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Real-world outcomes of nivolumab and cabozantinib in metastatic renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium

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ABSTRACT

Objectives In the present study, we explored the real-world efficacy of the immuno-oncology checkpoint inhibitor nivolumab and the tyrosine kinase inhibitor cabozantinib in the second-line setting.

Methods Using the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) dataset, a retrospective analysis of patients with metastatic renal cell carcinoma (MRCC) treated with nivolumab or cabozantinib in the second line after prior therapy targeted to the vascular endothelial growth factor receptor (VEGFR) was performed. Baseline characteristics and IMDC risk factors were collected. Overall survival (OS) and time to treatment failure (TTF) were calculated using Kaplan–Meier curves. Overall response rates (ORRS) were determined for each therapy. Multivariable Cox regression analysis was performed to determine survival differences between cabozantinib and nivolumab treatment.

Results The analysis included 225 patients treated with nivolumab and 53 treated with cabozantinib. No significant difference in median OS was observed: 22.10 months [95% confidence interval (CI): 17.18 months to not reached] with nivolumab and 23.70 months (95% CI: 15.52 months to not reached) with cabozantinib ($p = 0.61$). The TTF was also similar at 6.90 months (95% CI: 4.60 months to 9.20 months) with nivolumab and 7.39 months (95% CI: 5.52 months to 12.85 months) with cabozantinib ($p = 0.20$). The adjusted hazard ratio (HR) for nivolumab compared with cabozantinib was 1.30 (95% CI: 0.73 to 2.3), $p = 0.38$. When adjusted by IMDC criteria and age, the HR was 1.32 (95% CI: 0.74 to 2.38), $p = 0.35$.

Conclusions Real-world IMDC data indicate comparable OS and TTF for nivolumab and cabozantinib. Both agents are reasonable therapeutic options for patients progressing after initial first-line VEGFR-targeted therapy.

Key Words Renal cell carcinoma, metastatic; targeted therapy; checkpoint inhibitors; nivolumab; cabozantinib

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INTRODUCTION

The treatment landscape for metastatic renal cell carcinoma (MRCC) has changed considerably in recent years. Inhibitors of the vascular endothelial growth factor receptor (VEGFR) family and the mechanistic target of rapamycin pathways have long dominated. Positive

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results from the pivotal METEOR and CheckMate 025 trials led, respectively, to approval of the novel agents cabozantinib and nivolumab[1,2].

In the METEOR trial, 658 patients with mRCC were randomized to either cabozantinib or everolimus after at least 1 previous line of treatment with VEGFR tyrosine kinase inhibitor[1]. Cabozantinib has a unique mechanism of action whereby it targets VEGFR as well as MET and AXL, thus targeting multiple signalling pathways at once[1,3,4]. The final results of the METEOR trial demonstrated, for the cabozantinib and everolimus groups, an overall survival (OS) of 21.4 months and 16.5 months respectively and a progression-free survival of 7.4 months and 3.8 months respectively[5]. Patients treated with cabozantinib experienced an independently-assessed objective response rate (ORR) of 17%, compared with 3% with everolimus[5]. As a result, cabozantinib became the first drug in the second-line setting to show significant improvements in the endpoints of OS, progression-free survival, and ORR. Grade 3 or greater toxicity was observed in 68% of the patients receiving cabozantinib, and 60% of the patients required dose reductions[1,5].

The CheckMate 025 trial randomized 823 patients with clear-cell mRCC to nivolumab or everolimus after 1 or 2 prior antiangiogenic therapy regimens[2]. Nivolumab is an inhibitory monoclonal antibody directed against PD-1, allowing for an effective T cell–mediated immune response to cancer cells[2–4]. In CheckMate 025, the OS duration was 25 months for the nivolumab-treated group[2]. The progression-free survival reported for the nivolumab and everolimus groups was 4.6 months and 4.4 months respectively[2]. The investigator-assessed ORR in the nivolumab group was 25%[2]. Further subgroup analyses showed that a response to nivolumab was still observed in cancers with apparently low or absent PD-L1 expression[2]. Grades 3 and 4 treatment-related adverse events were experienced by 19% of patients[6].

Populations meeting the eligibility criteria for clinical trials might not be the same as those receiving treatment in the real-world setting[7,8]. Furthermore, no head-to-head comparisons of nivolumab and cabozantinib in the second-line setting have been published. Given that context, we used the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) dataset to examine the real-world efficacy of both drugs in the second-line setting.

METHODS

Patient Population

Contributors of patient data to the IMDC include 38 international cancer centres in Canada, the United States, Denmark, Greece, South Korea, Australia, New Zealand, Japan, Singapore, Italy, and Belgium. The data are obtained through registry, pharmacy, or consecutive clinic lists. Individual retrospective chart reviews using standardized database templates were performed to collect patient data. The data included patients accrued between 2005 and October 2017.

