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ORIGINAL RESEARCH

Real-world experience of cabozantinib in Asian patients with advanced renal cell carcinoma following treatment with VEGFR tyrosine kinase inhibitors and/or immune-checkpoint inhibitors

Darren MC Poon[1,2], Kuen Chan[3], Angus Kwong-Chuen Leung[4], Brian Ng[5], Foon-Yiu Cheung[6], Steven Wai-Kwan Siu[7], Hong Kong Society of Uro-Oncology

[1]Comprehensive Oncology Centre, Hong Kong Sanatorium & Hospital, Hong Kong SAR, China; [2]Department of Clinical Oncology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China; [3]Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, China; [4]AMO Oncology Centre, Hong Kong SAR, China; [5]Department of Oncology, Princess Margaret Hospital, Hong Kong SAR, China; [6]Hong Kong Integrated Oncology Centre, Hong Kong SAR, China; [7]Department of Clinical Oncology, Queen Mary Hospital, Hong Kong SAR, China

Abstract

Background: There is a lack of real-world data on the use of cabozantinib in Asian patients with metastatic renal cell carcinoma.

Methods: We conducted a retrospective study to investigate the toxicity and efficacy of cabozantinib in this patient population who progressed on tyrosine kinase inhibitors and/or immune-checkpoint inhibitors from six oncology centres in Hong Kong. The primary endpoint was the incidence of serious adverse events (AEs) attributed to cabozantinib. Secondary safety endpoints included dose reductions and AE-led treatment terminations. Secondary effectiveness endpoints included overall survival, progression-free survival, and objective response rate.

Results: A total of 24 patients were included. Half received cabozantinib as a third-line or later-line treatment, whilst 50% received prior immune-checkpoint inhibitors, primarily nivolumab. Overall, 13 (54.2%) patients reported at least one cabozantinib-related AE of grades 3–4. The most commonly reported AEs were hand-foot skin reactions (9; 37.5%) and anaemia (4; 16.7%). Fifteen (65.2%) patients required dose reductions. Three patients discontinued treatment because of AEs. The median progression-free survival and overall survival were 10.3 months and 13.2 months, respectively; 6 (25%) patients achieved partial responses, and 8 (33.3%) achieved stable disease.

Conclusion: Cabozantinib was generally well tolerated and efficacious in Asian patients with metastatic renal cell carcinoma who were heavily pretreated.

Keywords: immuno-oncology, metastatic renal cell carcinoma, real-world effectiveness, sequential therapies, targeted therapy, tyrosine kinase inhibitors, vascular endothelial growth factor receptor.

Citation

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Introduction

Kidney cancer is amongst the ten most frequently diagnosed malignancies in men worldwide,[1] with more than 400,000 new cases per year, and an increasing trend for the incidence has been observed in European countries and in the younger population.[2] Renal cell carcinoma (RCC), the predominate type of kidney cancer, accounts for 2–3% of all adult malignancies.[3] Approximately 85%

of all RCCs are clear cell tumours.[4] The remaining subtypes include papillary RCC, chromophobe RCC and oncocytoma as well as other minor subtypes. Approximately 20–30% of patients have metastatic disease at the time of diagnosis,[5] and about 20% will develop metastatic disease after being diagnosed with early-stage disease.[6] Patients with RCC and distant metastases have a poor prognosis, with a 5-year relative survival rate of 13%, according to the Surveillance, Epidemiology and End Results (SEER) database in the United States.[7]

The treatment landscape for metastatic RCC (mRCC) has changed dramatically over the past decade, largely due to advances in the understanding of tumour biology. The introduction of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) has changed the prognosis for patients with mRCC. These targeted therapies have been shown to improve progression-free survival (PFS) and overall survival (OS) compared with traditional non-specific immunotherapy such as IFNα.[6] In current international clinical guidelines,[8–10] both sunitinib and pazopanib remain first-line therapy options for favourable-risk mRCC. The more recent introduction of immune-checkpoint inhibitors (ICIs) heralds a further shift in the treatment paradigm. These agents include pembrolizumab, nivolumab and ipilimumab, which are recommended in combination with a newer-generation TKI or an ICI for the treatment of mRCC in the first-line setting.[8–10]

