European Journal of Cancer 177 (2022) 63–71

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Nivolumab plus ipilimumab plus cabozantinib triplet combination for patients with previously untreated advanced renal cell carcinoma: Results from a discontinued arm of the phase III CheckMate 9ER trial

Andrea B. Apolo [a,*], Thomas Powles [b], Bernard Escudier [c], Mauricio Burotto [d], Joshua Zhang [e], Burcin Simsek [f], Christian Scheffold [g], Robert J. Motzer [h,1], Toni K. Choueiri [i,1]

[a] *Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA*
[b] *Department of Genitourinary Oncology, Barts Cancer Institute, Cancer Research UK Experimental Cancer Medicine Centre, Queen Mary University of London, Royal Free National Health Service Trust, London, UK*
[c] *Department of Medical Oncology, Gustave Roussy, Villejuif, France*
[d] *Bradford Hill Clinical Research Center, Santiago, Chile*
[e] *Department of Clinical Research, Bristol Myers Squibb, Princeton, NJ, USA*
[f] *Department of Global Biometrics and Data Science, Bristol Myers Squibb, Princeton, NJ, USA*
[g] *Department of Clinical Development, Exelixis, Alameda, CA, USA*
[h] *Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA*
[i] *Department of Medical Oncology, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA*

Received 25 July 2022; received in revised form 20 September 2022; accepted 21 September 2022
Available online 4 October 2022

KEYWORDS
Cabozantinib;
Clinical trial;
Ipilimumab;
Nivolumab;
Renal cell carcinoma

Abstract ***Background:*** The phase III CheckMate 9ER trial originally included a nivolumab plus ipilimumab plus cabozantinib triplet arm, which was discontinued early due to the evolving treatment landscape for first-line advanced renal cell carcinoma (aRCC). We report an exploratory analysis of patients randomised to the triplet regimen before enrolment discontinuation.

Methods: Patients with clear-cell aRCC received nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) Q3W for four cycles with once-daily cabozantinib (40 mg), then nivolumab (240 mg) Q2W plus once-daily cabozantinib (40 mg). CheckMate 9ER primary (progression-free survival

* *Corresponding author*: Genitourinary Malignancies Branch, National Cancer Institute, 10 Center Dr, Room 13N240, Bethesda, MD 20892, USA.
E-mail address: andrea.apolo@nih.gov (A.B. Apolo).
[1] Served as co-senior authors.

https://doi.org/10.1016/j.ejca.2022.09.020

[PFS] by blinded independent central review [BICR]) and key secondary (overall survival [OS], objective response rate [ORR] by BICR, and safety) endpoints were applied, along with investigator-assessed PFS and ORR.

Results: Fifty patients were randomised to the triplet regimen. After a median follow-up of 39.1 months (range, 33.4–44.5), median PFS (95% CI) was 9.9 (5.7–16.8) months by BICR and 13.9 (7.3–24.7) months by investigator; median OS (95% CI) was 37.0 (31.8-not estimable) months. ORR (95% CI) was 44.0% (30.0–58.7; complete response, 8.0%) by BICR and 48.0% (33.7–62.6; all partial responses) by investigator. Grade 3–4 treatment-related adverse events (TRAEs) occurred in 84.0%, most commonly alanine aminotransferase increased (20.0%), aspartate aminotransferase increased (16.0%), and hepatotoxicity (16.0%). Grade 3–4 hepatic immune-mediated AEs occurred in 40.0%. There were no grade 5 TRAEs.

Conclusions: These results suggest that the nivolumab plus ipilimumab plus cabozantinib triplet combination has clinical activity in patients with previously untreated aRCC, although monitoring of overlapping toxicities will be important in future studies of this regimen.

ClinicalTrials.gov registration: NCT03141177.

1. Introduction

Treatment of advanced renal cell carcinoma (aRCC) has been transformed by the emergence of novel immunotherapies and immunotherapy-based combination approaches. As an example, in the past 5 years, combinations of nivolumab plus ipilimumab (a programmed death 1 [PD-1] inhibitor plus a cytotoxic T-lymphocyte–associated antigen 4 inhibitor) and nivolumab plus cabozantinib (a PD-1 inhibitor plus a small-molecule tyrosine kinase inhibitor) have demonstrated long-term overall survival (OS) benefits as first-line treatments for aRCC in the CheckMate 214 and CheckMate 9ER trials, respectively [1–4], and both doublet regimens are now approved by the US Food and Drug Administration and European Medicines Agency for previously untreated aRCC [5,6]. Despite these recent advances, investigations continue to evaluate alternative combination strategies and new immunotherapeutic targets to further improve outcomes and address continuing unmet needs in aRCC [7–9].

