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Characterization of responders in the phase 3 CheckMate 9ER trial: nivolumab plus cabozantinib versus sunitinib in patients with previously untreated advanced renal cell carcinoma

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Introduction

- In the phase 3 CheckMate 9ER trial, first-line NIVO+CABO demonstrated superiority over SUN in patients with aRCC after a minimum follow-up of 10.6 months[1]
  - Based on these results, NIVO+CABO was approved by the FDA and the EMA in this setting[2,3]
- Superior efficacy with NIVO+CABO over SUN was maintained after 16.0 months minimum follow-up (median follow-up for OS in ITT patients, 23.5 months)[4]

Outcome[4]	NIVO+CABO (n = 323)	SUN (n = 328)	HR (95% CI)
Median PFS (95% CI), months	17.0 (12.6-19.4)	8.3 (6.9-9.7)	0.52 (0.43-0.64)
Median OS (95% CI), months	NR (NE)	29.5 (28.4-NE)	0.66 (0.50-0.87)
ORR (95% CI), %	54.8 (49.2–60.3)	28.4 (23.5–33.6)	–
Duration of response (95% CI), months	21.7 (17.3-NE)	12.7 (9.6-20.7)	–

- Here, we present a post hoc analysis of patients with a confirmed best overall response of CR or PR in CheckMate 9ER to better characterize patients with aRCC who responded to NIVO+CABO versus SUN

aRCC, advanced or metastatic renal cell carcinoma; CABO, cabozantinib; CR, complete response; EMA, European Medicines Agency; FDA, US Food and Drug Administration; NIVO, nivolumab; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SUN, sunitinib.

1. Choueiri TK, et al. *N Engl J Med* 2021;384:829–841. 2. US Food and Drug Administration. FDA approves nivolumab plus cabozantinib for advanced renal cell carcinoma. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-nivolumab-plus-cabozantinib-advanced-renal-cell-carcinoma. Accessed August 23, 2021. 3. European Medicines Agency. Opdivo. https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo. Accessed August 23, 2021. 4. Motzer RJ, et al. Poster presentation at the Genitourinary Cancers Symposium; February 11–13, 2021; Virtual. Abstract 308.

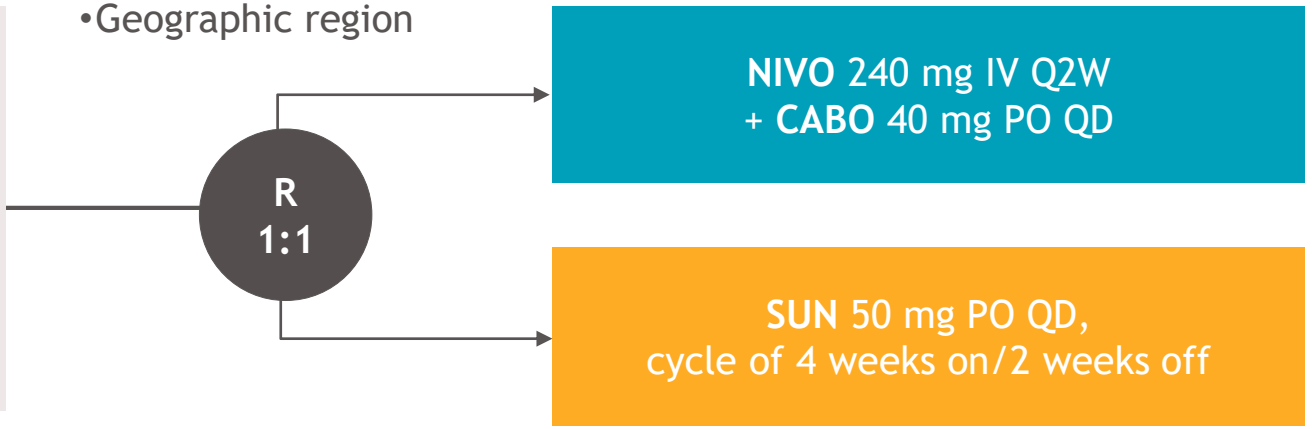
CheckMate 9ER study design and methods

N = 651

Key inclusion criteria[1,2]

- Previously untreated advanced or metastatic RCC
- Clear cell component
- Any IMDC risk group

Stratification factors:
- IMDC risk score
- Tumor PD-L1 expression
- Geographic region



Treat until RECIST v1.1–defined progression or unacceptable toxicity[a]

