Poster Abstract N22

Nivolumab plus cabozantinib vs sunitinib in patients with advanced renal cell carcinoma and bone metastasis: subgroup analysis of the phase 3 CheckMate 9ER trial

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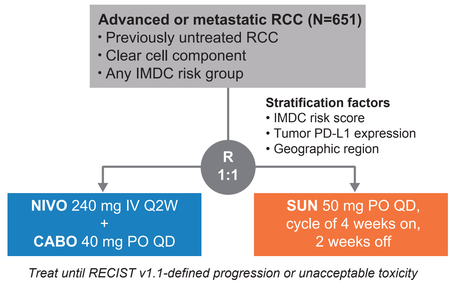
INTRODUCTION

- In the phase 3 CheckMate 9ER trial (NCT03141177), first-line nivolumab plus cabozantinib (NIVO+CABO) significantly improved progression-free survival (PFS) vs sunitinib (SUN) at a minimum follow-up of 10.6 months (median follow-up, 18.1 months) in all randomized patients with advanced renal cell carcinoma (aRCC) leading to US Food and Drug Administration approval of NIVO+CABO for first-line aRCC[1,2]
  - PFS: HR, 0.51, $p < 0.001$; overall survival (OS): HR, 0.60, $p = 0.001$; and objective response rate (ORR): 55.7% vs 27.1%, $p < 0.001$
- The superior efficacy of NIVO+CABO over SUN was maintained at minimum follow-up of 16.0 months (median follow-up, 23.5 months) in all randomized patients[3]
  - In exploratory subgroup analyses, efficacy benefits with NIVO+CABO vs SUN were observed regardless of International Metastatic RCC Database Consortium (IMDC) risk status, organ site of metastases, or extent of tumor burden at baseline[4]
- This post-hoc exploratory analysis evaluated outcomes (per blinded independent central review [BICR] by RECIST v1.1) by bone metastasis status at baseline at 16.0-month minimum follow-up

Figure 1. Study Design[1]



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

METHODS

- Treatment-related and all-cause adverse events (AEs) were reported for patients through 30 days after the end of treatment
- In this post-hoc exploratory analysis, PFS, OS, and ORR were evaluated with respect to baseline bone metastasis status. Bone metastasis status at baseline was per investigator assessment (CT/MRI, n=150; bone scan, n=1)

RESULTS

- Overall, 651 patients were randomized to NIVO+CABO (N = 323) or SUN (N = 328)
- The median follow-up for all randomized patients at data cutoff (September 10, 2020) was 23.5 months (range, 16.0–36.0)
- Median duration of treatment (range) for NIVO+ CABO vs SUN was 16.2 months (0.5–28.1) vs 5.8 months (0.9–33.1) for patients with bone metastasis and 18.6 months (0.2–32.2) vs 10.4 months (0.5–32.7) for patients without bone metastasis

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ABBREVIATIONS
a, advanced; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BICR, blinded independent central review; CABO, cabozantinib; CI, confidence interval; CT, computed tomography; HR, hazard ratio; IMDC, International Metastatic RCC Database Consortium; ITT, intention-to-treat; IV, intravenous; mo, month(s); MRI, magnetic resonance imagining; NE, not estimable; NIVO, nivolumab; OR, objective response; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PO, oral; PPE, palmar-plantar erythrodysesthesia; Q2W, once every 2 weeks; Q3W, once every 3 weeks; QD, once daily; R, randomization; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; SUN, sunitinib; y, year

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Table 1. Patient Demographics and Clinical Characteristics at Baseline

