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First-line nivolumab plus cabozantinib versus sunitinib in patients with advanced renal cell carcinoma in subgroups based on prior nephrectomy in the CheckMate 9ER trial

Camillo Porta,[1*] Mauricio Burotto,[2] Cristina Suárez,[3] Maria T. Bourlon,[4] James Hsieh,[5] Amishi Y. Shah,[6] Alketa Hamzaj,[7] Jens Bedke,[8] David Pook,[9] Elizabeth R. Kessler,[10] Yoshihiko Tomita,[11] Alexandra Drakaki,[12] Joshua Zhang,[13] Burcin Simsek,[13] Gisela Schwab,[14] Bernard Escudier,[15] Robert J. Motzer,[16] Toni K. Choueiri,[17] Andrea B. Apolo,[18] Thomas Powles[19]

[1]University of Pavia, Pavia, Italy; [2]Bradford Hill Clinical Research Center, Santiago, Chile; [3]Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [4]Urologic Oncology Clinic, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [5]Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO, USA; [6]MD Anderson Cancer Center, Houston, TX, USA; [7]Ospedale San Donato, Istituto Toscano Tumori, Arezzo, Italy; [8]University Hospital, Eberhard Karls University Tübingen, Tübingen, Germany; [9]Cabrini Monash University, Cabrini Health, Malvern, VIC, Australia; [10]University of Colorado School of Medicine, Aurora, CO, USA; [11]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [12]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [13]Bristol Myers Squibb, Princeton, NJ, USA; [14]Exelixis, Inc., Alameda, CA, USA; [15]Gustave Roussy, Villejuif, France; [16]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [17]Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA; [18]Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; [19]Barts Cancer Institute, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, Royal Free National Health Service Trust, London, UK

**Camillo Porta is now with University of Bari 'A. Moro,' Bari, Italy*

Background

- First-line nivolumab plus cabozantinib (NIVO+CABO) significantly improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) versus sunitinib (SUN) in intent-to-treat (ITT) patients with advanced renal cell carcinoma (aRCC) in the phase 3 CheckMate 9ER trial with 10.6 months minimum follow-up[1]
 - On the basis of these results, the combination of NIVO+CABO was approved by the European Commission and the US Food and Drug Administration for the first-line treatment of patients with aRCC[2,3]
 - Superior efficacy with NIVO+CABO over SUN was maintained in CheckMate 9ER with 16.0 months minimum follow-up[4]
- Patients with aRCC who do not have upfront nephrectomy usually have a poor prognosis, and represent a population that historically has not been studied in clinical trials[5-7]; limited data are available for these patients regarding outcomes with targeted therapies or with newer immunotherapy combination regimens[8-10]
 - SUN alone was noninferior to initial nephrectomy followed by treatment with SUN in patients with aRCC and Memorial Sloan Kettering Cancer Center intermediate- or poor-risk disease in the prospective CARMENA trial[8]
 - CABO demonstrated improved PFS, ORR, OS, and renal tumor reduction compared with everolimus in patients with aRCC irrespective of nephrectomy status in the METEOR trial[9]
 - NIVO plus ipilimumab showed survival benefits and renal tumor reduction versus SUN in patients with aRCC without prior nephrectomy and with an evaluable primary tumor in CheckMate 214 with long-term follow-up[10]
- In this exploratory post hoc analysis of CheckMate 9ER, we assessed efficacy outcomes with NIVO+CABO versus SUN in patient subgroups defined by baseline nephrectomy status after a minimum follow-up of 16.0 months

