Outcomes with first-line nivolumab plus cabozantinib versus sunitinib in patients with advanced renal cell carcinoma and treatment-related adverse event timing/management in CheckMate 9ER

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Background

- First-line nivolumab plus cabozantinib (NIVO+CABO) demonstrated superiority 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, leading to US Food and Drug Administration and European Medicines Agency approval of NIVO+CABO in this setting[1-3]
- The superior efficacy of NIVO+CABO over SUN was maintained with extended follow-up, and the safety profile of NIVO+CABO remained manageable (16.0 months minimum, 23.5 months median follow-up for overall survival [OS] in ITT patients)[4]
  - Median progression-free survival (PFS; 95% confidence interval [CI]) was 17.0 (12.6–19.4) months with NIVO+CABO versus 8.3 (6.9–9.7) months with SUN (hazard ratio [HR], 0.52; 95% CI, 0.43–0.64); the HR for OS was 0.66 (95% CI, 0.50-0.87); and the objective response rate (ORR) was 54.8% with NIVO+CABO versus 28.4% with SUN[4]
  - Treatment-related adverse events (AEs) occurred in 96.9% versus 93.1% of patients treated with NIVO+CABO versus SUN; 62.2% versus 52.5% had grade ≥ 3 treatment-related AEs, a nominal respective increase from those reported after 10.6 months minimum follow-up[1,4]
- To further inform clinical decision making, timing and management of grade ≥ 3 treatment-related AEs with NIVO+CABO and SUN in CheckMate 9ER were described and outcomes in patients with these events were assessed after 16.0 months minimum follow-up

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]
- The primary trial endpoint was PFS in ITT patients; secondary endpoints included OS and ORR (both in ITT patients), and safety in all treated patients[1]
- In this post hoc exploratory analysis, timing and management of grade ≥ 3 treatment-related AEs and outcomes in patients with these events were assessed using descriptive statistics
  - Treatment-related AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0, and classified according to the Medical Dictionary for Regulatory Activities, v23.0; grade ≥ 3 treatment-related AEs were reported between first dose and 30 days after last dose of study therapy
  - Dose delays for AEs were permitted for all trial drugs, however, dose reductions were not allowed for NIVO and were permitted for CABO and SUN
  - Dose reductions were permitted for CABO at 20 mg daily (first) and 20 mg every other day (second); and SUN at 37.5 mg daily (first) and 25 mg daily (second)
  - Discontinuation assessments for NIVO and CABO were made independently; if discontinuation criteria were met for just 1 drug, treatment with the other could continue
  - Both PFS outcomes and confirmed response outcomes were assessed per blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Results