The CheckMate 9ER trial was initiated in August 2017 and originally included three treatment arms designed to compare outcomes for nivolumab plus cabozantinib versus sunitinib and nivolumab plus ipilimumab plus cabozantinib versus sunitinib in patients with previously untreated clear-cell aRCC. Shortly after the trial began, data from CheckMate 214 demonstrated the OS superiority of nivolumab plus ipilimumab versus sunitinib for patients with International Metastatic Renal-Cell Carcinoma Database Consortium (IMDC) intermediate- or poor-risk previously untreated aRCC [1], suggesting an immediate role for nivolumab plus ipilimumab as standard of care for this patient population. Based on this evolving aRCC treatment landscape, the CheckMate 9ER triplet arm was discontinued early via a protocol amendment in December 2017.

Recent early-phase studies of the nivolumab plus ipilimumab plus cabozantinib triplet have shown preliminary evidence of clinical activity in patients with metastatic urothelial carcinoma and other advanced genitourinary tumours, including aRCC [10], as well as in patients with advanced hepatocellular carcinoma [11]. Moreover, this triplet regimen is currently under investigation for various RCC populations in phase II (NCT04413123) and III (COSMIC-313; NCT03937219) clinical trials [12,13]. Of note, COSMIC-313, a trial evaluating the triplet regimen versus nivolumab plus ipilimumab plus placebo in patients with intermediate- or poor-risk previously untreated aRCC, recently met its primary endpoint, demonstrating significant improvement in PFS at the primary analysis [14,15]. We report results from an exploratory analysis of patients randomised to nivolumab plus ipilimumab plus cabozantinib in CheckMate 9ER before enrolment discontinuation.

2. Methods

2.1. Study design

CheckMate 9ER is a phase III randomised, open-label clinical trial. Per the original study design and before discontinuation of the triplet regimen arm, patients were randomised 1:1:1 to either nivolumab plus cabozantinib, nivolumab plus ipilimumab plus cabozantinib, or sunitinib monotherapy. Stratification factors for randomisation were IMDC prognostic risk score (0 [favourable] versus 1–2 [intermediate] versus 3–6 [poor]), tumour programmed death ligand 1 (PD-L1) expression ($\geq$1% versus <1% or indeterminate), and geographic region

(United States, Canada, Western Europe, Northern Europe versus rest of the world).

2.2. Patient population

Eligibility criteria for CheckMate 9ER have been reported previously [3]. In brief, enrolled patients were adults with histologically confirmed locally advanced or metastatic RCC with a clear-cell component (including those with sarcomatoid features), no previous systemic therapy for RCC (except for one previous adjuvant/neoadjuvant therapy for resectable RCC if it did not include agents targeting VEGF or VEGF receptors), a Karnofsky performance status score of $\geq$70, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 and any IMDC prognostic risk score. Exclusion criteria included active CNS metastases, active or suspected autoimmune disease, conditions requiring corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days before randomisation, and prior treatment with therapy targeting VEGF, MET, AXL, KIT or RET (the most prominent targets of cabozantinib) or agents specifically targeting T-cell co-stimulation or checkpoint pathways.

The trial was approved by the institutional review board or ethics committee at each study site and was conducted in accordance with Good Clinical Practice guidelines, as defined by the International Council for Harmonisation. All enrolled patients provided written informed consent according to Declaration of Helsinki principles.

2.3. Procedures

Patients randomised to the triplet arm received intravenous infusions of nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four cycles with concurrent administration of oral cabozantinib 40 mg once daily. This was followed by intravenous nivolumab 240 mg every 2 weeks and continuation of oral cabozantinib 40 mg once daily. Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent or end of study, with a maximum duration of 24 months of nivolumab treatment (from first dose of nivolumab plus ipilimumab), whichever occurred first. Dose delays for management of adverse events (AEs) were allowed for all three study treatments, with delay criteria assessed separately for nivolumab plus ipilimumab and cabozantinib from cycles 1 to 4 and separately for nivolumab and cabozantinib from cycle 5 onward. Dose reductions were allowed only for cabozantinib. Assessments for treatment discontinuation were made separately for nivolumab, ipilimumab, and cabozantinib; if discontinuation criteria were met for one drug but not others, treatment could continue with the drug(s) believed to be unrelated to the reported toxicity.