Methods

- In this phase 3 open-label trial, adults with confirmed aRCC with a clear cell component were randomized 1:1 to NIVO (240 mg every 2 weeks) plus CABO (40 mg once daily) versus SUN (50 mg once daily for 4 weeks; 6-week cycle) as reported in detail previously[1,4]
- The primary endpoint was PFS in ITT patients
- Secondary endpoints included OS and ORR (both in ITT patients), and safety in all treated patients
- PFS and confirmed response outcomes were assessed per blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- In this post hoc exploratory analysis, PFS, OS, ORR, and response outcomes (including duration of response [DOR]) were evaluated using descriptive statistics in patient subgroups defined by baseline nephrectomy status (with or without prior nephrectomy)
 - Consistent with primary/secondary efficacy endpoints in ITT patients, PFS and response outcomes were evaluated per RECIST v1.1 by BICR in these subgroups

Results

Patients

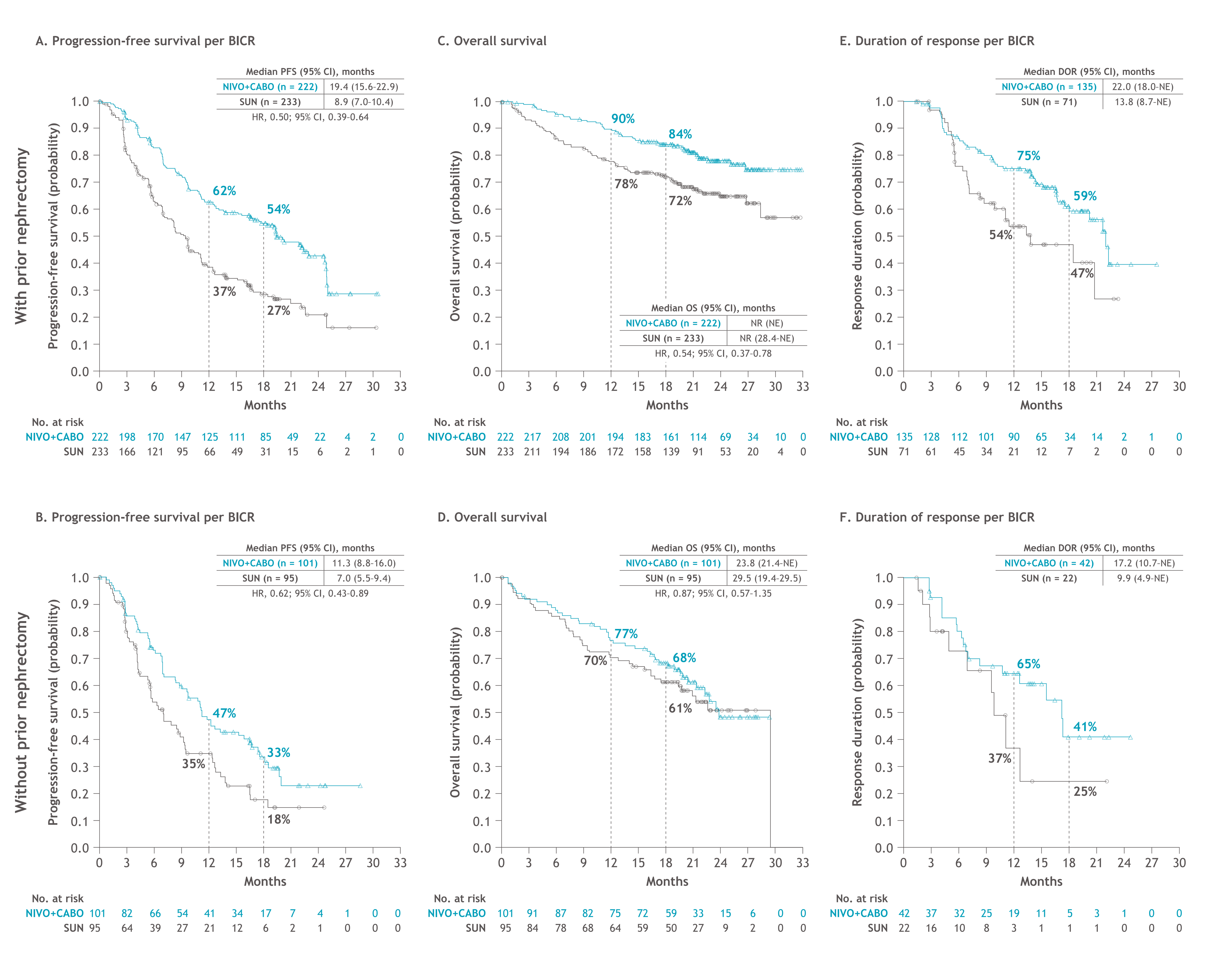
- Of 651 ITT patients, 455 had prior nephrectomy (NIVO+CABO, n = 222; SUN, n = 233) and 196 had no prior nephrectomy (NIVO+CABO, n = 101; SUN, n = 95)
- Baseline characteristics were generally similar between arms within each subgroup, and are summarized in **Table 1**; of note, more patients had International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) favorable-risk disease in the subgroup of patients with prior nephrectomy in both treatment arms