One of the newer-generation TKIs is cabozantinib, which is an oral multitargeted TKI for VEGFR, MET and AXL kinases.[11] In the phase II randomized CABOSUN trial,[12] cabozantinib significantly improved PFS and objective response rate (ORR) compared with sunitinib in treatment-naive patients with mRCC of intermediate or poor risk. Recently, the phase III open-label CheckMate 9ER study[13] showed that cabozantinib plus nivolumab offered significant benefits over sunitinib in terms of PFS, OS, and ORR in patients with previously untreated mRCC. There was also evidence supporting the use of cabozantinib in the second-line setting. In the phase III METEOR study,[14] cabozantinib significantly improved PFS, OS and ORR compared with everolimus in patients who had progressed on previous VEGFR TKI treatment. The antitumour activity of cabozantinib was also demonstrated in patients with prior exposure to ICIs,[15] in whom the optimal subsequent treatment remains undefined due to a lack of relevant studies.

Despite offering similar efficacy, TKIs were shown to have a distinct toxicity profile and suboptimal tolerance in Asian patients compared with white patients. In a meta-analysis of 33 studies that involved ~10,000 patients treated with sunitinib for mRCC,[16] higher incidences of hand-foot skin reaction (all grades), fatigue (grade >2) and thrombocytopenia (grade >2) were observed in Asian patients *versus* white patients. In a *post hoc* analysis of a phase III trial that compared pazopanib with sunitinib as a first-line treatment for mRCC,[17] Asian patients (n=363) had higher prevalence of haematological toxicities, cytopenia, increased liver enzymes and hand-foot skin reaction but lower prevalence of gastrointestinal toxicities compared with non-Asian patients (n=703). Thus, the tolerability profiles of newer-generation TKIs, such as cabozantinib, amongst Asian patients with mRCC are worth further investigation.

Clinical data on later-line treatment options for mRCC, particularly after prior use of ICIs and in the Asian population, remain limited. In this study, we investigated the toxicity and efficacy of cabozantinib in Chinese patients who progressed on VEGFR TKIs and/or ICIs in real-life clinical practice.

Methods

Study design and participants

We performed a multicentre retrospective cohort analysis of patients aged ≥18 years with advanced RCC or mRCC (regardless of subtype) who received cabozantinib treatment after progression on VEGFR TKI and/or ICI treatment. Data were collected from patients treated in six oncology centres in Hong Kong. All of the respective research ethics committees (RECs) of the relevant affiliated institutions (REC of Hong Kong Sanatorium & Hospital, the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical REC; Hong Kong East Cluster REC; Kowloon West Cluster REC; and the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster) waived the need for ethics approval and the need to obtain patient consent for the collection, analysis and publication of the retrospectively obtained and anonymized data for this observational study.

Procedures

Data were obtained from retrospective chart review by investigators at each centre between 2018 and 2020. Demographic, pathological, surgical and systemic therapy data were captured in uniform formats to ensure consistency.

For cabozantinib, the following data were collected: starting dose and date, dose modifications and reasons, last dose and date, reasons for discontinuation, dates of progression, best response, death and last follow-up, and adverse events (AEs) and grading. If data were available, objective response was assessed by the site investigator and categorized using the Response Evaluation Criteria in Solid Tumours version 1.1. Toxicities were graded using the Common Terminology Criteria for Adverse Events version 4.0.

Outcomes

The primary objective was to evaluate the safety of cabozantinib as a second-line or later-line therapy for Asian patients with advanced RCC or mRCC in terms of the incidence of possibly drug-related serious AEs. Secondary safety endpoints were the number of dose modifications (including reductions or treatment interruptions) and discontinuations of cabozantinib due to AEs. Secondary effectiveness endpoints were survival outcomes (including OS and PFS), ORR, clinical benefit rate, duration of response, duration of cabozantinib treatment, and time to next treatment. OS was calculated from the initiation of cabozantinib treatment until death or censored at the date of last follow-up. PFS was calculated from treatment initiation to discontinuation for progressive disease or death or censored at the last follow-up. ORR was defined as the proportion of patients with complete or partial responses as the best radiological response on cabozantinib. Clinical benefit rate was defined as the proportion of patients who achieved an objective response plus stable disease. OS and PFS were calculated with the Kaplan–Meier method. All statistical analyses were performed using SAS (version 8).