2.4. Assessments

The primary endpoint of CheckMate 9ER was progression-free survival (PFS) as assessed by blinded independent central review (BICR). Secondary endpoints were OS, objective response rate (ORR; defined as the proportion of randomised patients achieving a partial or complete response per RECIST v1.1 as assessed by BICR), time to and duration of objective response, and safety. These endpoints were applied to this exploratory analysis, with additional supportive endpoints of PFS and ORR as assessed by the study-site investigators.

AEs (non-serious and serious) were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events v.4.0 and are reported between first dose and 30 days after last dose of study therapy. Immune-mediated AEs (i.e. those consistent with an immune-mediated mechanism or component for which non-inflammatory aetiologies, e.g. infection or tumour progression, were ruled out) are reported up to 100 days after last dose of study drug. Classification of AEs as 'immune-mediated' was performed by the study investigators and was not related to assignment of causality to any specific study drug.

Tumour assessments were performed by computed tomography or magnetic resonance imaging of the chest, abdomen, pelvis, brain (baseline only), and all known sites of disease at baseline (within 28 days before randomisation), at week 12 ($\pm$7 days), then every 6 weeks ($\pm$7 days) until week 60, then every 12 weeks ($\pm$14 days) until radiographic progression (as assessed by the investigator and confirmed by BICR) or treatment discontinuation. PD-L1 expression status was evaluated using the validated PD-L1 IHC 28-8 pharmDx immunohistochemical assay (Dako, an Agilent Technologies company, Santa Clara, CA, USA).

2.5. Statistical analyses

Protocol-defined statistical analyses for CheckMate 9ER have been described previously [3]. Because this report pertains to data from a single treatment arm with no formal comparisons, descriptive statistics are used throughout. ORRs and corresponding two-sided exact 95% confidence intervals (CIs) were calculated using Clopper–Pearson methodology [16]. PFS, OS, and time to and duration of objective response were estimated using the Kaplan–Meier method [17].

3. Results

Fifty eligible patients were randomised to receive nivolumab plus ipilimumab plus cabozantinib triplet combination in CheckMate 9ER before enrolment discontinuation. Baseline characteristics for this cohort

are shown in Table 1. The largest proportions of enrolled patients were from Chile (n = 11; 22.0%), Mexico (n = 11; 22.0%) and the United States (n = 10; 20.0%). Overall, 11 patients (22.0%) had IMDC favourable-risk, 31 (62.0%) had intermediate-risk and eight (16.0%) had poor-risk characteristics; 14 patients (28.0%) had tumour PD-L1 expression ≥1%. As of the database lock for this analysis (24 June 2021), 45 patients had discontinued treatment, with five (10.0%) continuing study treatment (Table S1); primary reasons for treatment discontinuation were disease progression (n = 24; 48.0%) and study drug toxicity (n = 11; 22.0%). In the first 6 months of the treatment period, 15 patients (30.0%) discontinued treatment.

Table 1
Patient demographic and clinical characteristics at baseline (all randomised patients).

	Nivolumab + ipilimumab + cabozantinib (N = 50)
Median age (range), years	60 (40–84)
Age category, *n* (%)	
< 65 years	31 (62.0)
≥ 65 years	19 (38.0)
Sex, *n* (%)	
Male	34 (68.0)
Female	16 (32.0)
Race, *n* (%)	
White	43 (86.0)
Black or African American	0
Asian	0
Other[a]	7 (14.0)
Geographic region, *n* (%)[b]	
United States, Canada, or Europe	22 (44.0)
Rest of the world	28 (56.0)
Karnofsky performance status score, *n* (%)	
90 or 100	42 (84.0)
70 or 80	8 (16.0)[c]
IMDC prognostic risk score, *n* (%)	
Favourable: 0	11 (22.0)
Intermediate: 1 or 2	31 (62.0)
Poor: 3-6	8 (16.0)
Tumour PD-L1 expression, *n* (%)	
≥ 1%	14 (28.0)
< 1% or indeterminate	35 (70.0)
Not evaluable	1 (2.0)
Sarcomatoid features, *n* (%)	
Yes	9 (18.0)
No	40 (80.0)
Not reported	1 (2.0)
Previous radiotherapy, *n* (%)	6 (12.0)
Previous nephrectomy, *n* (%)	41 (82.0)
No. of sites with target or non-target lesions, *n* (%)	
1	5 (10)
≥ 2	45 (90.0)
Most common sites of metastasis, *n* (%)	
Lung	34 (68.0)
Lymph node	24 (48.0)
Bone	13 (26.0)
Liver	11 (22.0)
Adrenal gland	7 (14.0)

IMDC, International Metastatic Renal-Cell Carcinoma Database Consortium; PD-L1, programmed death ligand 1.
[a] Other race included Hispanic, Latino, unknown or not specified.
[b] Countries with highest enrolment were Chile (n = 11), Mexico (n = 11) and the United States (n = 10).
[c] No patients had a Karnofsky performance status score of 70.