The patients included in the study had mRCC and had previously been treated with 1 line of VEGFR-targeted therapy before starting either nivolumab or cabozantinib. Patients with non-clear-cell mRCC were included in the analysis. Institutional review board approval was obtained from each participating centre.

Statistical Analysis

Statistical analyses were performed using the SAS software application (version 9.4: SAS Institute, Cary, NC, U.S.A.). Kaplan–Meier curves were used to evaluate OS and TTF. Overall survival was defined as the time from the start of either nivolumab or cabozantinib to death or last follow-up (censored). Time to treatment failure was defined as the time from the start of nivolumab or cabozantinib to treatment discontinuation because of death, progression (based on the Response Evaluation Criteria in Solid Tumors), treatment toxicity, or last follow-up (censored). Proportional hazards regression modelling was performed to adjust for baseline imbalances in IMDC risk criteria as measured at initiation of cabozantinib or nivolumab therapy.

Patients were stratified into prognostic groups using the following 6 factors included in the IMDC prognostic model[9]:

- Score less than 80% on the Karnofsky performance scale
- Time from diagnosis to initiation of targeted therapy less than 1 year
- Hypercalcemia
- Anemia
- Neutrophilia
- Thrombocytosis

In the analysis, all variables except for time from diagnosis to initiation of first-line targeted therapy less than 1 year were collected at the start of second-line therapy with nivolumab or cabozantinib. Patients were stratified into IMDC favourable risk (0 prognostic factors), IMDC intermediate risk (1–2 prognostic factors), and IMDC poor risk (3–6 prognostic factors). A chi-square test was performed to examine for differences between the prognostic groups in patients receiving nivolumab or cabozantinib.

RESULTS

Baseline Characteristics of the Patients

At the time of analysis, the IMDC dataset included 8798 patients, of whom 4656 (53%) went on to receive second-line therapy. In the second-line setting, 225 patients received nivolumab, and 53 received cabozantinib. The most commonly used first-line drugs in the nivolumab group (Table I) were sunitinib (53%) and pazopanib (37%). In the cabozantinib group, 56% of the patients had received sunitinib and 40% had received pazopanib in the first-line setting (Table I). Table II shows the baseline characteristics of the patients at initiation of either nivolumab or cabozantinib in the second-line setting. In the nivolumab group, 29% of the patients were 70 years of age or older; 9% in the cabozantinib group had attained that age ($p = 0.0033$). No other baseline parameters were significantly different between the groups. Table II also shows the IMDC prognostic subgroups for each treatment group ($p = 0.88$).

Survival Outcomes and Response Rates

Median OS duration from initiation of second-line treatment was 22.10 months for nivolumab and 23.70 months for cabozantinib ($p = 0.60$, Figure 1). Figure 2 shows a TTF duration of 6.90 months for nivolumab and 7.39 months for cabozantinib ($p = 0.20$). The ORR was 21% for patients treated with nivolumab, and 20% for those treated with cabozantinib (Table III). Excluding the patients with non-clear-cell disease, OS duration was 20.64 months with nivolumab [95% confidence interval (CI): 15.51 months to not reached] and 25.85 months with cabozantinib (95% CI: 12.50 months to not reached), $p = 0.31$; and the TTF duration was 6.47 months for the nivolumab group (95% CI: 3.71 months to 9.93 months) and 8.28 months for the cabozantinib group (95% CI: 6.41 months to 14.42 months), $p = 0.24$. Additionally, the ORR did not change substantially when limited to patients with clear-cell disease (nivolumab 22%, cabozantinib 27%; $p = 0.91$).

In multivariable analysis with adjustments for IMDC criteria, the hazard ratio for OS for nivolumab compared with cabozantinib was 1.30 (95% CI: 0.73 to 2.31), $p = 0.38$. Because of the differences in age in the two groups, another multivariable analysis of OS adjusting for IMDC criteria and for age was performed, resulting in a hazard ratio of 1.32 (95% CI: 0.74 to 2.38), $p = 0.35$. Figure 3 shows the hazard ratios for additional subgroups (including patients with liver and bone metastases), with no significant differences being observed for those subgroups.