Results

A total of 24 patients were included (Table 1), most of whom were men (23; 95.8%) and had clear cell histology (22; 91.7%). The median age at diagnosis was 51 years. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of ≥1. International Metastatic RCC Database Consortium (IMDC) intermediate-risk and poor-risk mRCC accounted for 70.9% of patients. The most common metastatic sites included the bone (21; 87.5%), lung (20; 83.3%) and lymph nodes (14; 58.3%). Half of the patients received cabozantinib as a third-line or later-line treatment. Sunitinib and pazopanib were the most frequently used prior TKIs. Half of the patients had used ICIs, primarily nivolumab, before initiation of cabozantinib treatment.

The median duration of exposure to cabozantinib was 4.4 (range, 1–18.5) months. The median starting and last doses were 60 mg/day and 40 mg/day, respectively. The median time to first dose modification was 40 days. Dose reductions were required in 15 (62.5%) patients. The most common dose-limiting toxicity was hand-foot skin reaction (Table 2). Three patients discontinued treatment because of AEs (not related to disease progression; Table 2). Overall, 13 (54.2%) patients reported at least one adverse event of grades 3–4 possibly related to cabozantinib (Table 3). The most commonly reported adverse events were hand-foot skin reaction (9; 37.5%) and anaemia (4; 16.7%). There were ten deaths recorded,

Table 1. Patient characteristics.

	All patients (*n*=24)
Median age, years	51
Sex	
Male	23 (95.8%)
Female	1 (4.2%)
Histology	
Clear cell	22 (91.7%)
Papillary	2 (8.3%)
ECOG performance status	
0	0
1	16 (66.7%)
2	6 (25.0%)
3	2 (8.3%)
IMDC risk category	
Favourable	7 (29.2%)
Intermediate	13 (54.2%)
Poor	4 (16.7%)
Metastatic site	
Bone	21 (87.5%)
Lung	20 (83.3%)
Lymph node	14 (58.3%)
Liver	3 (12.5%)
Brain	2 (8.3%)
Other	7 (29.2%)
Type of prior systemic therapy	
VEGFR TKI	23 (95.8%)
ICI ± VEGFR TKI	12 (50.0%)[a]
Previous nephrectomy	
Cytoreductive nephrectomy	8 (33.3%)
Prior nephrectomy for localised RCC	9 (37.5%)
Line of cabozantinib treatment	
Second line	12 (50.0%)
Third line	6 (25.0%)
Fourth line	4 (16.7%)
Fifth line	2 (8.3%)

[a]Includes nivolumab (*n*=9), nivolumab + ipilimumab (*n*=1), pembrolizumab (*n*=1), and pembrolizumab + axitinib (*n*=1).
ECOG, Eastern Cooperative Oncology Group; ICI, immune-checkpoint inhibitor; IMDC, International Metastatic RCC Database Consortium; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

Table 2. Adverse events that led to dose reductions and discontinuations of cabozantinib.

	All patients (*n*=24)	
	Number of dose reductions (*n*=15)	**Number of discontinuations (*n*=15)[b]**
Hand-foot skin reaction	10 (66.7%)[a]	1 (6.7%)
Arthralgia	1 (6.7%)	0
Diarrhoea	1 (6.7%)	0
Fatigue	1 (6.7%)[a]	0
Hypertension	1 (6.7%)	0
Hypothyroidism	1 (6.7%)	1 (6.7%)
Liver enzyme elevation	1 (6.7%)	1 (6.7%)[c]

[a]One patient cited both hand-foot skin reaction and fatigue as the reason for dose reduction.
[b]Twelve patients discontinued treatment because of disease progression.
[c]The patient also experienced disease progression.

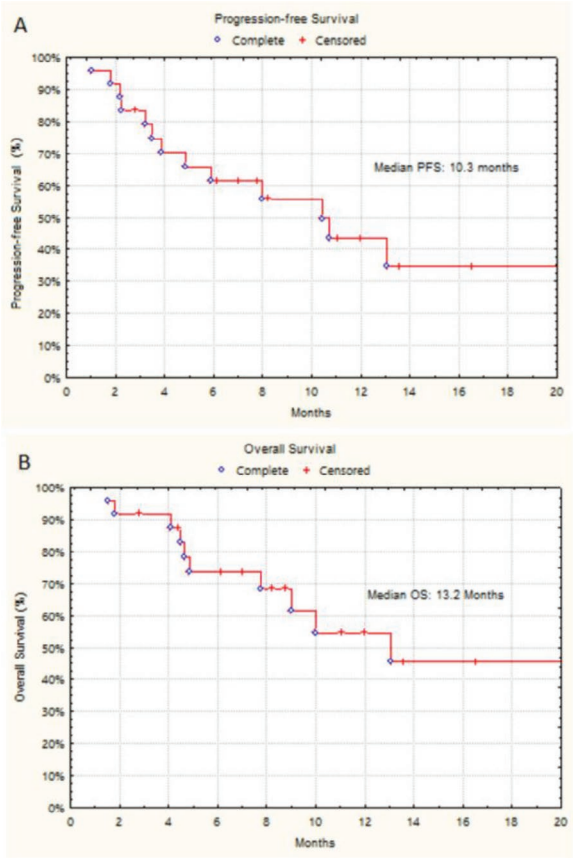
Table 3. Incidence of all adverse events considered possibly related to cabozantinib.