Twenty-two patients (44.0%) received any subsequent anticancer therapy (started on or after the day of first study drug administration), with 20 (40.0%) receiving subsequent systemic anticancer therapy. The most common subsequent systemic anticancer treatments were VEGF/VEGFR-targeted therapies, received by 17 patients (34.0%), including sunitinib, pazopanib, cabozantinib, and axitinib. Additionally, four patients (8.0%) received subsequent mTOR inhibitor therapy and two patients (4.0%) received subsequent PD-1/PD-L1 inhibitor therapy.

At a median follow-up of 39.1 (range, 33.4–44.5) months for OS, median PFS (95% CI) by BICR was 9.9 (5.7–16.8) months with a 24-month PFS rate (95% CI) of 30.0% (17.2–43.9) (Fig. 1A). Median PFS (95% CI) by investigator was 13.9 (7.3–24.7) months with a 24-month PFS rate (95% CI) of 39.3% (25.1–53.1) (Fig. 1B). Median OS (95% CI) was 37.0 (31.8-not estimable) months with a 24-month OS rate (95% CI) of 73.3% (58.4–83.5) (Fig. 1C). Confirmed ORR (95% CI) by BICR was 44.0% (30.0–58.7), with four patients (8.0%) achieving complete responses and 18 (36.0%) achieving partial responses (Table 2). Confirmed ORR (95% CI) by investigator was 48.0% (33.7–62.6), consisting of 24 patients (48.0%) achieving partial responses. Median time to objective response (interquartile range) by BICR was 2.8 (2.6–4.2) months and median duration of response by BICR (95% CI) was 21.4 (13.8–30.6) months (Table 2).

Treatment exposure is summarised in Table S2. Overall median (range) duration of treatment was 15.9 (0.0–38.8) months. The median (range) number of doses received was 19 (1–51) for nivolumab and four (1–4) for ipilimumab; median (range) average daily dose of cabozantinib was 23.5 (10–40) mg/day. Among treated patients, 39 of 50 (78.0%) had ≥1 nivolumab dose delay and 19 of 50 (38.0%) had ≥1 ipilimumab dose delay, with most delays due to AEs. Of the 49 patients treated with cabozantinib, 43 (87.8%) had ≥1 cabozantinib dose delay and 33 (67.3%) had ≥1 cabozantinib dose reduction, with most dose adjustments due to AEs (Table S2).

Treatment-related AEs occurred in 48 patients (96.0%), the most common being diarrhoea (n = 27; 54.0%), increased alanine aminotransferase (n = 24; 48.0%), increased aspartate aminotransferase (n = 19; 38.0%) and palmar-plantar erythrodysaesthesia syndrome (n = 19, 38.0%) (Table 3). Grade 3–4 treatment-related

