Original Study

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Early Clinical Experience with Cabozantinib for Advanced Renal Cell Carcinoma in the UK: Real-World Treatment Pathways and Clinical Outcomes

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Abstract

This retrospective study, CERES (NCT03696407), describes early clinical experience with cabozantinib in patients with advanced renal cell carcinoma (aRCC) enrolled in the UK managed access programme (MAP). Cabozantinib demonstrated clinically meaningful activity in all patients across multiple lines of therapy. Charlson Comorbidity Index score warrants further investigation as a prognostic/predictive marker. Our results provide a benchmark for future real-world studies in aRCC.

Background: Cabozantinib monotherapy is approved in the UK for patients with treatment-naïve intermediate- or poor-risk advanced renal cell carcinoma (aRCC), or patients who received prior vascular endothelial growth factor-targeted therapy. Data are limited on the real-world use of cabozantinib for aRCC. **Patients and Methods:** CERES (NCT03696407) was a retrospective study of patients with aRCC who received cabozantinib through the UK managed access programme (MAP; August 2016–July 2017), at which time cabozantinib had European regulatory approval for second- or later-line use only. The study objectives were to characterize aRCC treatment patterns and evaluate cabozantinib effectiveness. Outcomes were stratified by cabozantinib treatment line, MAP treatment date (months 0-7 vs. 8-12) and (*post hoc*) Charlson Comorbidity Index (CCI; $\geq$ 6 vs. $<$ 6). **Results:** Of 100 patients included, 99% had stage IV disease, 63% had a CCI $\geq$ 6 and 81% had an Eastern Cooperative Oncology Group Performance Status 0-1. Median (range) duration of follow-up was 10.8 (0.4-33.5) months. Cabozantinib was administered as second-line, third-line and fourth- or later-line in 41%, 31% and 28% of patients, respectively. Most patients (84%) initiated cabozantinib at 60 mg. Average (range) cabozantinib dose was 45.5 (19.6-59.8) mg/day; 66% of patients had $\geq$ 1 dose reduction. Disease progression was the most common reason for discontinuation (65.1%). Median (95% confidence interval) progression-free survival (PFS) and overall survival (OS) were 6.01 (5.16-7.85) and 10.84 (7.92-16.85) months, respectively. Overall response rate was 34.5%; disease control rate 70.1% and duration of response 6.9 (1.8-26.9) months. No significant differences in survival estimates were observed between treatment line or treatment date subgroups. Total CCI score $\leq$ 6 (vs. $>$ 6) was associated with prolonged median PFS and OS. **Conclusion:** Cabozantinib demonstrated clinical activity in this UK real-world aRCC population. The results provide a benchmark for future real-world studies in aRCC.

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Introduction

Among patients with renal cell carcinoma (RCC), approximately one-third present with metastatic disease at the time of diagnosis,[1,2] and one-third of patients undergoing radical nephrectomy will relapse.[3]

One current treatment for patients with advanced RCC (aRCC) is cabozantinib, an oral inhibitor of multiple receptor tyrosine kinases, including vascular endothelial growth factor (VEGF) receptors, the hepatocyte growth factor receptor protein MET, and the GAS6 receptor AXL.[4] In the phase III METEOR trial (NCT01865747), cabozantinib significantly improved clinical outcomes (overall survival [OS], progression-free survival [PFS] and objective response rate [ORR]) compared with everolimus in patients with aRCC who had progressed after prior VEGF-targeted therapy.[5,6] Furthermore, the CABOSUN trial (NCT01835158) reported significant clinical benefit in PFS for treatment-naïve patients with intermediate- or poor-risk metastatic RCC treated with cabozantinib compared with sunitinib.[7,8] The findings from these trials led to the approval of cabozantinib for treatment-naïve, intermediate- or poor-risk patients with aRCC, or those who have received prior VEGF-targeted therapy by the European Medicines Agency.[9]

While under assessment by the National Institute for Health and Care Excellence (NICE) and Scottish Medicines Consortium (SMC) in 2016/17 for reimbursement in patients with aRCC following prior VEGF-targeted therapy, cabozantinib was made available in the UK to patients with aRCC via a managed access programme (MAP). Cabozantinib was approved for reimbursement by NICE in early August 2017 for adults with aRCC after VEGF-targeted therapy,[10] at which point it was eligible for reimbursement in England and Wales for this indication and the MAP was discontinued.

Given the limited data available on the real-world use of cabozantinib after prior VEGF-targeted therapy in the UK,[11] the present study (Clinical Experience with cabozantinib in patients with advanced REnal cell carcinoma in the UK Study [CERES], NCT03696407) aimed to describe treatment pathways and treatment-related outcomes in patients with aRCC treated with cabozantinib via the UK MAP.

Materials and Methods

Study Design and Patient Population

CERES was a multicentre, retrospective, non-interventional study involving patients with aRCC treated with cabozantinib after prior VEGF-targeted therapy through the MAP, between August 2016 and July 2017, at six specialist centres across the UK (Supplemental Figure 1). The MAP closed to new patients after the approval of cabozantinib by NICE in August 2017.[10]

The study period included: i) a pre-cabozantinib initiation period (evaluating patient and disease characteristics, and prior therapies); ii) a post-cabozantinib period with an 'index date' defined as the date of the first cabozantinib dose; and iii) a 24-month follow-up period immediately after cabozantinib initiation or until the patient's death (whichever occurred earlier) during which treatment was administered in accordance with institutions' standard-of-care.