Primary endpoint: PFS per BICR using RECIST v1.1 in ITT patients
Secondary endpoints: OS, ORR per BICR using RECIST v1.1 in ITT patients, and safety in all treated patients
Follow-up for OS in ITT patients: Median 23.5 months (minimum, 16.0 months)

Current analysis: Baseline characteristics, disposition, treatment exposure, duration of response, and safety outcomes in all responders and in patients with a BOR of CR or PR

[a]NIVO dosing may not exceed a total of 2 years (from cycle 1); CABO and SUN treatment may continue beyond 2 years in the absence of progression or unacceptable toxicity. Dose reductions were not allowed for NIVO but were permitted for CABO and SUN. Patients may be treated beyond progression.
BICR, blinded independent central review; BOR, best overall response; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IV, intravenously; PD-L1, programmed death ligand 1; PO, orally; Q2W, every 2 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.
1. Choueiri TK, et al. *N Engl J Med* 2021;384:829–841. 2. Choueiri TK et al. Oral presentation at ESMO 2020. 696O.

Objective response and best overall response per BICR

Outcome	NIVO+CABO (n = 323)	SUN (n = 328)
ORR (95% CI), %	54.8 (49.2-60.3)	28.4 (23.5-33.6)
Odds ratio estimate (95% CI)	3.2 (2.3-4.4)	
Complete response, n (%)	30 (9.3)	14 (4.3)
Partial response, n (%)	147 (45.5)	79 (24.1)
Stable disease, n (%)	108 (33.4)	136 (41.5)
Progressive disease, n (%)	20 (6.2)	45 (13.7)
Unable to determine, n (%)	18 (5.6)	53 (16.2)
Not reported, n (%)	0	1 (0.3)

Follow-up for OS in ITT patients: median 23.5 months (minimum, 16.0 months).

1. Motzer RJ, et al. Poster presentation at the Genitourinary Cancers Symposium; February 11–13, 2021; Virtual. Abstract 308.

Select baseline demographic and disease characteristics

Characteristics[a]	ITT[1]		Patients with CR		Patients with PR	
	NIVO+CABO (n = 323)	SUN (n = 328)	NIVO+CABO (n = 30)	SUN (n = 14)	NIVO+CABO (n = 147)	SUN (n = 79)
Median age (range), years	62 (29-90)	61 (28-86)	62 (36-78)	59 (42-71)	61 (35-79)	63 (41-79)
Male, %	77	71	80	71	77	72
IMDC prognostic score, %						
Favorable (0)	23	22	27	50	28	32
Intermediate (1-2)	58	57	67	43	59	61
Poor (3-6)	19	21	7	7	14	8
Tumor PD-L1 expression, %[b]						
≥ 1%	26	25	27	29	25	19
< 1% or indeterminate	74	75	73	71	75	81
Region, %						
US/Europe	49	49	77	57	50	49
Rest of the world	51	51	23	43	50	51
No. of sites with at least 1 lesion, %[c]						
1	20	21	70	79	27	38
≥ 2	80	78	30[d]	21[d]	73	62
Most common sites of metastasis, %[e]						
Lung	74	76	60	79	79	80
Lymph node	40	40	33	57	39	35
Bone	24	22	17	0	22	10
Liver	23	16	3	7	24	13
Median sum of reference diameters of target lesions (range), mm	73 (10-338)	70 (10-392)	33 (13-154)	21 (16-50)	67 (11-330)	58 (10-265)

[a]IMDC risk, PD-L1 status, and region were recorded using IRT among ITT patients; IMDC risk and region were reported per IRT, and PD-L1 was reported per CRF in both responder subgroups (CR or PR). [b]Defined as the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry 28-8 pharmDx assay. [c]Includes both target and non-target lesions. [d]No patient with CR in either arm had > 2 sites with at least 1 lesion. [e]Includes the 4 most common organ sites in ITT patients (investigator-assessed baseline lesions).

CRF, case report form; IRT, interactive response technology 1. Choueiri TK, et al. *N Engl J Med* 2021;384:829-841.