Table 1. Baseline characteristics in subgroups by prior nephrectomy status

	With prior nephrectomy		Without prior nephrectomy	
Characteristic[a]	NIVO+CABO (n = 222)	SUN (n = 233)	NIVO+CABO (n = 101)	SUN (n = 95)
Median age (range), years	62 (29-85)	61 (28-86)	61 (38-90)	62 (37-85)
Male, n (%)	177 (79.7)	160 (68.7)	72 (71.3)	72 (75.8)
IMDC prognostic score, n (%)				
Favorable (0)	63 (28.4)	59 (25.3)	11 (10.9)	13 (13.7)
Intermediate (1-2)	132 (59.5)	140 (60.1)	56 (55.4)	48 (50.5)
Poor (3-6)	27 (12.2)	34 (14.6)	34 (33.7)	34 (35.8)
Tumor PD-L1 expression, n (%)				
≥ 1%	61 (27.5)	64 (27.5)	20 (19.8)	17 (17.9)
< 1% or indeterminate	156 (70.3)	164 (70.4)	76 (75.2)	76 (80.0)
Not reported	5 (2.3)	5 (2.1)	5 (5.0)	2 (2.1)
Region, n (%)				
United States/Europe	115 (51.8)	115 (49.4)	43 (42.6)	46 (48.4)
Rest of the world	107 (48.2)	118 (50.6)	58 (57.4)	49 (51.6)
No. of organ sites with target/non-target lesions, n (%)				
1	46 (20.7)	58 (24.9)	15 (14.9)	10 (10.5)
≥ 2 or not reported	176 (79.3)	175 (75.1)	86 (85.1)	85 (89.5)
Most common organ sites of metastasis, n (%)[b]				
Lung	165 (74.3)	177 (76.0)	75 (74.3)	74 (77.9)
Lymph node	86 (38.7)	91 (39.1)	43 (42.6)	42 (44.2)
Bone	58 (26.1)	44 (18.9)	21 (20.8)	28 (29.5)
Liver	51 (23.0)	44 (18.9)	22 (21.8)	10 (10.5)

[a]IMDC risk status and geographic region were recorded at screening using interactive response technology; other information shown in the table is based on data collected with the use of a case report form. [b]Includes the 4 most common organ sites in the NIVO+CABO arm.