	All patients (*n*=24)	
	Grades 1–2	**Grades 3–4**
Any adverse event	11 (45.8%)	13 (54.2%)
Malaise	16 (66.7%)	0
Hypothyroidism	12 (50.0%)	0
Anaemia	9 (37.5%)	4 (16.7%)
Diarrhoea	8 (33.3%)	2 (8.3%)
Hypertension	8 (33.3%)	1 (4.2%)
Anorexia	7 (29.2%)	0
Oral mucositis	7 (29.2%)	1 (4.2%)
Hand-foot skin reaction	6 (25.0%)	9 (37.5%)
Nausea	6 (25.0%)	0
Rash	6 (25.0%)	0
Hypokalaemia	3 (12.5%)	0
Hyponatraemia	3 (12.5%)	0
Thrombocytopenia	3 (12.5%)	0
Fatigue	2 (8.3%)	0
Arthralgia	1 (4.2%)	0
Dysphonia	1 (4.2%)	0
Neutropenia	1 (4.2%)	1 (4.2%)
Liver enzyme elevation	0	1 (4.2%)

none of which were considered to be related to cabozantinib toxicity.

The median PFS and OS were 10.3 months and 13.2 months, respectively (Figure 1). The median time to best response was 3.3 months. No complete responses were observed. Six (25%) patients achieved a partial response, eight (33.3%) achieved stable disease, and ten (41.6%) had progressive disease. The calculated ORR and clinical benefit rates were 25% and 58.3%, respectively.

Figure 1. Kaplan–Meier estimates of time to progression-free survival (A) and overall survival (B).



Discussion

In this multicentre retrospective cohort study, we describe real-world data regarding the safety and antitumour activity of cabozantinib in Asian patients with advanced RCC or mRCC who had progressed on previous VEGFR TKIs and/or ICIs. We found that cabozantinib was generally well tolerated and efficacious in Asian patients compared with the results of the pivotal phase III METEOR trial, which compared cabozantinib with everolimus in patients (primarily white) with mRCC who had received previous TKI therapy.[14]

Our study cohort included heavily pretreated patients, with 50% receiving cabozantinib as a third-line or later-line systemic treatment and 70.9% having intermediate-risk or poor-risk disease. By comparison, the corresponding figures in the cabozantinib arm (*n*=330) in METEOR were 29% and 54%, respectively.[14] An analysis of regional differences in METEOR[18] showed that a lower proportion (17%) of patients (*n*=86) in the Asia-Pacific region (including Australia, South Korea and Taiwan) received cabozantinib as a third-line or later-line therapy. We also included higher proportions of patients with bone metastases (91.3% *versus* 23%) and brain metastases (8.7% *versus* <1%) compared with the METEOR cabozantinib arm. The use of cabozantinib in patients with RCC and bone metastases is worth further investigation as there is evidence showing that the agent may modulate the activity of osteoblasts and osteoclasts via MET inhibition.[19,20] A subgroup analysis of METEOR in patients with advanced RCC and bone metastases at baseline[21] showed that cabozantinib (*n*=77) significantly improved median PFS (7.4 months *versus* 2.7 months), median OS (20.1 months *versus* 12.1 months) and ORR (17% *versus* 0%) compared with everolimus (*n*=65).