	Patients with bone metastasis at baseline		Patients without bone metastasis at baseline	
	NIVO+ CABO (N=79)	SUN (N=72)	NIVO+ CABO (N=244)	SUN (N=256)
Median (range), y	63 (36–80)	61 (28–86)	62 (29–90)	61 (29–86)
Male, n (%)	61 (77)	53 (74)	188 (77)	179 (70)
Geographic region, n (%)				
USA or Europe	39 (49)	43 (60)	119 (49)	118 (46)
Rest of the world	40 (51)	29 (40)	125 (51)	138 (54)
Race, n (%)				
White	64 (81)	65 (90)	203 (83)	201 (79)
Asian	9 (11)	2 (3)	17 (7)	23 (9)
Native American or Alaska native	0	1 (1)	3 (1)	1 (<1)
Other	6 (8)	4 (6)	21 (9)	31 (12)
Karnofsky performance-status score, n (%)				
70	3 (4)	6 (8)	11 (5)	12 (5)
80	24 (30)	26 (36)	28 (11)	41 (16)
90	25 (32)	24 (33)	85 (35)	88 (34)
100	27 (34)	16 (22)	120 (49)	113 (44)
Not reported	0	0	0	2 (1)
IMDC prognostic risk score, n (%)				
Favorable: 0	22 (28)	7 (10)	52 (21)	66 (26)
Intermediate: 1 or 2	40 (51)	43 (60)	149 (61)	143 (56)
Poor: 3–6	17 (22)	22 (31)	43 (18)	46 (18)
Not reported	0	0	0	1 (<1)
Tumor PD-L1 expression, n (%)				
≥1%	18 (23)	22 (31)	63 (26)	59 (23)
<1% or indeterminate	61 (77)	48 (67)	171 (70)	192 (75)
Not reported	0	2 (3)	10 (4)	5 (2)
Previous radiotherapy, n (%)	25 (32)	26 (36)	21 (9)	19 (7)
Previous nephrectomy, n (%)	58 (73)	44 (61)	164 (67)	189 (74)
Most common sites of metastasis, n (%)				
Lung	56 (71)	55 (76)	184 (75)	196 (77)
Lymph node	31 (39)	35 (49)	98 (40)	98 (38)
Bone	79 (100)	72 (100)	0	0
Liver	15 (19)	17 (24)	58 (24)	37 (14)
Adrenal gland	10 (13)	7 (10)	26 (11)	30 (12)

Table 2. Prior/Current and Concomitant Use of Bone-Targeted Therapies in Patients With Bone Metastasis at Baseline

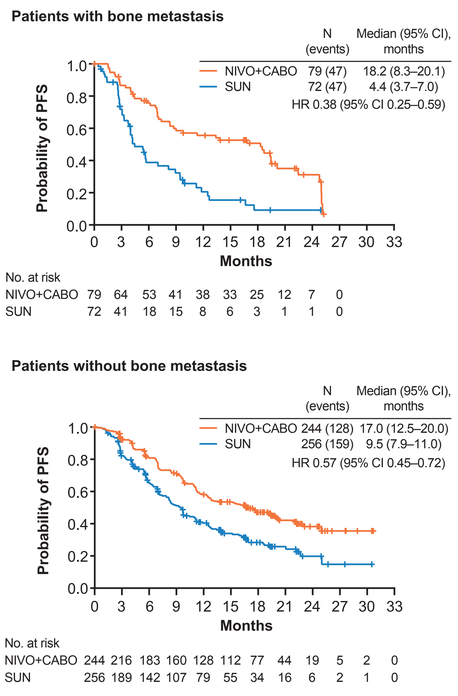
	NIVO+CABO (N=79)	SUN (N=72)
Bone-targeted therapy at baseline, n (%)*	3 (4)	5 (7)
Denosumab	3 (4)	1 (1)
Bisphosphonates	0	4 (6)
Concomitant, n (%)†	12 (15)	14 (19)
Denosumab	7 (9)	5 (7)
Bisphosphonates	5 (6)	9 (13)

*Includes medications with a start date before consent date and those with a start date before first date of study medication and stop date after consent date.
†Taken at any time on treatment.

Table 3. Tumor Response per BICR by RECIST v1.1

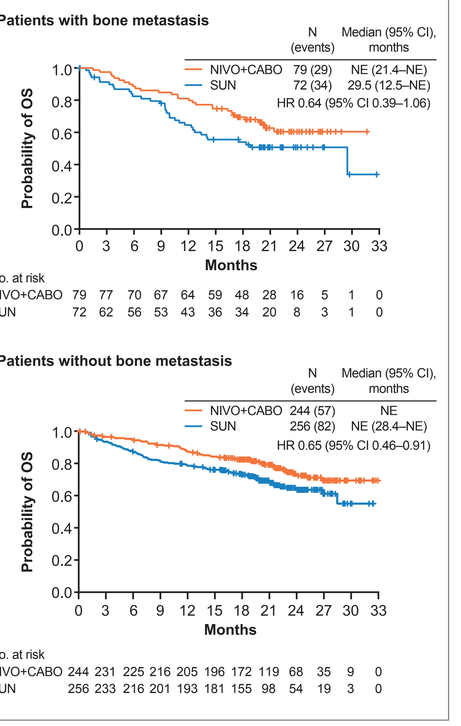
	Patients with bone metastasis at baseline		Patients without bone metastasis at baseline	
	NIVO+ CABO (N=79)	SUN (N=72)	NIVO+ CABO (N=244)	SUN (N=256)
Best overall response, n (%)				
Complete response	5 (6)	0	25 (10)	14 (5)
Partial response	33 (42)	8 (11)	114 (47)	71 (28)
Stable disease	27 (34)	29 (40)	81 (33)	107 (42)
Progressive disease	8 (10)	20 (28)	12 (5)	25 (10)
Unable to determine	6 (8)	15 (21)	12 (5)	39 (15)
ORR, % (95% CI)	48 (37–60)	11 (5–21)	57 (51–63)	33 (28–39)
Median time to OR (range), mo	3 (2–8)	6 (3–11)	3 (1–11)	4 (2–20)
Median duration of OR (95% CI), mo	18 (16–NE)	7 (5–NE)	22 (17–NE)	13 (10–21)