Eligible patients were aged 18 years or older at cabozantinib initiation, had a diagnosis of aRCC, and initiated cabozantinib via the MAP. Patients were identified by local clinical staff through a retrospective review of hospital medical records (pharmacy records, databases or electronic prescribing systems). Patients were excluded if their medical records were unavailable.

The study was performed in accordance with the recommendations of the Declaration of Helsinki and the International Ethical Guidelines for Epidemiological Studies. All the ethical, governance and legal compliance of the study protocol and supporting documents were approved by relevant Research Ethics Committees before the study start. For patients who were alive at the time of data collection, only those who had provided written informed consent were included. For deceased patients, data were collected and anonymized by members of the direct clinical care team to preserve confidentiality, in accordance with the UK National Health Service Confidentiality Code of Practice.

Endpoints and Outcomes

Baseline Characteristics and Treatment Patterns. Baseline patient demographics and clinical characteristics were described at date of cabozantinib initiation (ie, index date). Treatment patterns were analyzed over the 24-month period following index date. Endpoints of interest included: cabozantinib treatment line, dose at initiation, maintenance doses, rates and timings of dose reductions, interruptions, and treatment discontinuations. Systemic anticancer therapy (before and after cabozantinib use) and concomitant therapy (radiotherapy and treatment for bone metastases [denosumab and bisphosphonate]) were also evaluated.

Effectiveness. Clinical benefit was evaluated over the 24-month follow-up period. The primary effectiveness endpoint was median PFS, defined as the time from index date to the date of disease progression (based on clinical and/or radiological [local or according to Response Evaluation Criteria in Solid Tumors (RECIST)] findings, or death).

Secondary effectiveness endpoints included median OS (time from index date until death), time to treatment discontinuation, and tumor response. Tumor response was evaluated as: duration of response (DoR; time between date of first documented partial response [PR] or complete response [CR] to date of disease progression based on local assessment protocols); ORR (the proportion of patients with PR or CR); disease control rate (DCR; the proportion of patients with stable disease [SD], PR or CR); best response to cabozantinib (the best radiologically assessed response during the treatment period; responses include CR, PR, SD, progressive disease and not evaluable); and cause of death.

Tolerability. Cabozantinib safety data were collected and entered into the Global Safety Database as per the requirements of the MAP, but no explicit safety objectives were included in the study design. Patterns of dose interruptions, reductions and discontinuations do, however, provide inferential evidence of treatment tolerability.

Statistical Analysis

Descriptive statistics were used to characterize the study population and prescribing patterns (mean [standard deviation, SD], median [range or interquartile range (IQR)], percentages). Median (95% confidence interval [CI]) survival estimates were evaluated by Kaplan–Meier analyses. Statistical analyses were performed using Statistical Analysis System (SAS) version 9 (SAS Institute Inc., Cary, NC, USA).

The results of the treatment pattern and treatment effectiveness analyses were reported for the full analysis set (FAS), which included all eligible patients who initiated cabozantinib via the MAP at participating centres. Pre-specified subgroups included patients with index dates between August 2016 and February 2017 (early MAP treatment group) and those with index dates between March 2017 and July 2017 (later MAP treatment group). These treatment groups were pre-specified in anticipation of possible temporal changes in prescribing practice and sequencing pathway, influenced by increasing clinical experience with cabozantinib. Stratification of outcomes by cabozantinib treatment line (second-line [2L], third-line [3L] or fourth- or later-line [≥ 4L]) was also specified *a priori*.

A minimum sample size of 100 patients was specified to ensure adequate precision in the calculation of proportions and in the median (95% CI) PFS estimates for the FAS and pre-specified subgroups. The calculation of precision was based on the median (95% CI) PFS reported for cabozantinib in the METEOR study (7.4 [6.6-9.1] months).[6]

A *post hoc* analysis stratified outcomes by Charlson Comorbidity Index (CCI) total score (≤ 6 and > 6) to assess the impact of baseline comorbidities on patient survival. The CCI weights each pre-specified comorbidity according to its associated risk of death (scores 1-6); a higher CCI total score indicates a higher risk of death.[12] The presence of metastatic solid tumor accounts for 6 points and was chosen as a cut-off point.

Results

Patient Characterization

In total, 106 patients were enrolled in the study, of whom 100 had initiated cabozantinib between August 2016 and February 2017 in the MAP and were eligible for analysis (Supplemental Figure 1). Overall, patients had a mean (SD) age of 62.8 (10.3) years at the date of initiating cabozantinib, and 68 (68.0%) were male. Median (range) duration of follow-up was 10.8 (0.4-33.5) months (Table 1). Ninety-nine patients had stage IV RCC and one had locally advanced disease (stage III). The median (range) number of metastatic sites was 2.0 (1.0-5.0), with lung being the most common site (75.8%, Table 1). Brain metastases occurred in 5 patients. Most patients (86.0%) had clear cell histology.