TABLE I Prior therapies received in the first-line setting in the nivolumab and cabozantinib groups

First-line drug	Nivolumab (*n*=220)		Cabozantinib (*n*=48)	
	(*n*)	(%)	(*n*)	(%)
Sunitinib	115	53	27	56)
Sorafenib	2	1	0	0
Axitinib	10	5	1	2
Bevacizumab	1	1	0	0
Temsirolimus	2	1	1	2
Pazopanib	81	37	18	40
Everolimus	0	0	1	2
Other	9	4	0	0

DISCUSSION

Populations in clinical trials often do not have a profile that matches the profile of populations seen in clinical practice[10]. Large retrospective cohorts such as the IMDC can be more representative of the real-world population by including patients with brain metastases and non-clear-cell histology. In the IMDC patient series used for the present study, only a small proportion of patients were treated in phase III clinical trials. Our analysis did not demonstrate substantial differences between the two drugs for either OS or TTF in the second-line setting. The OS durations of 22.1 months for nivolumab and 23.7 months for cabozantinib

TABLE II Patient characteristics at initiation of nivolumab ($n = 225$) or cabozantinib ($n = 53$)

Characteristic	Pts (*n*)	Nivolumab [*n* (%)]	Pts (*n*)	Cabozantinib [*n* (%)]	*p* Value
Sex (men)	225	179 (80)	53	43 (81)	0.80
Age >70 years	225	65 (29)	53	5 (9)	0.0033
KPS <80	178	38 (21)	48	8 (17)	0.47
Dx to Tx <1 year	222	107 (48)	51	32 (63)	0.061
Prior nephrectomy	223	199 (89)	52	44 (85)	0.35
Hypercalcemia	182	15 (8)	44	1 (2)	0.17
Anemia	188	144 (77)	46	30 (65)	0.11
Neutrophilia	193	13 (7)	46	4 (9)	0.64
Thrombocytosis	194	19 (10)	45	3 (7)	0.51
Non–clear cell histology	167	26 (16)	42	8 (19)	0.59
Sarcomatoid features	164	27 (16)	43	6 (14)	0.69
Metastasis					
>1 Site	188	155 (82)	48	42 (88)	0.40
To brain	162	10 (6)	37	1 (3)	0.40
To bone	179	67 (37)	39	14 (36)	0.86
To liver	165	36 (22)	37	8 (22)	0.98
IMDC risk					
Favourable	157	21 (13)	39	6 (15)	0.88
Intermediate	157	107 (68)	39	27 (69)	
Poor	157	29 (19)	39	6 (15)	

Pts = patients with relevant data; KPS = Karnofsky performance status; Dx = diagnosis; Tx = treatment; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium.

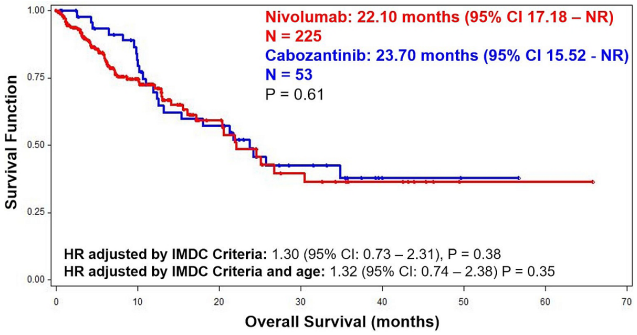

FIGURE 1 Kaplan–Meier curve depicting overall survival from initiation of nivolumab (n = 225) or cabozantinib (n = 53), with complete prognostic information. CI = confidence interval; NR = not reached; HR = hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium.

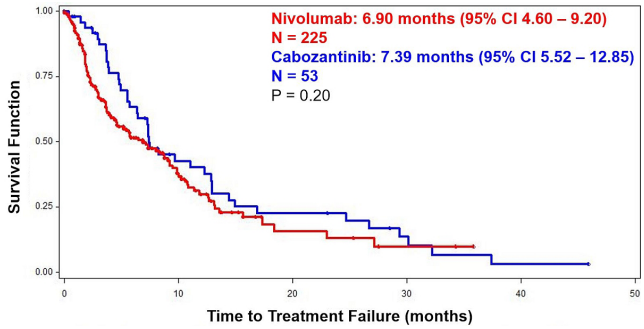

FIGURE 2 Kaplan–Meier curve depicting time to treatment failure from initiation of nivolumab (n = 225) or cabozantinib (n = 53), with complete prognostic information. CI = confidence interval.

TABLE III Best response at second-line therapy with cabozantinib in 40 patients and nivolumab in 140 patients

Response	Cabozantinib [*n* (%)]	Nivolumab [*n* (%)]
Complete response	1 (3)	2 (1)
Partial response	7 (18)	28 (20)
Stable disease	23 (58)	48 (34)
Progressive disease	9 (23)	62 (44)
Overall response rate	8 (20)	30 (21)
		p=0.85

were comparable to the durations reported in CheckMate 025 (25 months) and METEOR (21.4 months)[2,5]. The slightly increased proportion of patients with progressive disease in both treatment groups in our real-world cohort could be attributable to patients with more comorbidities, lower scores on the Karnofsky performance scale, and brain metastasis being included. Furthermore, the lack of a difference in ORR for the entire cohort of patients compared with the clear-cell cohort indicates that our findings are not driven by the non-clear-cell patients that were included. Overall, the data suggest that real-world outcomes are relatively similar to those obtained in the