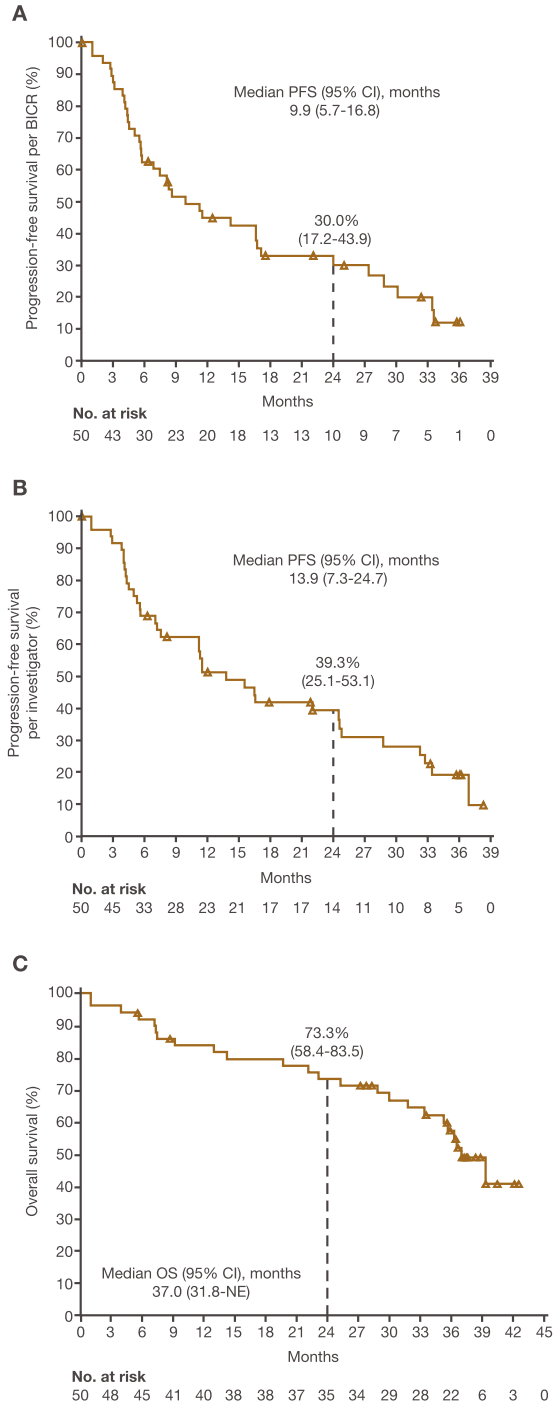

Fig. 1. Kaplan–Meier plots of (A) PFS per BICR, (B) PFS per study investigators, and (C) OS. BICR, blinded independent central review; CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival. 24-month survival probabilities are presented with 95% CIs.

AEs occurred in 42 patients (84.0%), the most common being alanine aminotransferase increased (n = 10; 20.0%), aspartate aminotransferase increased (n = 8; 16.0%) and hepatotoxicity (n = 8; 16.0%) (Table 3). No patients experienced a grade 5 treatment-related AE. Treatment-related serious AEs occurred in 15 patients

Table 2
Objective response outcomes (all randomised patients).

Variable as assessed by BICR	Nivolumab + ipilimumab + cabozantinib (N = 50)
Confirmed ORR (95% CI), %[a]	44.0 (30.0–58.7)
BOR, n (%)	
Complete response	4 (8.0)
Partial response	18 (36.0)
Stable disease	19 (38.0)
Progressive disease	4 (8.0)
Unable to determine[b]	5 (10.0)
Median time to response (IQR), months[c]	2.8 (2.6–4.2)
Median duration of response (95% CI), months[c]	21.4 (13.8–30.6)
Variable as assessed by study investigators	**Nivolumab + ipilimumab + cabozantinib (N = 50)**
Confirmed ORR (95% CI), %[a]	48.0 (33.7–62.6)
BOR, n (%)	
Complete response	0
Partial response	24 (48.0)
Stable disease	20 (40.0)
Progressive disease	2 (4.0)
Unable to determine[d]	4 (8.0)

BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; IQR, interquartile range; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

[a] Confirmed complete or partial response per RECIST v.1.1.

[b] Reasons for classification as 'unable to determine' by BICR included death prior to tumour assessment (n = 3), lost to follow-up prior to tumour assessment (n = 1), and receipt of subsequent anti-cancer therapy (n = 1).

[c] Median time to response and median duration of response were calculated only for the 22 patients who had a complete or partial response per BICR.

[d] Reasons for classification as 'unable to determine' by study investigators included death prior to tumour assessment (n = 3) and lost to follow-up prior to tumour assessment (n = 1).

(30.0%), with all experiencing a grade 3–4 event; the most common any-grade and grade 3–4 treatment-related serious AEs were hepatic events, occurring in six patients (12.0%).

Treatment-related AEs led to discontinuation of either nivolumab, ipilimumab or cabozantinib in a total of 23 patients (46.0%); nine patients (18.0%) discontinued nivolumab plus ipilimumab only, five (10.0%) discontinued cabozantinib only, eight (16.0%) discontinued all three treatments simultaneously and one (2.0%) discontinued all three treatments sequentially (Table S3). Overall, the most common treatment-related AEs leading to discontinuation were hepatic in nature (e.g. increased alanine or aspartate aminotransferase and hepatitis).

Immune-mediated AEs are summarised in Table 4. The most common events were hepatic immune-mediated AEs, occurring in 22 patients (44.0%) at any grade and 20 patients (40.0%) at grade 3–4. Median (range) time to

Table 3
Summary of treatment-related AEs (all treated patients).