Figure 2. Kaplan-Meier Analyses of Progression-Free Survival per BICR by RECIST v1.1



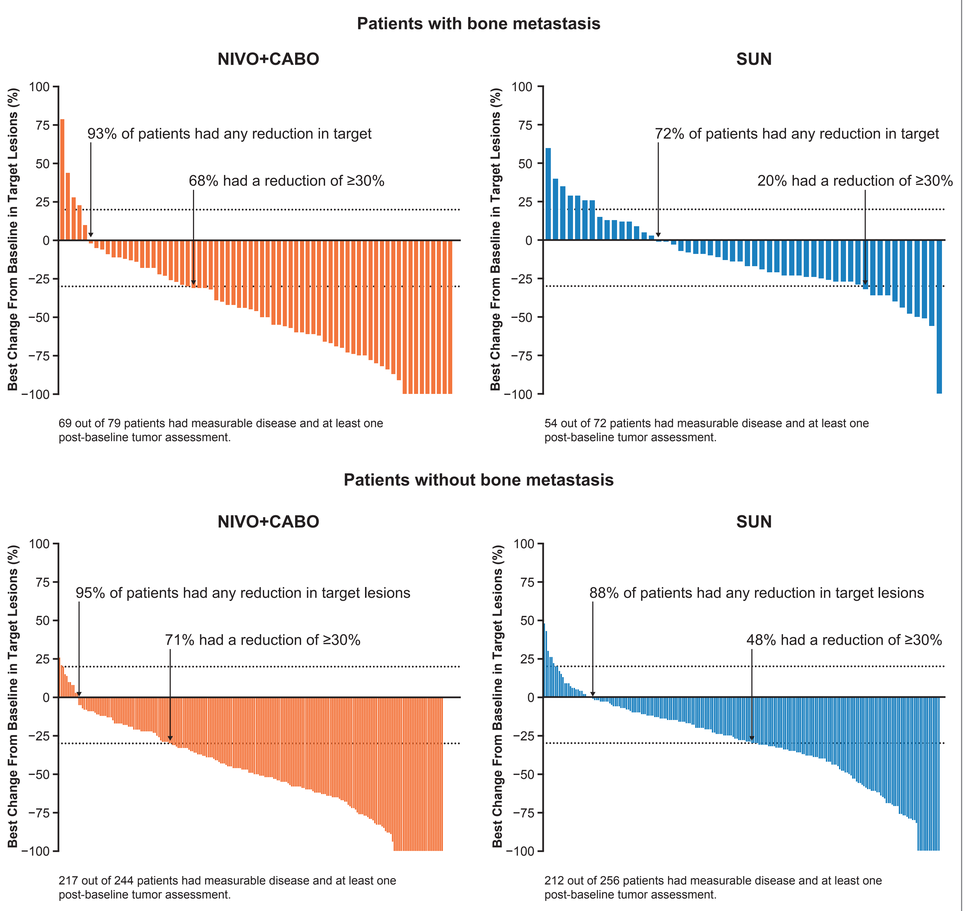
- Patients treated with NIVO+CABO had longer PFS and OS and higher ORR vs SUN regardless of bone metastasis status
- PFS with NIVO+CABO was similar in patients with vs without bone metastasis (HR 1.26, 95% CI 0.90–1.76), while OS was shorter for patients with vs without bone metastasis (HR 1.72, 95% CI 1.10–2.69)

Figure 3. Kaplan-Meier Analyses of Overall Survival



- PFS and OS with SUN were shorter in patients with vs without bone metastasis: HR 1.85 (95% CI 1.33–2.56) and HR 1.69 (95% CI 1.13–2.52), respectively
- ORR with NIVO+CABO was numerically similar in patients with and without bone metastasis while it was lower with SUN in patients with bone metastasis vs those without bone metastasis

Figure 4. Best Change from Baseline in Sum of Target Lesions per BICR by RECIST v1.1



Waterfall plots show best change from baseline in all target lesions.
Percentages are calculated based on patients with measurable disease and at least one post-baseline measurement.