Figure 1. Efficacy outcomes in subgroups by prior nephrectomy status



A. Progression-free survival per BICR
Median PFS (95% CI), months
NIVO+CABO (n = 222) 19.4 (15.6-22.9)
SUN (n = 233) 8.9 (7.0-10.4)
HR, 0.50; 95% CI, 0.39-0.64
With prior nephrectomy
Progression-free survival (probability)
62%
54%
37%
27%
Months
No. at risk
NIVO+CABO 222 198 170 147 125 111 85 49 22 4 2 0
SUN 233 166 121 95 66 49 31 15 6 2 1 0
C. Overall survival
Overall survival (probability)
90%
84%
78%
72%
Median OS (95% CI), months
NIVO+CABO (n = 222) NR (NE)
SUN (n = 233) NR (28.4-NE)
HR, 0.54; 95% CI, 0.37-0.78
No. at risk
NIVO+CABO 222 217 208 201 194 183 161 114 69 34 10 0
SUN 233 211 194 186 172 158 139 91 53 20 4 0
E. Duration of response per BICR
Median DOR (95% CI), months
NIVO+CABO (n = 135) 22.0 (18.0-NE)
SUN (n = 71) 13.8 (8.7-NE)
Response duration (probability)
75%
59%
54%
47%
No. at risk
NIVO+CABO 135 128 112 101 90 65 34 14 2 1 0
SUN 71 61 45 34 21 12 7 2 0 0 0
B. Progression-free survival per BICR
Median PFS (95% CI), months
NIVO+CABO (n = 101) 11.3 (8.8-16.0)
SUN (n = 95) 7.0 (5.5-9.4)
HR, 0.62; 95% CI, 0.43-0.89
Without prior nephrectomy
47%
33%
35%
18%
No. at risk
NIVO+CABO 101 82 66 54 41 34 17 7 4 1 0 0
SUN 95 64 39 27 21 12 6 2 1 0 0 0
D. Overall survival
Median OS (95% CI), months
NIVO+CABO (n = 101) 23.8 (21.4-NE)
SUN (n = 95) 29.5 (19.4-29.5)
HR, 0.87; 95% CI, 0.57-1.35
77%
68%
70%
61%
No. at risk
NIVO+CABO 101 91 87 82 75 72 59 33 15 6 0 0
SUN 95 84 78 68 64 59 50 27 9 2 0 0
F. Duration of response per BICR
Median DOR (95% CI), months
NIVO+CABO (n = 42) 17.2 (10.7-NE)
SUN (n = 22) 9.9 (4.9-NE)
65%
41%
37%
25%
No. at risk
NIVO+CABO 42 37 32 25 19 11 5 3 1 0 0
SUN 22 16 10 8 3 1 1 1 0 0 0

CI, confidence interval; HR, hazard ratio; NE, not estimable; NR, not reached.

Outcomes in ITT patients

- Median (range) follow-up for OS in ITT patients was 23.5 (16.0-36.0) months; outcomes in ITT patients were previously reported[4]
 - Median PFS (95% CI) was 17.0 (12.6-19.4) months with NIVO+CABO versus 8.3 (6.9-9.7) months with SUN (HR, 0.52; 95% CI, 0.43-0.64; *P* < 0.0001)
 - Median OS (95% CI) was NR (NE) with NIVO+CABO versus 29.5 (28.4-NE) months with SUN (HR, 0.66; 95% CI, 0.50-0.87; *P* = 0.0034)
 - ORR (95% CI) was 54.8% (49.2-60.3) with NIVO+CABO versus 28.4% (23.5-33.6) with SUN (odds ratio, 3.2; 95% CI, 2.3-4.4); 9.3% versus 4.3% of patients had a complete response
 - The adverse event profile with NIVO+CABO remained consistent with previous reports for each agent as monotherapy, and no new safety signals were identified among all treated patients

Outcomes in patients with and without prior nephrectomy

- Regardless of nephrectomy status, the HR for progression favored NIVO+CABO, median PFS was longer, and PFS probabilities were higher with NIVO+CABO versus SUN (**Figure 1A,B**)
- Although median OS was NR with NIVO+CABO or SUN in patients with prior nephrectomy, OS probabilities were consistently higher with NIVO+CABO and the HR favored NIVO+CABO over SUN (**Figure 1C**)
- OS probabilities at 12 and 18 months were higher with NIVO+CABO versus SUN among patients without prior nephrectomy, yet no notable overall difference between arms was observed; longer follow-up may be needed to determine survival benefits with either treatment in this subgroup (**Figure 1D**)
- ORR was higher with NIVO+CABO versus SUN in both subgroups of patients with and without prior nephrectomy (**Table 2**); responses were also more durable with NIVO+CABO versus SUN in both subgroups (**Figure 1E,F**)
 - Median time to response was shorter and the complete response rate was notably higher with NIVO+CABO versus SUN in both subgroups

