (10.0)	2 (0.6)	7 (2.2)	0
Dyspepsia	22 (6.9)	0	33 (10.3)	1 (0.3)
Thrombocytopenia <sup>a</sup>	21 (6.6)	1 (0.3)	65 (20.3)	15 (4.7)
Gastroesophageal reflux disease	19 (5.9)	0	33 (10.3)	0
Neutropenia	18 (5.6)	3 (0.9)	55 (17.2)	15 (4.7)
Platelet count decreased <sup>b</sup>	18 (5.6)	0	59 (18.4)	14 (4.4)

Includes events reported between first dose and 30 days after last dose of study therapy. Treatment-related deaths per investigator over the course of the study: NIVO+CABO, n = 1 (small-intestine perforation); SUN, n = 3 (pneumonia; respiratory distress; sudden death).

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NIVO+CABO, nivolumab plus cabozantinib; PPE, palmar-plantar erythrodysesthesia; SUN, sunitinib.

<sup>a</sup>Reported within the blood and lymphatic system disorders system organ class.

<sup>b</sup>Reported within the investigations system organ class.

risk groups, irrespective of the systemic therapy received.<sup>12</sup> Furthermore, this analysis was descriptive, exploratory, and not powered to detect such differences. To this point, although comparisons across trials are not recommended, a lack of OS benefit in IMDC favorable-risk patients appears to be a feature common to other phase III trials comparing ICI/VEGF-TKI combinations with SUN.<sup>13,14</sup> For example, in the phase III CLEAR trial of pembrolizumab plus lenvatinib versus SUN with 4-year follow-up, the HR for OS was 0.94 (95% CI 0.58-1.52).<sup>13</sup> Additionally, in the phase III KEYNOTE-426 trial of pembrolizumab plus axitinib versus SUN with a 43-month follow-up, the HR for OS was 1.2 (95% CI 0.76-1.8).<sup>14</sup> Nevertheless, ICI/VEGF-TKI combinations, including NIVO+CABO, are recommended as first-line systemic therapy options for advanced clear cell RCC across all IMDC risk groups, including favorable risk (with the latter based on PFS and objective response data as well as the overall OS benefit seen in the ITT population).<sup>1-3</sup>

Liver, bone, and lung are common sites of metastasis in patients with RCC.<sup>15</sup> In descriptive exploratory analyses of efficacy in patient subgroups based on the presence of liver, bone, or lung metastases at baseline, PFS, OS, and ORR favored NIVO+CABO versus SUN in each subgroup. Among other first-line regimens, the CLEAR trial also found that pembrolizumab plus lenvatinib was more efficacious than SUN in patients with liver, bone, or lung metastases.<sup>16</sup> In our analyses, a sustained improvement in the three key efficacy outcomes in patients with bone metastases supports the use of NIVO+CABO over SUN in this patient population prone to skeletal-related events.<sup>6,8</sup> This is consistent with the suggested use of CABO-containing systemic therapies in some treatment guidelines.<sup>1</sup> Nevertheless, these analyses were descriptive, exploratory, and were not part of the pre-specified formal statistical analysis. In addition, not all guidelines suggest a CABO-based regimen for patients with advanced RCC and bone metastases.<sup>2,3</sup>

Safety and tolerability with long-term follow-up were manageable and generally consistent with previous follow-ups.<sup>6,8,9</sup> The occurrence of grade 3-4 treatment-related AEs with NIVO+CABO increased from 60.6% in the primary analysis (18.1 months median follow-up) to 67.8% after 5.6 years of follow-up. The management of AEs by dose delay or dose reduction resulted in only a small proportion of patients discontinuing both NIVO and CABO (6.3% simultaneously; 1.3% sequentially) due to any-grade treatment-related AEs, highlighting the effectiveness of these supportive care measures. No new safety signals emerged, and no further treatment-related deaths occurred in either arm since the 32.9-month median follow-up.

Evaluation of subsequent systemic anticancer therapy in patients who discontinued study treatment confirmed previous findings that a VEGF(R)-inhibitor-based regimen in the NIVO+CABO arm and a PD-(L)1 inhibitor-based regimen in the SUN arm were the most common classes of subsequent systemic anticancer therapy.<sup>6,8,9</sup> These findings generally reflect current treatment guidelines; however, selection of second-line therapy is still evolving. Furthermore, patients who completed the per-protocol 2 years of NIVO treatment experienced a 35.0-month median time to initiation of subsequent systemic therapy, highlighting the durable antitumor response with NIVO+CABO.

The primary disclosure for CheckMate 9ER demonstrated statistically significant PFS, OS, and ORR benefits for NIVO+CABO versus SUN.<sup>6</sup> However, the present analysis, which is based on long-term follow-up data, was exploratory and descriptive in nature, and was not statistically powered to detect differences between treatment arms when stratified by IMDC risk groups or by specific organ sites of metastases.

The pivotal role of immunotherapy in the RCC landscape has revolutionized first-line treatment, marking a shift from VEGF-TKI monotherapy to more effective immunotherapy-based regimens.<sup>17-19</sup> The CheckMate 9ER trial established NIVO+CABO as a standard first-line treatment of patients with advanced RCC, regardless of IMDC risk group, offering improved survival outcomes, the potential for durable

responses, and manageable safety compared with SUN.<sup>6</sup> While these advancements have significantly enhanced treatment options, the mode of drug administration has also evolved, potentially offering an alternative to standard intravenous delivery. In CheckMate 9ER, NIVO was administered by intravenous bolus infusion; however, the US Food and Drug Administration and the European Commission recently approved NIVO and human recombinant hyaluronidase for subcutaneous injection, on the basis of the phase III CheckMate 67T trial in patients with advanced RCC, showing that subcutaneous NIVO was noninferior to intravenous NIVO.<sup>20-23</sup>

In conclusion, these final results with 5.6 years of median follow-up from the CheckMate 9ER trial demonstrated the durable clinical benefits of NIVO+CABO with a manageable safety profile and reaffirm NIVO+CABO as a standard of care for previously untreated advanced RCC.

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### DISCLOSURE

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## DATA SHARING

Bristol Myers Squibb's policy on data sharing may be found at <https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html>.

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