Table 4. Treatment-Related Grade 3/4 Adverse Events

	Patients with bone metastasis at baseline		Patients without bone metastasis at baseline	
	NIVO+ CABO (N=79)	SUN (N=69)	NIVO+ CABO (N=241)	SUN (N=251)
Patients with at least one event, n (%)	56 (71)	29 (42)	143 (59)	138 (55)
Lipase increased	9 (11)	3 (4)	11 (5)	12 (5)
Hyponatremia	8 (10)	2 (3)	14 (6)	11 (4)
Hypertension	7 (9)	6 (9)	30 (12)	33 (13)
Hypophosphatemia	6 (8)	0	11 (5)	3 (1)
Asthenia	5 (6)	0	5 (2)	8 (3)
PPE	4 (5)	3 (4)	20 (8)	23 (9)
Rash	4 (5)	0	2 (1)	0
Pulmonary embolism	4 (5)	1 (1)	4 (2)	1 (<1)
ALT increased	3 (4)	0	13 (5)	3 (1)
Diarrhea	2 (3)	2 (3)	19 (8)	12 (5)
Amylase increased	1 (1)	2 (3)	11 (5)	5 (2)
Neutrophil count decreased	1 (1)	2 (3)	0	15 (6)
Anemia	0	4 (6)	2 (1)	6 (2)
Platelet count decreased	0	2 (3)	0	12 (5)
Thrombocytopenia	0	2 (3)	1 (<1)	12 (5)

Grade 3/4 AE that occurred in ≥5% of patients in any treatment group are summarized; includes AEs that occurred after the first dose and through 30 days after the end of treatment.

- All-causality Grade 3/4 AEs for NIVO+CABO vs SUN were 78% vs 67% and 71% vs 68% in patients with and without bone metastasis, respectively
- Treatment-related Grade 3/4 AEs for NIVO+CABO vs SUN were 71% vs 42% and 59% vs 55% in patients with and without bone metastasis, respectively

Table 5. Immune-Mediated Adverse Events With NIVO+CABO

Preferred term, n (%)	Patients with bone metastasis at baseline (N=79)		Patients without bone metastasis at baseline (N=241)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hypothyroidism	23 (29)	0	63 (26)	1 (<1)
Hyperthyroidism	7 (9)	0	23 (10)	2 (1)
Rash	5 (6)	2 (3)	16 (7)	2 (1)
Hepatotoxicity	4 (5)	2 (3)	8 (3)	5 (2)
Diarrhea	4 (5)	1 (1)	13 (5)	5 (2)
Rash maculo-papular	3 (4)	0	6 (2)	0
Adrenal insufficiency	3 (4)	1 (1)	10 (4)	5 (2)
Pneumonitis	3 (4)	1 (1)	9 (4)	4 (2)
ALT increased	1 (1)	1 (1)	11 (5)	7 (3)
AST increased	1 (1)	1 (1)	7 (3)	3 (1)

AEs of any grade that occurred in ≥3% of patients in either subgroup with NIVO+CABO are summarized. Includes AEs that occurred after the first dose and through 100 days after the end of treatment.
Overall, 18% (14/79) of patients with bone metastasis and 22% (53/244) of patients without bone metastasis received high-dose corticosteroids (≥40 mg of prednisone daily or equivalent) to manage immune-mediated AEs; 11% and 4% with bone metastasis and 6% and 3% without bone metastasis received high-dose corticosteroids for ≥14 days and ≥30 days, respectively.

CONCLUSIONS

- In this post-hoc exploratory analysis, treatment with NIVO+CABO vs SUN improved PFS, OS, and ORR in patients with first-line aRCC irrespective of bone metastasis at baseline, consistent with outcomes reported in all randomized patients
- The overall safety profile of NIVO+CABO was comparable among patients with and without bone metastasis and consistent with all randomized patients
- Patients with bone metastasis had longer duration of therapy with NIVO+CABO vs SUN and higher incidence of grade 3/4 adverse events

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