Table 2. Best overall response per BICR in subgroups by prior nephrectomy status

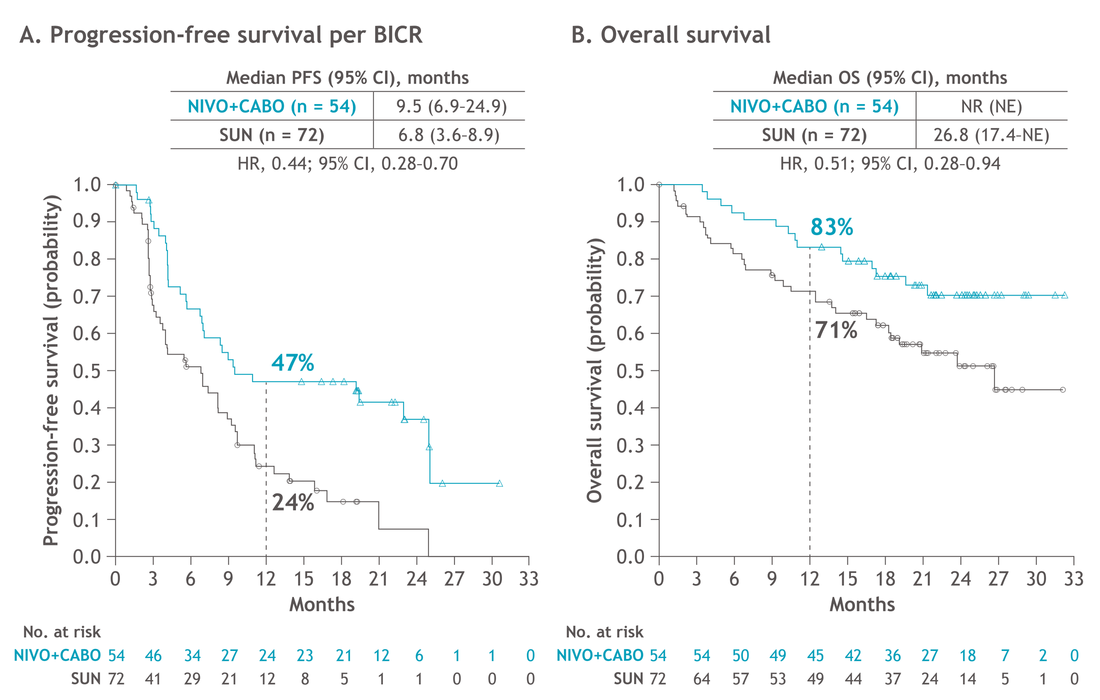
	With prior nephrectomy		Without prior nephrectomy	
Outcome	NIVO+CABO (n = 222)	SUN (n = 233)	NIVO+CABO (n = 101)	SUN (n = 95)
Confirmed ORR (95% CI), %	60.8 (54.1-67.3)	30.5 (24.6-36.8)	41.6 (31.9-51.8)	23.2 (15.1-32.9)
Best overall response, n (%)				
Complete response	25 (11.3)	14 (6.0)	5 (5.0)	0
Partial response	110 (49.5)	57 (24.5)	37 (36.6)	22 (23.2)
Stable disease	67 (30.2)	93 (39.9)	41 (40.6)	43 (45.3)
Progressive disease	13 (5.9)	31 (13.3)	7 (6.9)	14 (14.7)
Unable to determine	7 (3.2)	38 (16.3)	11 (10.9)	15 (15.8)
Not reported	0	0	0	1 (1.1)
Median (Q1-Q3) time to response, months	2.8 (2.8-3.3)	4.1 (2.8-7.1)	2.8 (2.8-5.4)	5.5 (4.0-8.3)

Q, quartile.