Of 89 patients with evaluable Eastern Cooperative Oncology Group Performance Status (ECOG PS), 72 (80.9%) had a score of 0 or 1. Among all patients, 48 (48.0%) and 23 (23.0%) were categorized, at the start of cabozantinib treatment, as having intermediate and poor risk, respectively, according to International Metastatic RCC Database Consortium (IMDC) risk scores. Excluding metastatic solid tumors, the most common comorbidities were moderate-to-severe chronic kidney disease (investigator-defined, 52.0%) and uncomplicated diabetes mellitus (11.0%) (Supplemental Table 1). Median (IQR) CCI total score was 8.0 (6.0-8.0) and 63.0% of patients had a total CCI score of more than 6.

Treatment Patterns

Cabozantinib Use. In total, 41 patients (41.0%) received cabozantinib as 2L therapy, 31 (31.0%) as 3L therapy and 28 (28.0%) as ≥ 4L therapy (Figure 1). Most patients initiated cabozantinib at the recommended dose of 60 mg/day (84.0%), while 16.0% initiated at lower doses of 40 mg/day (15.0%) and 20 mg/day (1.0%). The median (range) average daily cabozantinib dose was 45.5 (19.6-59.8) mg/day (Supplemental Table 2).

The median (range) duration of cabozantinib treatment was 6.0 (0.3-30.5) months. Two-thirds (n = 66) of patients had at least 1 dose reduction; of these, 57 (86.4%) had 1 reduction and 9 (13.6%) had 2 reductions. The most common reasons for dose reduction were adverse events (AEs; 57.6%) and clinical decisions (other unspecified reason at the physician's discretion; 37.9%). Median (range) time to first dose reduction was 2.0 (0.3-15.9) months (Supplemental Table 2). Temporary dose interruptions were reported in 23 patients (23.0%), with the first interruption occurring at a median (range) of 1.5 (0.1-14.5) months after cabozantinib initiation (Supplemental Table 2).

At the end of the 24 months follow-up period, 86 patients (86.0%) had discontinued cabozantinib. The most common reasons for treatment discontinuation were disease progression (56 patients, 65.1%) and AEs (19 patients, 22.1%) (Supplemental Table 2, Supplemental Figure 1).

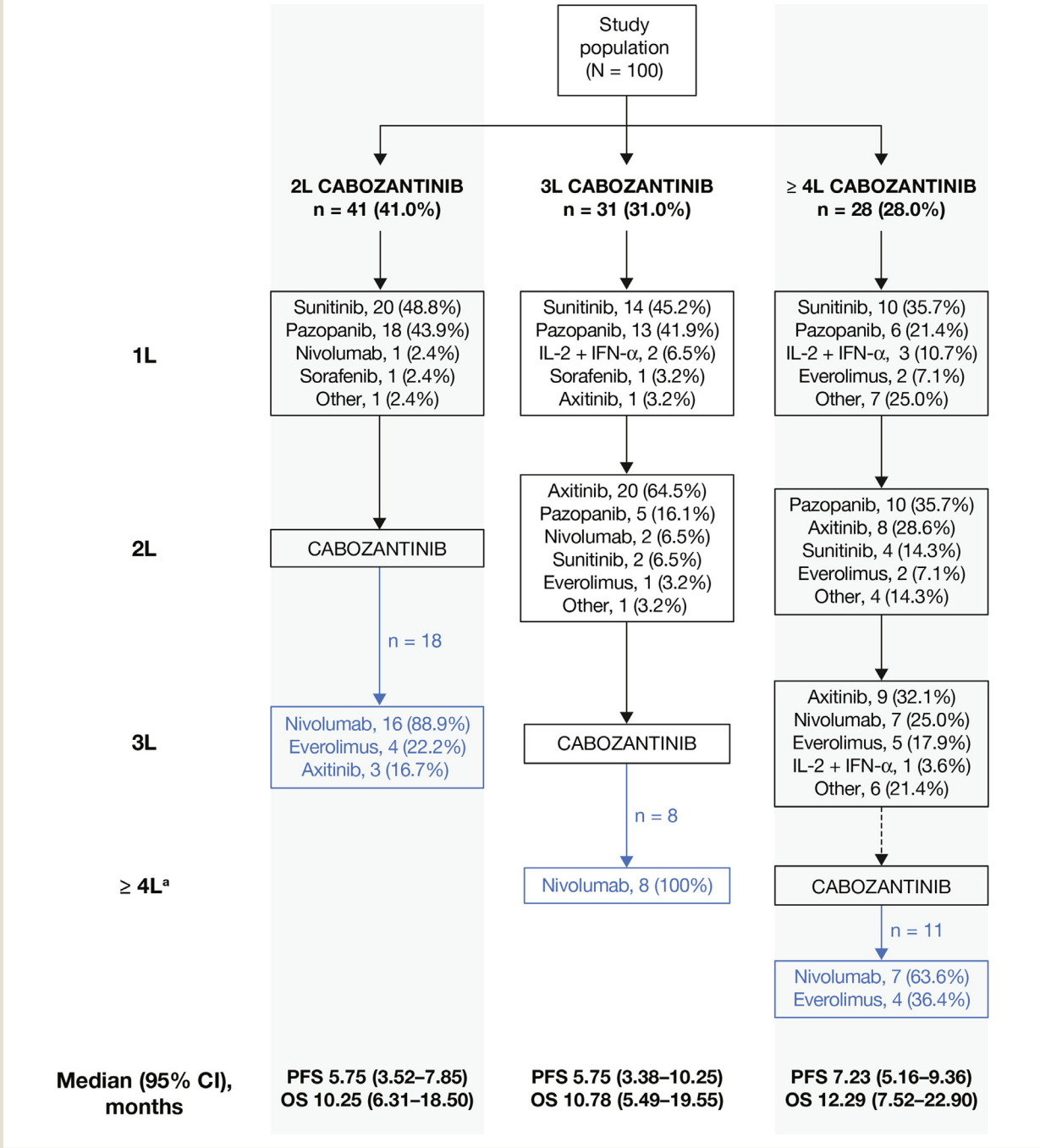
Pre- and Post-Cabozantinib Anticancer Treatment. The most commonly prescribed anticancer treatments prior to cabozantinib initiation were pazopanib (53.0%), sunitinib (51.0%) and axitinib (43.0%) (Supplemental Table 3). In terms of treatment sequencing, 2L cabozantinib was most commonly preceded by 1L sunitinib (48.8%) or pazopanib (43.9%), and 3L cabozantinib was most commonly preceded by 2L axitinib (64.5%) or pazopanib (16.1%) (Figure 1).