Treatment-related AEs, *n* (%)[a]	Nivolumab + ipilimumab + cabozantinib (*N* = 50)		
	Any grade	Grade 3	Grade 4
At least one adverse event	48 (96.0)	28 (56.0)	14 (28.0)
Diarrhoea	27 (54.0)	2 (4.0)	0
ALT increased	24 (48.0)	8 (16.0)	2 (4.0)
AST increased	19 (38.0)	6 (12.0)	2 (4.0)
PPE syndrome	19 (38.0)	7 (14.0)	0
Fatigue	16 (32.0)	1 (2.0)	0
Nausea	16 (32.0)	0	0
Rash	15 (30.0)	2 (4.0)	0
Hypothyroidism	15 (30.0)	0	0
Lipase increased	14 (28.0)	3 (6.0)	4 (8.0)
Hypertension	14 (28.0)	4 (8.0)	0
Decreased appetite	14 (28.0)	1 (2.0)	0
Mucosal inflammation	13 (26.0)	1 (2.0)	0
Hepatotoxicity	10 (20.0)	6 (12.0)	2 (4.0)
Anaemia	10 (20.0)	6 (12.0)	0
Amylase increased	10 (20.0)	2 (4.0)	1 (2.0)
Pruritus	10 (20.0)	0	0
Asthaenia	9 (18.0)	3 (6.0)	0
Abdominal pain	8 (16.0)	1 (2.0)	0
Dysgeusia	8 (16.0)	0	0
Weight decreased	8 (16.0)	0	0
Myalgia	7 (14.0)	1 (2.0)	0
Blood alkaline phosphatase increased	6 (12.0)	1 (2.0)	0
Blood bilirubin increased	6 (12.0)	1 (2.0)	0
Maculo-papular rash	6 (12.0)	1 (2.0)	0
Arthralgia	6 (12.0)	0	0
Blood creatinine increased	6 (12.0)	0	0
Dysphonia	6 (12.0)	0	0
Headache	6 (12.0)	0	0
Muscle spasms	6 (12.0)	0	0
Stomatitis	6 (12.0)	0	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysaesthesia syndrome.
[a] Includes individual treatment-related AEs occurring in ≥6 patients (≥12%) during treatment or within 30 days after the last dose of study therapy.

immune-mediated hepatic AEs was 6.4 (3.0–35.1) weeks for any-grade events and 8.9 (3.1–28.7) weeks for grade 3–4 events (Table 4). Overall, 26 patients (52.0%) received continuous glucocorticoids (≥40 mg of prednisone or equivalent) to manage immune-mediated AEs; 20 (40.0%) and 10 (20.0%) patients received glucocorticoids continuously for ≥14 days and ≥30 days, respectively.

In total, 24 patients (48.0%) had died as of the database lock, 19 due to disease progression and five due to other reasons; no deaths were related to study drug toxicity.

4. Discussion

This exploratory analysis of patients randomised to nivolumab plus ipilimumab plus cabozantinib triplet combination before enrolment discontinuation in CheckMate 9ER showed that the regimen has clinical activity in patients with previously untreated aRCC, with a median PFS of 9.9 months by BICR and 13.9 months by investigator, an ORR of 44.0% by BICR and 48.0% by investigator, and a median OS of 37.0 months after a median follow-up of 39.1 months. However, although the safety profile of nivolumab plus ipilimumab plus cabozantinib was generally as expected based on studies of the individual components and phase I combination data, there was a noteworthy incidence of reported treatment-related and immune-mediated hepatic AEs.

Published detailed safety data specific to the triplet combination of nivolumab plus ipilimumab plus cabozantinib are currently limited to a dose-escalation study of this regimen for patients with advanced or metastatic genitourinary tumours, including aRCC [10], and several associated expansion cohorts [18]. In that dose-escalation study, while hepatitis was the most common immune-related AE requiring high-dose corticosteroids, the overall incidence of reported hepatic AEs was notably lower than observed in our exploratory analysis. Similarly, although treatment-related and immune-mediated hepatic AEs were reported with the separate component doublet combinations, namely nivolumab plus ipilimumab (in CheckMate 214) and nivolumab plus cabozantinib (in CheckMate 9ER), the incidence of these events was uniformly lower than seen for the triplet arm in this analysis [3,19]. Taken together these findings emphasise the importance of education around toxicity management as cancer treatments become more complex [20].