Outcomes in patients with prior nephrectomy within 3 months of enrollment

- Overall, 54 of 222 (24.3%) patients who underwent nephrectomy in the NIVO+CABO arm and 72 of 233 (30.9%) in the SUN arm did so within 3 months of enrollment, representing a subgroup of RCC patients with advanced disease who had cytoreductive nephrectomy shortly before initiation of first-line therapy
- PFS and OS benefits were observed with NIVO+CABO versus SUN in this subgroup (**Figure 2**)
- ORR (95% CI) was higher with NIVO+CABO versus SUN (50.0% [36.1-63.9] vs 22.2% [13.3-33.6]) in this subgroup
 - Overall, 5.6% (NIVO+CABO) versus 2.8% (SUN) of patients achieved a complete response and 44.4% versus 19.4% achieved a partial response, respectively

Figure 2. PFS and OS in patients with prior nephrectomy within 3 months of enrollment

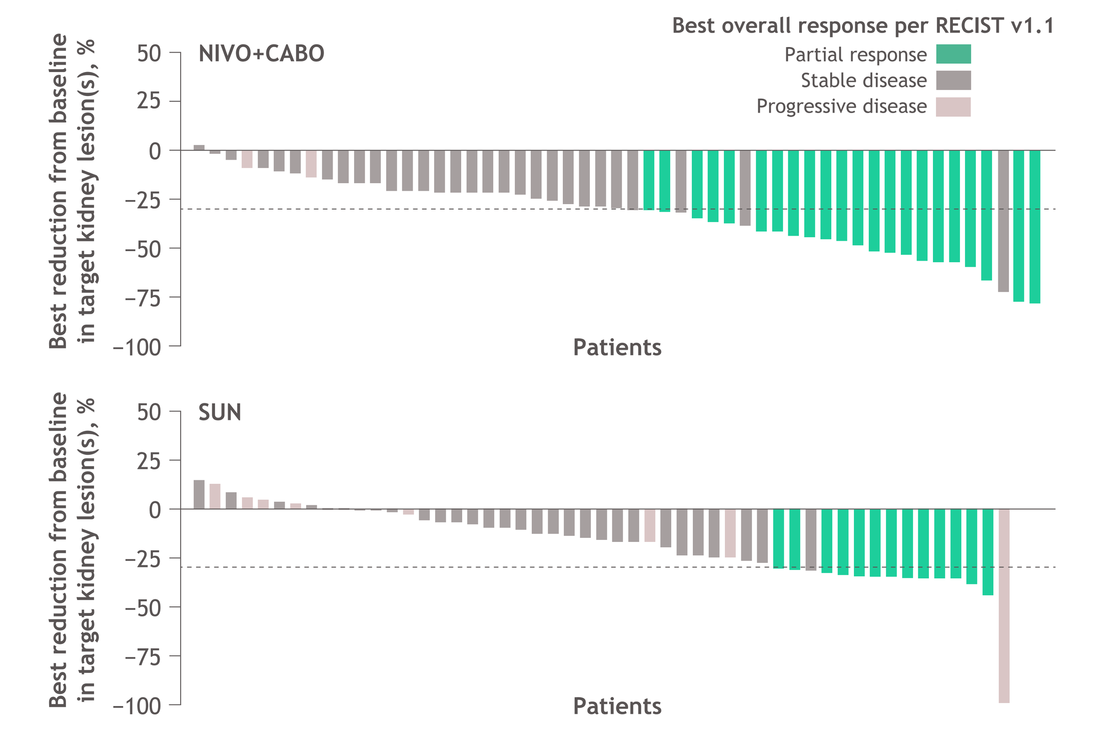


A. Progression-free survival per BICR
Median PFS (95% CI), months
NIVO+CABO (n = 54) 9.5 (6.9-24.9)
SUN (n = 72) 6.8 (3.6-8.9)
HR, 0.44; 95% CI, 0.28-0.70
Progression-free survival (probability)
47%
24%
Months
No. at risk
NIVO+CABO 54 46 34 27 24 23 21 12 6 1 1 0
SUN 72 41 29 21 12 8 5 1 1 0 0 0
B. Overall survival
Median OS (95% CI), months
NIVO+CABO (n = 54) NR (NE)
SUN (n = 72) 26.8 (17.4-NE)
HR, 0.51; 95% CI, 0.28-0.94
Overall survival (probability)
83%
71%
No. at risk
NIVO+CABO 54 54 50 49 45 42 36 27 18 7 2 0
SUN 72 64 57 53 49 44 37 24 14 5 1 0

Outcomes in patients without prior nephrectomy and with target kidney lesion(s)

- Of patients without prior nephrectomy, 62 of 101 (61.4%) in the NIVO+CABO arm and 63 of 95 (66.3%) in the SUN arm also had target kidney lesion(s)
- ORR (95% CI) was higher with NIVO+CABO versus SUN (35.5% [23.7-48.7] vs 20.6% [11.5-32.7]) in this subgroup; zero patients achieved a complete response in either arm
- Of evaluable patients in this subgroup, reduction of ≥ 30% in target kidney lesion(s) was achieved by 27 of 53 (50.9%) patients with NIVO+CABO versus 15 of 51 (29.4%) with SUN (**Figure 3**), and median (Q1-Q3) reduction in target kidney lesion(s) was 30% (21%-46%) with NIVO+CABO versus 16% (2%-32%) with SUN

Figure 3. Maximum percent reduction from baseline in target kidney lesion(s) in all response-evaluable patients without prior nephrectomy