Table 1 Patient Demographics and Clinical Characteristics at Index Date

	Full Analysis Set (N = 100)
Male, n (%)	68 (68.0)
Age at advanced RCC diagnosis, mean (SD) years	58.9 (10.1)
Age at cabozantinib initiation, mean (SD) years	62.8 (10.3)
Duration of follow-up (months), median (range)	10.84 (0.4-33.5)
ECOG PS[a], n	89
0, n (%)	23 (25.8)
1, n (%)	49 (55.1)
2 or 3, n (%)	17 (19.1)
Histological type	
Clear cell	86 (86.0)
Papillary type I	3 (3.0)
Papillary type II	6 (6.0)
Other[b]	5 (5.0)
RCC stage, n (%)	
Locally advanced (III)	1 (1.0)
Metastatic (IV)	99 (99.0)
Prior nephrectomy, n (%)	77 (77.0)
Number of metastatic sites[c]	
Median (range)	2.0 (1.0-5.0)
1	19 (19.2)
2	40 (40.4)
≥ 3	40 (40.4)
Metastatic site, n[c,d]	99
Lungs, n (%)	75 (75.8)
Bones, n (%)	44 (44.4)
Liver, n (%)	36 (36.4)
Lymph nodes, n (%)	43 (43.4)
Visceral other, n (%)	15 (15.2)
Brain, n (%)	5 (5.1)
Other, n (%)	14 (14.1)
IMDC risk group score, n	100
Favorable, n (%)	19 (19.0)
Intermediate, n (%)	48 (48.0)
Poor, n (%)	23 (23.0)
Unknown, n (%)	10 (10.0)
MSKCC risk score group, n	100
Favorable, n (%)	12 (12.0)
Intermediate, n (%)	42 (42.0)
Poor, n (%)	29 (29.0)
Unknown, n (%)	17 (17.0)
Charlson Comorbidity Index	
Total score, median (IQR)	8.0 (6.0-8.0)
Total score ≤ 6, n (%)[e]	37 (37.0)
Total score > 6, n (%)[e]	63 (63.0)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IQR = interquartile range; MAP = managed access programme; MSKCC = Memorial Sloan Kettering Cancer Center; NR = not reported; RCC = renal cell carcinoma; SD = standard deviation.
[a] Reported in patients who had ECOG PS (Eastern Cooperative Oncology Group Performance Status) performed. 0, fully active; 1, restricted in physically strenuous activity; 2, ambulatory and capable of all selfcare; 3, capable of only limited selfcare.
[b] 'Other' includes one each of chromophobe RCC (renal cell carcinoma), renal medullary carcinoma, unclassified carcinoma, spindle cell carcinoma and one unknown histological type.
[c] Reported for patients with metastatic RCC (renal cell carcinoma).
[d] More than one metastatic site possible per patient.
[e] Analyses performed *post hoc*.

Figure 1 aRCC Treatment Pathways and Clinical Outcomes in the MAP Stratified by Cabozantinib Treatment Line
[a] Patients received cabozantinib as the 4L, 5L or later-line therapy.
Abbreviations: 1L = first line; 2L = second-line; 3L = third-line, 4L = fourth-line; ≥ 4L = fourth- or later-line; 5L = fifth-line; aRCC = advanced renal cell carcinoma; CI = confidence interval; IFN-α = interferon-α; IL-2 = interleukin-2; MAP = managed access programme; OS = overall survival; PFS = progression-free survival.



The majority of the 37 patients who received anticancer treatment after cabozantinib received 1 subsequent line of therapy (83.8%); 6 patients (16.2%) received 2 or more further lines of therapy. The most commonly prescribed treatment after cabozantinib was nivolumab in 83.8% of all patients receiving post-cabozantinib treatment, and in 88.9%, 100.0% and 63.6% of patients who received cabozantinib as 2L, 3L and ≥ 4L therapy, respectively (Figure 1, Supplemental Table 3).