Patients and AE management

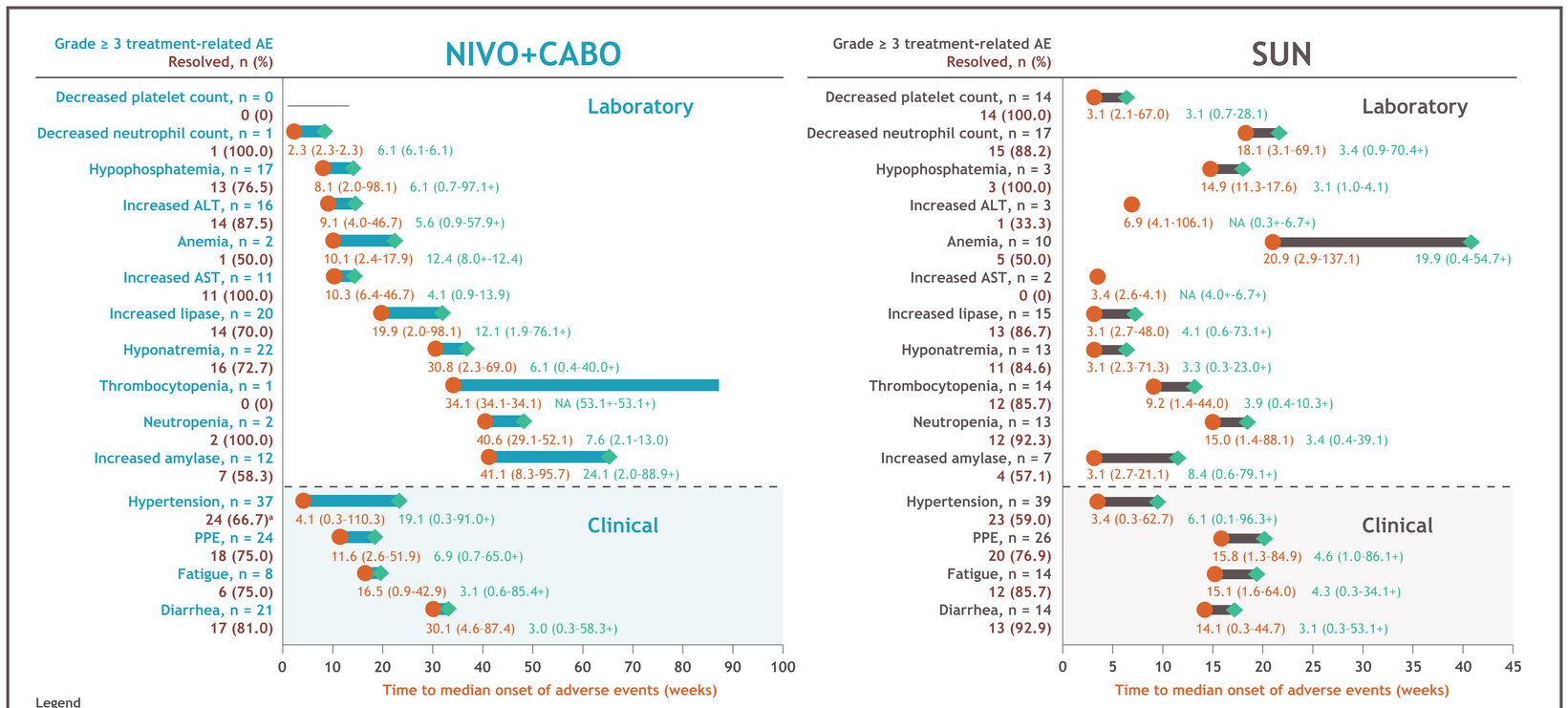
- Overall, 651 patients were randomized to NIVO+CABO (N = 323) or SUN (N = 328)
- Of all treated patients (n = 320 in each arm), 310 (NIVO+CABO) versus 298 (SUN) had any-grade treatment-related AEs and 199 versus 168 had grade ≥ 3 treatment-related AEs
  - Zero patients had a grade 5 treatment-related AE with NIVO+CABO. There was 1 fatal grade 4 treatment-related AE (small-intestine perforation) with NIVO+CABO and 2 fatal treatment-related AEs with SUN (1 grade 5 respiratory distress and 1 grade 4 pneumonia)[1]
- Baseline characteristics in patients with grade ≥ 3 treatment-related AEs were largely balanced between treatment arms (data not shown)
- Dose delays or reductions due to any AE occurring in patients after the onset of the first grade ≥ 3 treatment-related AE(s) are summarized in **Table 1**
  - Dose reduction and delay patterns were generally similar in both arms, and most patients with at least 1 dose delay or reduction continued on therapy in both arms
  - Patients in the NIVO+CABO arm experienced a longer time to dose reduction or delay versus SUN
- Overall, 52 of 199 (26.1%) treated patients in the NIVO+CABO arm with grade ≥ 3 treatment-related AEs received corticosteroids (≥ 40 mg of prednisone daily or equivalent) due to any AE occurring after the first grade ≥ 3 treatment-related AE in the NIVO+CABO arm
  - Twenty of 199 (10.1%) patients received corticosteroids continuously for at least 14 days
  - Nine of 199 (4.5%) patients received corticosteroids continuously for at least 30 days

Table 1. Summary of dose delays or reductions due to any AE occurring in patients after grade ≥ 3 treatment-related AEs

Patients with grade ≥ 3 treatment-related AEs[a]	NIVO+CABO (n = 199)			SUN (n = 168)
	NIVO	CABO	Overall	
With ≥ 1 dose delay, n (%)	98 (49.2)	77 (38.7)	122 (61.3)	94 (56.0)
Continuing treatment, n (%)	94 (95.9)	77 (100.0)	117 (95.9)	94 (100.0)
Median time to first dose delay (range), weeks	4.9 (0.9-91.3)	7.0 (0.3-99.9)	4.1 (0.3-81.3)	1.1 (0.3-77.4)
With ≥ 1 dose reduction (range), n (%)	-	89 (44.7)	-	97 (57.7)
Continuing treatment, n (%)	-	89 (100.0)	-	96 (98.9)
Median time to first dose reduction (range), weeks	-	4.9 (0.3-64.3)	-	4.0 (0.3-66.1)
With ≥ 1 dose delay or reduction, n (%)	-	-	143 (71.9)	118 (70.2)
Continuing treatment, n (%)	-	-	138 (96.5)	117 (99.2)
Median time to first dose delay or reduction (range), weeks	-	-	3.6 (0.3-63.4)	1.7 (0.3-37.4)

[a]Includes patients with grade ≥ 3 TRAEs reported between first dose and 30 days after last dose of study therapy.