Best overall response per RECIST v1.1
Partial response
Stable disease
Progressive disease
NIVO+CABO
SUN
Best reduction from baseline in target kidney lesion(s), %
Patients

Patients with target lesion at baseline and at least 1 on-treatment tumor assessment of target kidney lesion(s) were included. Best reduction is maximum reduction in sum of diameters of target kidney lesion(s) (negative value means true reduction; positive value means increase only observed over time). Horizontal reference line indicates the 30% reduction consistent with a RECIST v1.1 response. Different colored bars represent overall systemic responses (including but not limited to responses in the primary tumor) based on RECIST v1.1.

Conclusions

- In this exploratory subgroup analysis, notable PFS and ORR benefits were observed with NIVO+CABO versus SUN regardless of prior nephrectomy status in the CheckMate 9ER trial after a minimum follow-up of 16.0 months
 - The magnitudes of PFS and ORR benefits with NIVO+CABO versus SUN were greater in the subgroup with prior nephrectomy versus those without prior nephrectomy
 - Responses were more durable with NIVO+CABO versus SUN regardless of nephrectomy status
 - More patients without prior nephrectomy achieved a greater maximum reduction in sum of diameters of target kidney lesions with NIVO+CABO versus SUN
- OS benefits with NIVO+CABO versus SUN were observed in patients with prior nephrectomy. Although OS probabilities at 12 and 18 months were higher with NIVO+CABO in the subgroup without prior nephrectomy, longer follow-up is needed to better characterize OS outcomes between treatment arms in this subgroup
- PFS, OS, and ORR benefits were observed with NIVO+CABO versus SUN in patients who underwent nephrectomy within 3 months of trial enrollment
- These data, together with ongoing prospective studies exploring the role and sequence of nephrectomy in patients with aRCC who receive systemic therapy, will continue to inform optimal aRCC treatment strategies
- Overall, these results continue to support NIVO+CABO as a first-line treatment option for patients with aRCC

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Email: camillo.porta@gmail.com

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