Overall, 14 patients (14.0%) received concomitant radiotherapy (n = 4) or treatment for bone metastases (denosumab, n = 5; bisphosphonates, n = 6; Supplemental Table 3).

Effectiveness

In total, 74 patients (74.0%) who received cabozantinib via the MAP had died. The main cause of death was disease progression, accounting for 59 deaths (79.7%). There were no treatment-related deaths.

Median (95% CI) PFS for the FAS was 6.01 (5.16-7.85) months (Figure 2, Supplemental Figure 3); median (95% CI) OS was 10.84 (7.92-16.85) months (Figure 2, Supplemental Figure 3).

Among patients with evaluable data (n = 87), the overall response rate for the FAS was 34.5% (CR and PR in 2.3% and 32.2% of patients, respectively) and SD was noted in 35.6% of patients, giving a DCR of 70.1%. Progressive disease was reported in 28.7% of patients. Best response was not evaluable in 1 patient. For the 30 patients with CR or PR, the median (range) DoR to cabozantinib was 6.9 (1.8-26.9) months.

Subgroup Analyses

Early Vs. Late MAP Treatment and Cabozantinib Treatment Line. Demographic characteristics were generally balanced between the early (n = 57) and later (n = 43) MAP treatment subgroups (Supplemental Table 4). Compared with the later subgroup, the early subgroup had a higher median number of prior lines of therapy (1.0 vs. 2.0, respectively), a higher proportion of patients with moderate-to-severe kidney disease (41.9% vs. 59.6%, respectively), and a higher proportion of patients with at least 1 dose reduction (60.5% vs. 70.2%, respectively) (Supplemental Tables 4 and 5). In contrast, there was a trend towards poorer performance status and higher IMDC risk score in the later (vs. early) subgroup (Supplemental Table 4). The proportion of patients with temporary treatment interruptions was lower in the early subgroup than the later subgroup (19.3% vs. 27.9%, respectively) (Supplemental Figure 2, Supplemental Table 4, Supplemental Table 5). In both groups, AEs were the most common cause of dose reductions and interruptions. Similar proportions of patients (> 80%) discontinued treatment in each subgroup, most commonly owing to disease progression and AEs.

The distribution of anticancer tyrosine kinase inhibitors (TKIs) prescribed prior to cabozantinib initiation was broadly similar between the subgroups, most commonly sunitinib or pazopanib followed by axitinib. In both groups, nivolumab was most commonly prescribed after cabozantinib (Supplemental Table 6).

PFS and OS were similar for the early and later MAP treatment subgroups, and when assessed by cabozantinib treatment line (Figure 2).

CCI Subgroups. Demographic characteristics between the *post hoc* subgroups of patients with a CCI total score of 6 or less (n = 37) and those with a CCI total score of greater than 6 (n = 63) are shown in Supplemental Table 7. The proportion of patients with a poor risk score (based on IMDC categorization) was higher in the subgroup with a CCI total score of greater than 6 than in the subgroup with a CCI total score of 6 or less. Assessment of the impact of baseline comorbidities on clinical outcomes suggested an association between lower CCI total score (≤ 6 vs. > 6) and prolonged survival. Median (95% CI) OS and PFS were both longer in patients with CCI total scores of 6 or less than among those with CCI total scores of greater than 6: OS, 23.52 (16.26-not reached) months vs. 7.26 (5.75-9.17) months; PFS, 10.25 (6.80-13.54) months vs. 4.73 (2.92-5.85) months (Figure 3).