In this exploratory analysis, we did not see a clear increase in efficacy compared with that reported previously for the component doublet combinations (nivolumab plus ipilimumab or nivolumab plus cabozantinib) after similar follow-up [4,19], acknowledging the small sample size in the current analysis and the inherent shortcomings of non-statistical and cross-trial comparisons. The synergistic pathways driving tumour responses to novel combination therapies are complex and our understanding of these pathways continues to evolve. For example, in correlative immune subset studies using data from the aforementioned dose-escalation study, the nivolumab plus ipilimumab plus cabozantinib and nivolumab plus cabozantinib regimens showed distinct patterns of immune cell modulation, with the triplet regimen appearing to induce an overstimulated effector T-cell response ([21] and unpublished results). Another hypothetical reason for the observed lower than expected efficacy herein could be decreased time on therapy for patients in the triplet regimen arm due to early discontinuations for toxicities (see Table S2). Ultimately, the triplet arm of CheckMate 9ER and this associated analysis have several limitations that should be considered when evaluating the reported efficacy data, particularly the early enrolment discontinuation, the relatively limited clinical

Table 4
Summary of immune-mediated AEs (all treated patients).

Immune-mediated category[a]	All treated patients ($N = 50$)			
	Any grade, *n* (%)	Median (range) time to onset, weeks[b]	Grade 3–4, *n* (%)	Median (range) time to onset, weeks[b]
Hepatitis	22 (44.0)	6.4 (3.0–35.1)	20 (40.0)	8.9 (3.1–28.7)
Hypothyroidism/thyroiditis	13 (26.0)	–	0	–
Rash	10 (20.0)	5.8 (1.7–117.6)	3 (6.0)	8.0 (4.4–44.0)
Diarrhoea/colitis	5 (10.0)	20.9 (9.3–79.9)	0	–
Hyperthyroidism	3 (6.0)	–	0	–
Adrenal insufficiency	1 (2.0)	–	0	–
Hypersensitivity	1 (2.0)	4.3 (4.3–4.3)	0	–
Pneumonitis	1 (2.0)	9.0 (9.0–9.0)	0	–

AE, adverse event.
[a] Represents specific AEs reported between first dose and 100 days after last dose of study therapy, regardless of causality, requiring treatment with immune-modulating medication, and with no clear alternate aetiology based on investigator assessment, or with an immune-mediated component. Events included in the hypothyroidism/thyroiditis, hyperthyroidism and adrenal insufficiency categories were considered immune-mediated regardless of immune-modulating medication use, as these endocrine AEs were often managed without immune-modulating medication.
[b] Data are for non-endocrine immune-mediated AEs reported between first dose and 100 days after last dose of study therapy where immune-modulating medication was initiated. Time to onset of endocrine immune-mediated events is not presented.

experience of the triplet regimen at the start of this study in 2017, and the unplanned and exploratory nature of the analysis. Moreover, due to these and other limitations, there has not been an attempt to statistically compare the efficacy of the triplet regimen with the other two arms of CheckMate 9ER.

Very recently, top-line data from the randomised, phase III COSMIC-313 trial of nivolumab plus ipilimumab plus cabozantinib versus nivolumab plus ipilimumab plus placebo in patients with intermediate- or poor-risk, previously untreated advanced/metastatic RCC have been published [15]. The COSMIC-313 study met its primary endpoint by demonstrating a significant benefit in PFS with the triplet regimen (cabozantinib + nivolumab + ipilimumab) versus the control arm (placebo + nivolumab + ipilimumab) in previously untreated patients with aRCC of IMDC intermediate or poor risk. Among patients receiving the triplet regimen in COSMIC-313, the ORR (43%) was similar to that seen with the triplet regimen in CheckMate 9ER, but PFS per BICR appeared longer (median PFS not reached, 95% CI, 14.0-not estimable). In terms of safety, grade 3–4 treatment-related AEs occurred in 73% of patients and treatment-related AEs led to discontinuation of all 3 treatments due to the same AE in 12%, which is only marginally lower than the corresponding rates observed herein (84% and 18%, respectively) [15]. Publication of the full efficacy and safety dataset from COSMIC-313 is awaited with interest and will provide a more detailed understanding of the overall role for the triplet regimen as a treatment option for patients with previously untreated advanced/metastatic RCC.

5. Conclusion

Efficacy results from this exploratory analysis add to existing evidence suggesting clinical activity of nivolumab plus ipilimumab plus cabozantinib across multiple tumour types [10,11], and provide preliminary insights into possible outcomes among patients with previously untreated aRCC. Although no new safety signals were observed with nivolumab plus ipilimumab plus cabozantinib, careful monitoring and management of early toxicities, particularly hepatic AEs, will be important for future trials of this triplet combination in the first-line aRCC setting.

Author contributions

Andrea B. Apolo: Conceptualisation, Investigation, Writing - Original Draft, Writing - Review & Editing.