Disposition and exposure

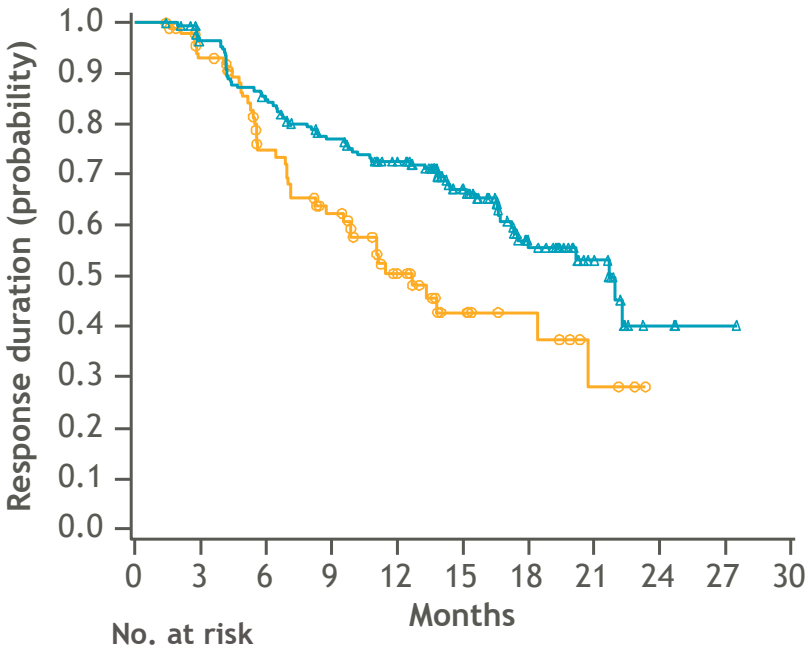
	All responders		Patients with CR		Patients with PR	
	NIVO+CABO (n = 177)	SUN (n = 93)	NIVO+CABO (n = 30)	SUN (n = 14)	NIVO+CABO (n = 147)	SUN (n = 79)
Continuing in the treatment period, %	63	52	70	64	61	49
Not continuing in the treatment period, %						
Disease progression	19	30	3	36	22	29
Study drug toxicity	7	6	3	0	8	8
AE unrelated to treatment	3	2	3	0	3	3
Completed treatment per protocol	2	0	7	0	1	0
Other[a]	5	10	13	0	3	11
Median duration of therapy (Q1-Q3), months	20.4 (14.9-24.4)	19.3 (12.7-21.9)	23.5 (19.6-26.1)	20.4 (19.3-21.9)	19.9 (12.7-23.9)	18.3 (10.9-22.1)
Relative dose intensity, %[b,c]	NIVO CABO	SUN	NIVO CABO	SUN	NIVO CABO	SUN
90 to < 110	77 33	39	83 27	64	76 35	34
70 to < 90	19 14	32	10 3	29	20 16	33
50 to < 70	5 36	25	7 50	0	4 33	29
< 50	0 18	4	0 20	7	0 17	4

[a]Other reasons responders did not continue in the treatment period included death (n = 1 in each arm), request to discontinue (n = 1 [NIVO+CABO]; n = 2 [SUN]), withdrawal of consent (n = 3 [SUN]), no longer met study criteria (n = 1 [NIVO+CABO]), maximum clinical benefit (n = 1 [NIVO+CABO]), not reported/other (n =5 [NIVO+CABO]; n = 3 [SUN]).
[b]No dose reductions were allowed for NIVO. Dose reductions for AE management were allowed for CABO and SUN; dose delays for management of AEs during NIVO, CABO, or SUN treatment were allowed. [c]Defined as the actual dose received relative to the planned dose.
AE, adverse event; Q, quartile.

Time to and duration of response

All responders

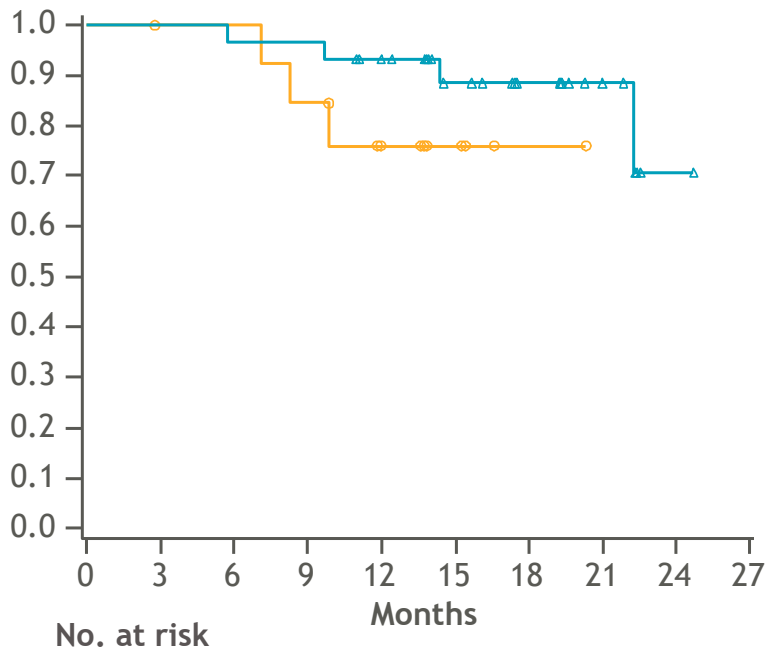
Median TTR (Q1-Q3), months	
NIVO+CABO	2.8 (2.8-3.9)
SUN	4.2 (2.8-7.1)
Median DOR (95% CI), months	
NIVO+CABO	21.7 (17.3-NE)
SUN	12.7 (9.6-20.7)