Discussion

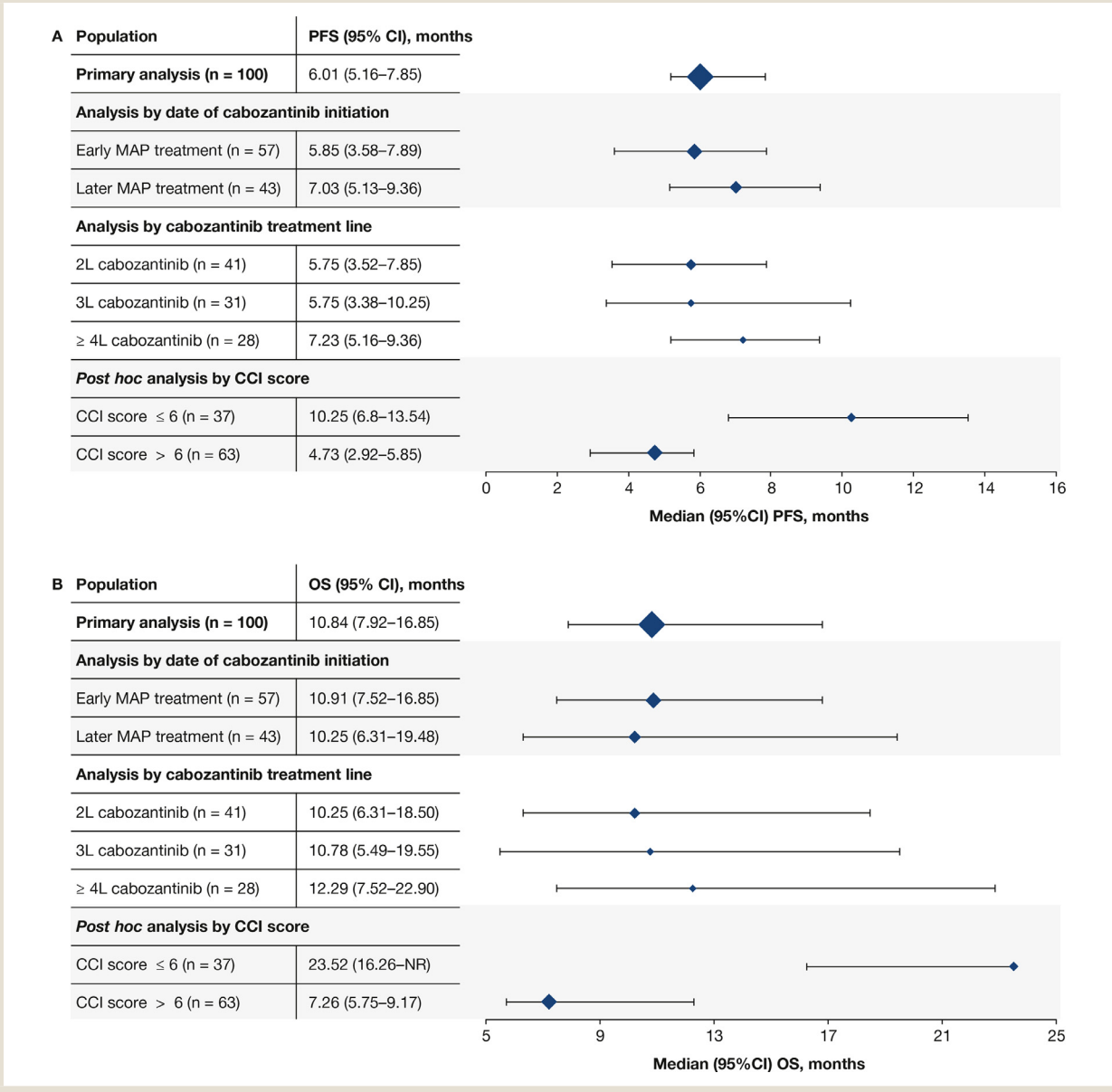
This retrospective analysis of data from the CERES study contributes to the limited body of real-world data on the use of cabozantinib for the treatment of patients with aRCC in routine care.

Within this unselected population, cabozantinib was most commonly prescribed as 2L therapy (41.0%). The majority of patients (84%) initiated cabozantinib at the recommended dose of 60 mg/day, but approximately two-thirds of patients had at least 1 subsequent dose reduction. Cabozantinib demonstrated clinical activity in the full study population, and across all treatment lines. In the *post hoc* CCI subgroup analyses, median (95% CI) OS and PFS were significantly longer in patients with a lower burden of comorbid disease at baseline (CCI score of 6 or lower) compared with those with a higher burden of disease (CCI score greater than 6). These findings suggest that CCI total score may hold potential as a prognostic and/or predictive indicator in patients with aRCC.[13-16]

Given the lack of available evidence on the use of cabozantinib in routine practice in the UK, this multicentre study provides valuable insights into how cabozantinib was used in a broad, unselected real-world patient population, and the clinical outcomes achieved. The findings serve as a benchmark against which to measure the effectiveness of RCC treatments in routine practice, as well as the impact of future changes in UK clinical practice. Furthermore, the sample size was informed by the median PFS estimates from the phase III METEOR trial,[6] which contributes to the reliability and robustness of the current analysis.

CERES was limited by its retrospective nature and by the use of data that were collected for the purposes of the MAP rather than for clinical research, limiting the scope of the variables collected and the level of data validation. PFS, for example, was evaluated in accordance