Thomas Powles: Conceptualisation, Investigation, Writing - Original Draft, Writing - Review & Editing.

Bernard Escudier: Conceptualisation, Investigation, Writing - Original Draft, Writing - Review & Editing.

Mauricio Burotto: Conceptualisation, Investigation, Writing - Original Draft, Writing - Review & Editing.

Joshua Zhang: Data curation, Validation, Writing - Original Draft, Writing - Review & Editing.

Burcin Simsek: Data curation, Formal analysis, Validation, Writing - Original Draft, Writing - Review & Editing.

Christian Scheffold: Conceptualisation, Writing - Original Draft, Writing - Review & Editing.

Robert J. Motzer: Conceptualisation, Investigation, Validation, Writing - Original Draft, Writing - Review & Editing.

Toni K. Choueiri: Conceptualisation, Investigation, Validation, Writing - Original Draft, Writing - Review & Editing.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

ABA has nothing to disclose.

TP reports grants from AstraZeneca, Roche, Bristol Myers Squibb (BMS), Exelixis, Ipsen, Merck, Merck Sharp and Dohme (MSD), Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas Pharma, Johnson & Johnson, and Eisai; consulting fees from BMS, Merck, AstraZeneca, Ipsen, Pfizer, Novartis, Incyte, Seattle Genetics, Roche, Exelixis, MSD, Merck Serono, Astellas Pharma, Johnson & Johnson, and Eisai; and travel support from Pfizer, MSD, AstraZeneca, Roche, and Ipsen.

BE reports institutional research grant from BMS; consulting fees from Pfizer, BMS, Ipsen, AVEO Pharmaceuticals, Oncorena, and Eisai; honoraria from Pfizer, BMS, Ipsen, Oncorena, and Eisai; and travel support from BMS, Ipsen, and MSD.

MB reports consulting fees from Roche/Genentech, BMS, MSD Oncology, Novartis, and AstraZeneca; and speakers bureau fees from Roche/Genentech, MSD Oncology, BMS, and AstraZeneca.

JZ is employed by and has stock ownership in BMS.

BS is employed by and has stock ownership in BMS.

CS is employed by and has stock ownership in Exelixis.

RJM reports advisory board fees from AstraZeneca, AVEO Pharmaceuticals, Eisai, EMD Serono, Exelixis, Genentech/Roche, Incyte, Lilly Oncology, Merck, Novartis, and Pfizer; and institutional funding from BMS, Eisai, Exelixis, Genentech/Roche, Merck, and Pfizer.

TKC reports research grants, consulting fees, honoraria, and advisory board fees from AstraZeneca, Aravive, AVEO Pharmaceuticals Bayer, BMS, Calithera, Circle Pharma, Eisai, EMD Serono, Exelixis, GlaxoSmithKline, IQVIA, Infinity, Ipsen, Janssen, Kanaph, Lilly, Merck, NiKang, Novartis, Pfizer, Precede Bio, Roche, Sanofi-Aventis, Surface Oncology, Takeda, Tempest, UpToDate, and CME events (Peerview, OncLive, MJH, and others), outside the submitted work; institutional patents filed on molecular biomarkers and immunotherapy, and ctDNA; past fees from NCCN, GU Steering Committee, ASCO, and ESMO; stock ownership in Pionyr, Tempest, Osel, and Precede Bio, outside the submitted work; other financial or non-financial interests include medical writing and editorial assistance support that may have been funded by communications companies in part; potential funding (in part) from non-US sources/foreign components for mentor of several non-US citizens on research projects; independent funding by drug companies and/or royalties potentially involved in research around the subject matter (institutional); support in part by the Dana-Farber/Harvard Cancer Center Kidney SPORE (2P50CA101942-16) and Program 5P30CA006516-56, the Kohlberg Chair at Harvard Medical School and the Trust Family, Michael Brigham, and Loker Pinard Funds for Kidney Cancer Research at DFCI.

Funding

This work was supported by Bristol Myers Squibb.

Acknowledgements

We thank the patients and their families for making this trial possible; the CheckMate 9ER global trial manager; and the staff of Dako, an Agilent Technologies company, for collaborative development of the PD-L1 IHC 28-8 pharmDx assay. Patients treated at Memorial Sloan Kettering Cancer Center were supported in part by Memorial Sloan Kettering Cancer Center Support Grant/Core Grant (P30 CA008748). Professional medical writing and editorial assistance was provided by Richard Daniel, PhD, of Parexel, funded by Bristol Myers Squibb.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.09.020.

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