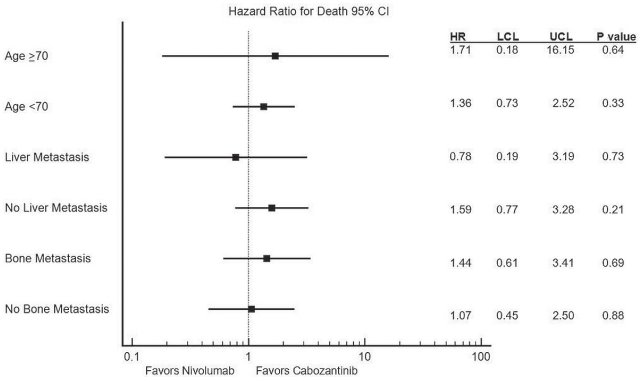

FIGURE 3 Forest plot depicting hazard ratios (HRs) for death by age group and presence or absence of liver and bone metastasis. LCL = lower confidence limit; UCL = upper confidence limit.

clinical trials and that either drug is a reasonable option in the second-line treatment of mRCC. Given similar efficacy and a lack of predictive biomarkers, decisions about which drug to use in the second-line setting are currently largely pragmatic, based on toxicity profiles, patient preference, and drug availability. Some patients might prefer to receive nivolumab intravenously; others might choose cabozantinib because it can be taken orally. Patients with autoimmune conditions such as uncontrolled or active lupus erythematosus, Crohn disease, or immunodeficiency might choose cabozantinib because nivolumab's mechanism of action requires a functional immune system. On the other hand, cabozantinib's side effect profile might prompt patients with mRCC and refractory hypertension to choose nivolumab.

Our study is limited by its retrospective design. However, the use of consecutive patient series (for example, registries and pharmacy databases) to prevent physician recall bias and reduce selection bias helps to mitigate some of the deficiencies. In addition, given that our analysis of the data is relatively early, the number of cabozantinib patients is small. Analyzing the real-world toxicity profile of the two agents will also be important.

Recently, the CheckMate 214 trial observed a benefit of using upfront combination immunotherapy with ipilimumab–nivolumab in patients with mRCC having an intermediate or poor IMDC risk[11]. That observation changes the treatment landscape in mRCC, because many intermediate- and poor-risk patients receiving checkpoint immunotherapy in the first-line setting might then receive cabozantinib in the second line. Many patients judged to be "favourable risk" will continue to have the choice of receiving single-agent nivolumab or cabozantinib after progression on sunitinib or pazopanib in the first line. However, some patients with an intermediate or poor IMDC risk will still receive a first-line tyrosine kinase inhibitor because of comorbidities, patient preference, and inability to tolerate or lack of access to checkpoint immunotherapy at their institutions.

Lastly, further studies are required to determine whether biomarkers such as PD-L1, PBRM1, BAP1, MET, or other candidate markers can help to identify patients who will benefit from treatment with cabozantinib or nivolumab[4,12,13].

CONCLUSIONS

Nivolumab and cabozantinib appeared to have similar efficacy in terms of both OS and TTF in our real-world population. These novel agents are both reasonable therapeutic options for mRCC patients progressing after initial first-line targeted therapy with an anti-VEGFR agent. Further studies are needed to identify population subgroups and predictive biomarkers that could help to better select patients likely to benefit from nivolumab or cabozantinib.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: FD declares research funding from Novartis, Pfizer, and Ipsen; TKC declares research funding from AstraZeneca, Bristol–Myers Squibb, Exelixis, Genentech, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, Roche, Tracon Pharmaceuticals, and Eisai, and consulting or advisory fees from AstraZeneca, Bayer, Bristol–Myers Squibb, Cerulean, Eisai, Foundation Medicine, Exelixis Genentech/Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, and Prometheus Labs; BB declares honoraria from Amgen, Pfizer, Janssen, and Bayer, and was also an investigator on the European Clinical Trials Database 2011-006085-40/MetaSun trial supported by Pfizer; NA declares consulting fees from Pfizer, Exelixis, Argos, and Cerulean; RK declares honoraria from Novartis, Pfizer, and Bayer; TY declares remuneration for a lecture from Pfizer Japan and Novartis Pharma Japan; DYCH declares consulting fees from Pfizer, Novartis, Bristol–Myers Squibb, Janssen Pharmaceuticals, and Astellas Pharma; IDD is supported by an Australian National Health and Medical Research Council Practitioner Fellowship (APP1102604), and has received research funding from Astellas and Exelixis. The remaining authors have no conflicts to disclose.

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