No. at risk										
NIVO+CABO										
177	165	144	126	109	76	39	17	3	1	0
SUN										
93	77	55	42	24	13	8	3	0	0	0

Patients with CR

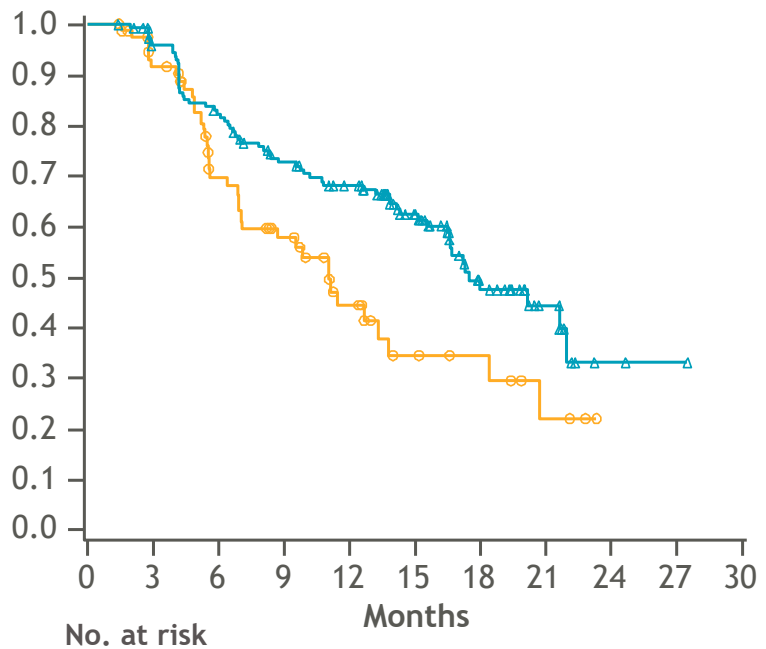
Median TTR (Q1-Q3), months	
NIVO+CABO	2.8 (2.8-2.9)
SUN	3.7 (2.8-6.9)
Median DOR (95% CI), months	
NIVO+CABO	NR (22.2-NE)
SUN	NR (9.9-NE)



No. at risk										
NIVO+CABO										
30	30	29	29	25	18	13	6	1	0	
SUN										
14	13	13	11	7	4	1	0	0	0	

Patients with PR

Median TTR (Q1-Q3), months	
NIVO+CABO	2.8 (2.8-4.2)
SUN	4.3 (2.8-7.3)
Median DOR (95% CI), months	
NIVO+CABO	17.5 (16.5-22.0)
SUN	11.1 (7.0-13.8)