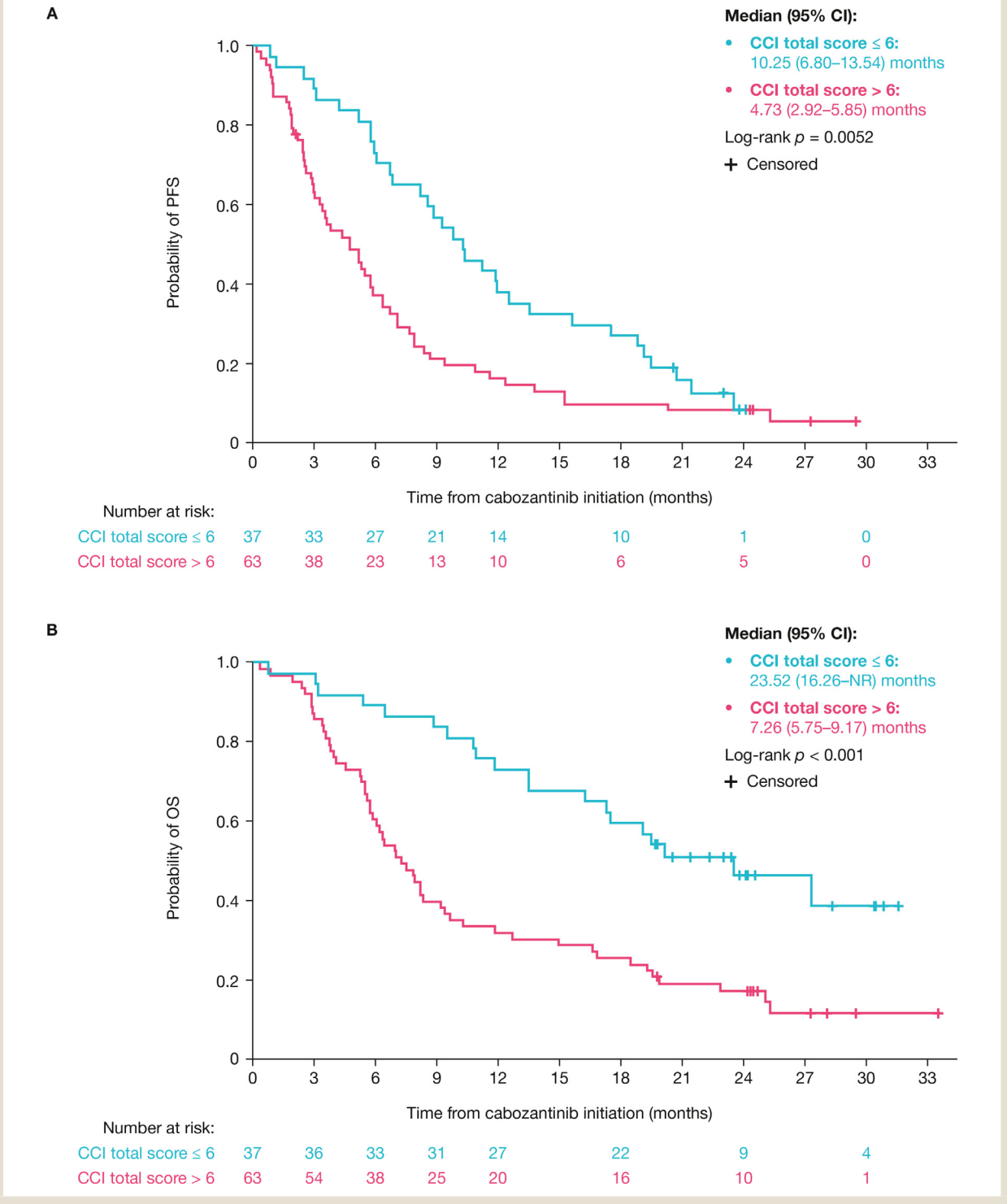
Figure 2 Survival Estimates for the FAS *a priori* and *post hoc* Subgroups of Interest, PFS (A) and OS (B)
Abbreviations: 2L = second-line; 3L = third-line; ≥ 4L = fourth- or later-line; CCI = Charlson Comorbidity Index; CI = confidence interval; FAS = full analysis set; MAP = managed access programme; NR = not reached; OS = overall survival; PFS = progression-free survival.



with local or RECIST findings (or death) and was not adjudicated by a central and independent review of radiological assessments across the participating centres. Caution must be taken when comparing median PFS for the CERES population with that reported for the METEOR randomized controlled trial (RCT) because of these differences in outcome validation.

Cabozantinib dose reductions occurred in two-thirds of patients, most commonly because of AEs (57.6% of patients). At the end of the 24-month follow-up period, however, the main reason for treatment discontinuation (56 of 86 patients [65.1%]) was disease progression; AEs only led to discontinuation in 19 (22.1%) patients. These findings suggest that collaborative care between physicians and their patients may help to tailor the optimum daily dose of cabozantinib to individual patient needs. Despite these inferential tolerability signals, the study provides only limited insight into the tolerability of cabozantinib in routine care, but this reflects the fact that AEs occurring during the MAP were reported directly to the regulatory authorities as part of the UK's Yellow Card reporting requirements for newly licensed therapies. As such, it is not possible to describe the AEs that led to the reported changes in the cabozantinib dosing regimen, or that led to discontinuation

Figure 3 Kaplan–Meier Survival Plots by CCI Total Score Subgroups, PFS (A) and OS (B)
Abbreviations: CCI = Charlson Comorbidity Index; CI = confidence interval; NR = not reached; OS = overall survival; PFS = progression-free survival.



of treatment during the study. In other real-world studies, however, the safety profile of cabozantinib used in routine care was similar to that observed in clinical trials.[17]

When interpreting the CERES findings, it is relevant to note that a large proportion of patients had received VEGF TKI therapy (pazopanib [53.0%], sunitinib [51.0%], axitinib [43.0%]) or radiotherapy (41.0%) prior to initiating cabozantinib; only 13% had received prior nivolumab (although nivolumab was the most commonly prescribed treatment in patients who received further systemic therapy after cabozantinib [83.8% of patients]). With the recent emergence of immune checkpoint inhibitor therapies and increasing use of 1L combination VEGF TKI/immune checkpoint inhibitor therapy in patients with aRCC,[18,19] these treatment patterns have become outdated, which may limit the ability to extrapolate these findings to current patient populations.