Despite the poor prognostic features of our patient cohort, the safety profile of cabozantinib appeared generally favourable. The proportion of patients who required dose reductions was 62.5%, comparable to that (60%) of patients enrolled in the cabozantinib arm of the METEOR study.[14] No treatment-related deaths or new safety signals were observed. Only three patients (12.5% *versus* 9% in the METEOR cabozantinib arm) discontinued treatment because of toxicity, suggesting that AEs with cabozantinib were generally manageable, possibly by dose modifications. Hand-foot skin reaction and fatigue were amongst the most common dose-limiting toxicities in both our study and METEOR,[14] whereas patients in our study experienced diarrhoea and hypertension less frequently. Notably, the overall rates of serious handfoot skin reaction and serious anaemia were higher in our cohort compared with METEOR.[14]

The antitumour activity of cabozantinib was promising in our study participants, with 25% achieving a partial response, compared with 17% in METEOR.[14] With respect to survival outcomes, our study reported a longer median PFS (10.3 *versus* 7.4 months) but a shorter median OS (13.2 *versus* 21.4 months) compared with METEOR,[14] which might be explained by the fact that the performance status of our study participants (33.3% with ECOG 2 or 3) was generally poorer than that of METEOR participants (all with ECOG 0 or 1). Half of our patients received cabozantinib as a third-line or later-line treatment, suggesting that they had limited effective treatment choices in the event of progression. This might have led to the small difference (2.9 months) between the median PFS and OS observed in our cohort.

In the regional analysis of METEOR,[18] patients treated with cabozantinib in the Asia-Pacific region had an ORR of 28%, which was higher than the figures for Europe (15%) and North America (16%), and consistent with the ORR in our patient cohort (25%). Additionally, patients in the Asia-Pacific region appeared to gain greater clinical benefits from cabozantinib over everolimus in terms of PFS (hazard ratios, 0.43 *versus* 0.54 for Europe and 0.50 for North America) and OS (hazard ratios, 0.49 *versus* 0.67 for Europe and 0.79 for North America) compared with their western counterparts.[18]

Our study findings were also consistent with other Asian data on cabozantinib. In the phase II C2001 study of cabozantinib in treatment-experienced Japanese patients with advanced RCC (*n*=35; the majority received one prior TKI therapy),[22] the ORR and clinical benefit rate were 20.0% and 85.7%, compared with 25% and 58.3% in our study. There were no significant discrepancies in the safety profile of cabozantinib between C2001 and our study. The rate of dose adjustments in C2001 was 91%, which was higher than the figures in our study and in METEOR; however, only 2 (5.7%) patients discontinued therapy due to AEs, suggesting that dose modification remains a method to improve the tolerability of cabozantinib.

From a pharmacokinetic perspective, cabozantinib is expected to offer comparable clinical benefits and safety profiles in Asian and non-Asian patients. In a population analysis of nine clinical trials of cabozantinib that involved healthy individuals (*n*=140) and patients (*n*=1,394) with various malignancy types (including participants from METEOR),[23] the effect of Asian ethnicity on apparent clearance was estimated to be minimal, with only an 8% difference between Asians (*n*=46) and non-Asians (*n*=1,488), suggesting that the pharmacokinetics of cabozantinib was similar in Asian and non-Asian populations. This finding is consistent with the metabolism of cabozantinib, which primarily involves cytochrome P450 3A4 (ref. [24]) and is not prone to genetic polymorphism.

Previous research investigated the roles of plasma biomarkers in optimizing cabozantinib treatment outcomes. In an exploratory analysis of METEOR,[25] plasma biomarkers from baseline and week 4 from 621 of 658 randomized participants were analysed for CA9, HGF, MET, GAS6, AXL, VEGF, VEGFR2 and IL-8. PFS and OS were improved with cabozantinib *versus* everolimus regardless of baseline levels (high or low) of all biomarkers (hazard ratios ≤0.78). Univariate analyses showed that low baseline levels of HGF, AXL and VEGF were prognostic for improvements in both PFS and OS with cabozantinib. A low level of AXL was predictive of relative improvement in PFS for cabozantinib *versus* everolimus. Multivariable analysis showed that a low baseline level of HGF was independently prognostic for improved PFS for both cabozantinib and everolimus; low levels of HGF, GAS6 and VEGF were independently prognostic for improved OS with cabozantinib. The researchers summarized that low baseline levels of HGF and GAS6, cognate ligands for MET and AXL, were prognostic for improved PFS or OS with cabozantinib treatment, supporting further prospective studies of the prognostic significance of these biomarkers in patients with mRCC, where several TKI–ICI combinations, such as cabozantinib plus nivolumab, have shown clinical benefit.