Figure 1. Onset and resolution of common grade ≥ 3 treatment-related AEs



Includes most common grade ≥ 3 treatment-related AEs by preferred term (occurring in ≥ 5.5% of patients with grade ≥ 3 treatment-related AEs in either treatment arm) reported between first dose and 30 days after last dose of therapy. Treatment-related AEs that returned to grade 0-1 were considered resolved; treatment-related AEs without a stop date or with a stop date equal to the date of death as well as grade 5 events were considered unresolved (plus indicates a censored value). TTO aligns with the x-axis (weeks since median onset of AE) as shown. TTR begins at the time of AE onset.

[a]N = 36, excluding 1 patient who experienced this treatment-related AE without worsening from baseline grade.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not available; PPE, palmar-plantar erythrodysesthesia syndrome; TTO, time to onset; TTR, time to resolution.

Safety kinetics

- Time to onset and time to resolution of common grade ≥ 3 treatment-related AEs occurring in either arm, together with the associated rates of resolution, are depicted in **Figure 1** (note, this exploratory analysis was not powered to detect significant between-arm differences)
  - The majority of patients who had grade ≥ 3 treatment-related AEs resolved, as shown on the y-axis of **Figure 1** (Resolved, n [%])

Efficacy

- Efficacy benefits were observed with NIVO+CABO versus SUN among patients with grade ≥ 3 treatment-related AEs
  - Time to response was shorter, ORR was higher, and more patients achieved a complete response with NIVO+CABO (**Table 2**)
  - Median PFS and median duration of response (DOR) were longer with NIVO+CABO versus SUN, and the respective HRs favored the combination (**Figure 2**)

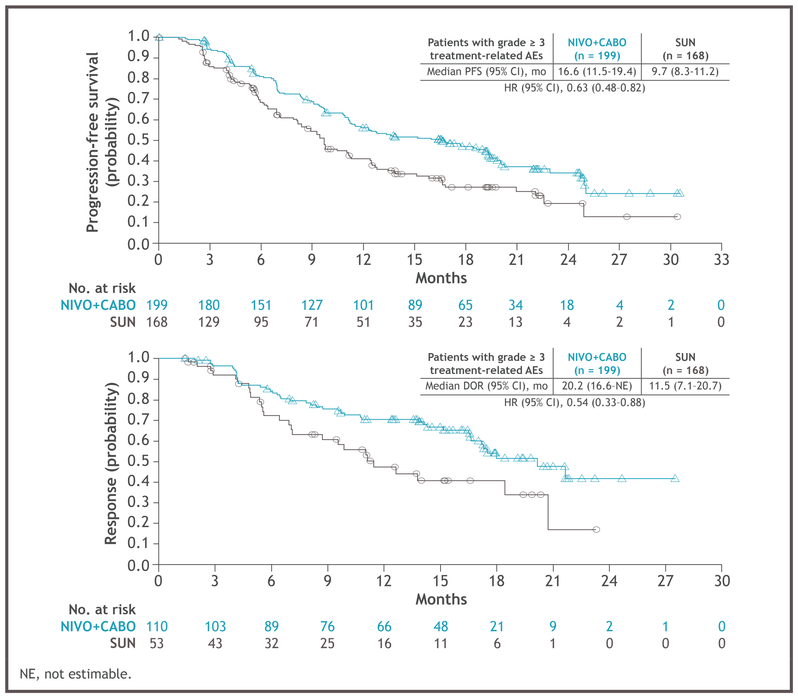
Table 2. Objective response outcomes per BICR

Patients with grade ≥ 3 treatment-related AEs	NIVO+CABO (n = 199)	SUN (n = 168)
Confirmed ORR (95% CI), %	55.3 (48.1-62.3)	31.5 (24.6-39.2)
Confirmed best overall response, n (%)		
Complete response	16 (8.0)	7 (4.2)
Partial response	94 (47.2)	46 (27.4)
Stable disease	73 (36.7)	76 (45.2)
Progressive disease	11 (5.5)	16 (9.5)
Unable to determine	5 (2.5)	23 (13.7)
Median time to response (range), months	2.8 (1.0-11.0)	4.3 (1.7-20.2)

Conclusions

- The safety profile of NIVO+CABO was manageable, and the majority of common grade ≥ 3 treatment-related AEs resolved in patients in the NIVO+CABO arm
- Frequencies of dose reductions and dose delays were largely balanced between treatment arms among patients with grade ≥ 3 treatment-related AEs, and almost all patients with at least 1 dose delay or reduction were able to subsequently continue therapy in both treatment arms
- Patients experiencing grade ≥ 3 treatment-related AEs in the NIVO+CABO arm derived similar efficacy benefits compared with the ITT population,[4] and PFS, ORR, and DOR were all improved with NIVO+CABO versus SUN in this subgroup regardless of dose delay or reduction patterns
- Data reported in this post hoc analysis help better inform the timely detection and proactive management of AEs that may occur with first-line NIVO+CABO versus SUN in patients with aRCC

Figure 2. Progression-free survival and duration of response



NE, not estimable.

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