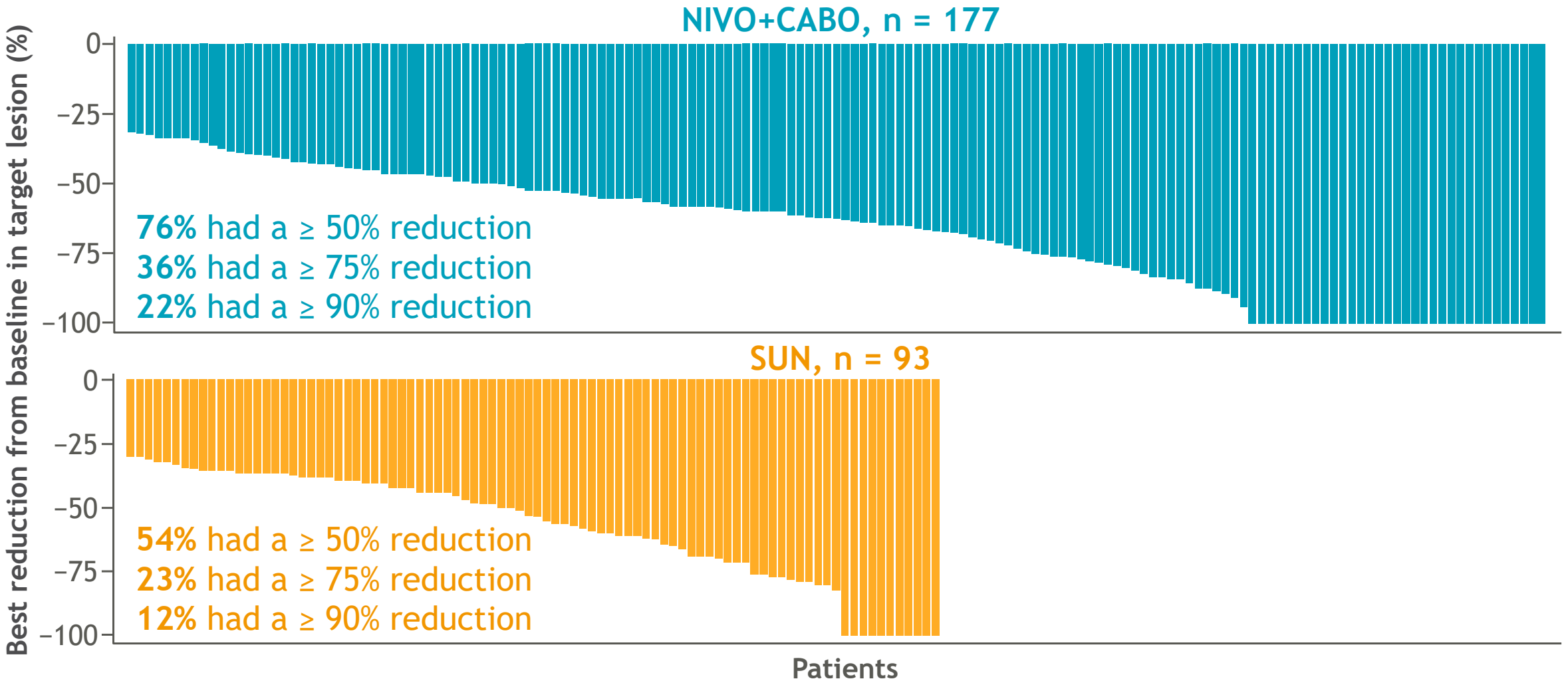


No. at risk											
NIVO+CABO											
147	135	115	97	84	58	26	11	2	1	0	
SUN											
79	64	42	31	17	9	7	3	0	0	0	

DOR, duration of response; TTR, time to response.

Best percent reduction from baseline in sum of diameter of target lesions per BICR in all responders

- More responders experienced a greater reduction from baseline with NIVO+CABO versus SUN



Includes patients with target lesion(s) at baseline and at least 1 on-treatment tumor assessment. Best reduction is maximum reduction in sum of diameters of target lesions (negative value means true reduction, positive value means increase only observed over time).