Our study provided insights on the use of cabozantinib as a subsequent treatment option after prior exposure to ICIs, which has been increasingly adopted in the treatment paradigm of mRCC. In the public healthcare setting in Hong Kong, because of treatment costs, TKI monotherapy, rather than ICIs, remains the first-line treatment for most patients with mRCC. Therefore, though half of our study patients received ICIs, most commonly nivolumab, they were most likely used in a second-line setting before initiation of cabozantinib treatment. A total of eight grade 3–4 AEs (grade 3 hand-foot skin reaction, *n*=5; grade 3 anaemia, *n*=2; grade 4 neutropenia, *n*=1) were reported in this group of patients. With respect to the best response to cabozantinib treatment, three patients achieved a partial response and four had stable disease, suggesting that cabozantinib may be considered as a feasible option in Asian patients with prior exposure to ICIs.

Cabozantinib plus nivolumab has been approved in multiple western countries for the first-line treatment of mRCC,[26,27] regardless of the risk category, following the phase III open-label CheckMate 9ER study demonstrating that the combination therapy was associated with significantly improved PFS, OS and ORR compared with sunitinib.[13] In our cohort, there was a large difference between the median duration of cabozantinib treatment and PFS (4.4 *versus* 10.3 months). We suspect that, in half of our patients, treatment with ICIs followed by cabozantinib resembled a combination therapy and that the likely synergistic effect might have prolonged PFS, even after discontinuation of cabozantinib treatment. However, the indication of cabozantinib plus nivolumab for mRCC was not approved in our jurisdiction during the study period; therefore, the role of cabozantinib in combination with an ICI or rechallenging with cabozantinib after prior exposure to cabozantinib plus nivolumab was not evaluated.

Although the optimal sequencing of treatment remains uncertain, based on real-world experience[28,29] and analyses of clinical trial data,[30,31] cabozantinib, a multi-kinase TKI, could serve as a feasible treatment option in patients with mRCC who have progressed on ICIs. A subgroup analysis of METEOR[30] showed that patients who received prior ICIs (*n*=32) obtained similar benefits from cabozantinib over everolimus (median PFS, not reached *versus* 4.1 months; median OS, not reached *versus* 16.3 months; ORR, 22% *versus* 0%) compared with patients who received prior sunitinib or pazopanib. In a pooled analysis of METEOR and the C2001 study,[31] cabozantinib offered comparable efficacy and safety outcomes in patients with (*n*=33) or without prior exposure to ICIs (*n*=332); no differences in AEs such as pneumonitis, endocrinopathy, or infusion-related reaction were observed between the two groups. Recently,

the National Comprehensive Cancer Network[9] and the European Society for Medical Oncology[10] have recommended cabozantinib as a second-line treatment option for patients with mRCC who progressed on prior TKI or ICI therapy.

Limitations

Limitations of our study included potential selection bias resulting from its retrospective nature. The small number of patients was another issue that might have affected the generalizability of the data. We hope that the accumulation of data on patients who receive cabozantinib treatment might facilitate the undertaking of a larger study in Hong Kong to verify the findings of this study. The median duration of cabozantinib treatment in our study was relatively short (4.4 months *versus* 7.6 months in the METEOR cabozantinib arm). We also lacked central pathological and radiographic review; however, this concern might have been mitigated by the strong genitourinary oncology expertise of the participating centres.

Conclusions

Our multicentre retrospective experience showed that cabozantinib was generally well tolerated and efficacious in Asian patients with advanced RCC or mRCC who had progressed on prior VEGFR TKIs and/or ICIs. Our study adds evidence for the safety and potential antitumour activity of cabozantinib in Asian patients with heavily pretreated advanced RCC in a real-world setting.

Contributions: Conceptualization, DMCP; methodology, DMCP.; software, all authors; validation, all authors; formal analysis, DMCP; investigation, DMCP; resources, all authors; data curation, all authors; original draft preparation, DMCP; review and editing, all authors; visualization, DMCP; supervision, DMCP; project administration, DMCP; funding acquisition, DMCP. All authors have read and agreed to the published version of the manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Correspondence: Darren MC Poon, Comprehensive Oncology Centre, Hong Kong Sanatorium & Hospital, Hong Kong SAR, China. Email: darren.poon@medionline.hk

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