Finally, although the results of the *post hoc* CCI analysis are of clinical interest, the study sample size was powered for precision in the treatment pathway and PFS outcomes. Therefore, results of the subgroup and *post hoc* analyses should be considered as hypothesis-generating only.

The CERES patient population had a substantial burden of comorbid disease: 63.0% had a CCI score of greater than 6, 19% were categorized with an ECOG PS score of at least 2, and over a fifth of patients were categorized as poor risk according to IMDC risk scores. As is common when comparing real-world and RCT populations, the patients enrolled in CERES had more severe disease than those in the METEOR trial of cabozantinib in patients with RCC who had progressed after prior VEGF-targeted therapy. In METEOR, cabozantinib was used as 3L or later-line therapy in approximately 30% of patients (compared with 59% in CERES); no patients in METEOR had an ECOG PS of 2 or higher and only 16% (in the primary PFS analysis) had an MSKCC poor-risk classification.[5,6] Furthermore, METEOR included only patients with clear cell RCC,[5,6] while 14% of patients treated via the MAP had RCC of non-clear cell histology.

Unsurprisingly, given the more severe disease profile of the CERES population, the median PFS in the present study (6.0 months; assessed locally by radiological and clinical parameters) was shorter than that reported in the METEOR trial (7.4 months; assessed by independent radiology committee per RECIST 1.1).[6] Median OS in CERES (10.8 months) was also markedly shorter than in the METEOR trial (21.4 [18.7-not estimable] months),[6] again likely reflecting clinically relevant differences between the populations.

The CERES population was more similar to that of CABOREAL (NCT03744585) – the largest study of cabozantinib in a real-world RCC population conducted to date.[20] CABOREAL included patients (n = 410) receiving cabozantinib treatment for RCC via the French Temporary Authorisation for Use (ATU) programme.[20] CCI score was not reported in CABOREAL, but 39.3% of included patients had an ECOG PS of at least 2, and approximately one-third of patients were categorized as having poor-risk IMDC (31.7%) and MSKCC (33.9%) scores.[20] Estimated median OS was slightly longer in CABOREAL than in CERES (14.4 vs. 10.8 months, respectively),[20] but published real-world estimates for OS vary widely for aRCC populations (7.7-23.7 months)[11,21,22] because of key differences in the design and eligibility for the associated studies. Similarly, PFS estimates vary considerably within the real-world literature, ranging from 6.7 to 12.5 months (compared with 6.0 months in CERES).[11,17,22-24]

In terms of insights for clinical practice from the present study, the occurrence of dose reductions in two-thirds of patients initiated on cabozantinib reinforces the need for collaborative care between physicians and their patients and for tailoring of doses to meet individual patient needs. A similar proportion of patients had cabozantinib dose reductions (from an initiation dose of 60 mg/day) in both METEOR (62%; median dose 43 mg/day)[6] and CABOREAL (57%).[20] Although AEs were the most commonly reported reason for cabozantinib dose reductions in CERES (57.6% of patients; n = 38), only 19 patients discontinued treatment because of AEs, potentially suggesting that timely dose titration and adjustments can avert AE-related treatment discontinuation.

Conclusion

The CERES study provides valuable insights into how cabozantinib was used in a broad, unselected patient population treated for aRCC in real-world clinical practice via the UK MAP; cabozantinib demonstrated clinically meaningful activity across multiple lines of therapy. These real-world data along with the data from randomized clinical trials helps clinicians and patients to make informed decisions in the treatment pathway. These findings are a useful benchmark for future studies of the effectiveness of cabozantinib and of other RCC treatment options in routine care, and for assessing the impact of future changes in UK clinical practice.

Clinical Practice Points

- Cabozantinib 60 mg/day is approved in the UK for the treatment of adults with advanced renal cell carcinoma (aRCC) who are treatment-naïve with intermediate- or poor-risk disease, or who have received prior vascular endothelial growth factor (VEGF)-targeted therapy for aRCC, but there are limited data regarding the use of cabozantinib in routine care.
- In this analysis of a UK managed access programme (MAP), cabozantinib demonstrated clinical activity in an unselected patient population receiving treatment for aRCC after prior VEGF-targeted treatment in routine practice.
- The CERES study provides insight into how cabozantinib treatment can be optimized for patients with aRCC who are managed in routine care within the context of the dynamic RCC treatment landscape. These results also provide evidence for the use of cabozantinib in patients who are disadvantaged by not being enrolled in clinical trials.
- Cabozantinib dose reductions occurred in two-thirds of patients enrolled in CERES; collaborative care between physicians and their patients may help to tailor the optimum daily dose of cabozantinib to individual patient needs.

- The CERES study provides a benchmark for future real-world studies of the effectiveness of cabozantinib and of other aRCC treatment options in routine care, and for assessing the impact of future changes in UK clinical practice.
- Exploratory analyses of the CERES data suggest that Charlson Comorbidity Index total score may be worth further investigation as a potential prognostic indicator in patients with aRCC.

CRediT Authorship Contribution Statement

All authors have made substantial contributions to study conception/design, or acquisition/analysis/interpretation of data, and to drafting of the publication, or revising it critically for important intellectual content. All authors have provided their final approval of the publication.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2021.09.005.

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