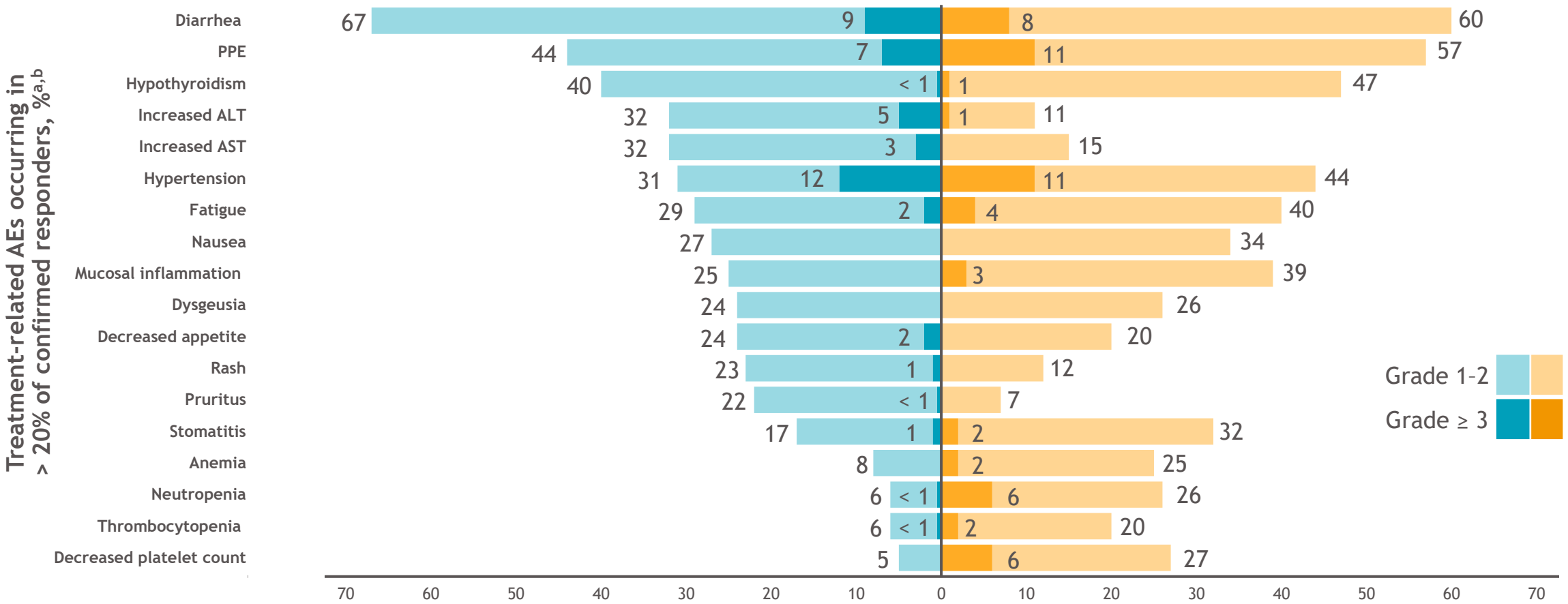
Subsequent therapy summary

	All responders		Patients with CR		Patients with PR	
	NIVO+CABO (n = 177)	SUN (n = 93)	NIVO+CABO (n = 30)	SUN (n = 14)	NIVO+CABO (n = 147)	SUN (n = 79)
Patients with any subsequent therapy, %[a]	**18**	**27**	**10**	**21**	**20**	**28**
Patients with subsequent systemic therapy, %	**11**	**24**	**3**	**21**	**12**	**24**
Anti-PD-(L)1	3	15	0	21	3	14
Anti-CTLA4	1	2	0	0	1	3
Combo anti-CTLA4 anti-PD1	< 1	1	0	0	< 1	1
VEGF targeted therapy	7	11	3	14	7	10
Other[b]	2	3	0	0	3	4
Patients with subsequent radiotherapy, %[c]	**6**	**9**	**7**	**14**	**6**	**8**
Patients with subsequent surgery, %	**4**	**3**	**0**	**0**	**5**	**4**

[a]Patients may have received more than 1 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). [b]One patient with PR in the NIVO+CABO arm received subsequent systemic therapy that was reported as unassigned; the "Other" category included everolimus, investigational antineoplastic agent, and combinations of antineoplastic agents. [c]Radiotherapy could have been palliative or curative.

Safety summary in all responders

Events, %[a]	NIVO+CABO, n = 177		SUN, n = 93	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Treatment-related AEs	99	62	99	57



[a]Includes events that occurred on therapy or within 30 days after the end of the treatment period of all confirmed responders. [b]Total bar represents treatment-related AEs of any grade > 20% in either treatment arm; of these events, none were grade 5. PPE, palmar-plantar erythrodysesthesia.

Summary

- ORR, CR, and PR rates were all approximately doubled with NIVO+CABO versus SUN in CheckMate 9ER after a minimum follow-up of 16.0 months
  - Responses were deeper, median time to CR or PR was shorter, and both CRs and PRs were more durable with NIVO+CABO versus SUN
- Meaningful response outcomes were observed regardless of appropriate dose modifications with CABO, and more responders remained on therapy with NIVO+CABO versus SUN
- Fewer responders required subsequent systemic therapy with NIVO+CABO versus SUN, and this trend was even more pronounced among patients with CR
- Grade 3-4 treatment-related AEs occurred among responders at similar frequencies in both arms
- These results continue to support NIVO+CABO as a first-line IO-TKI standard of care treatment option for patients with aRCC

IO-TKI, immunotherapy-tyrosine kinase inhibitor.

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