ORIGINAL RESEARCH ARTICLE

Cabozantinib and Axitinib After Vascular Endothelial Growth Factor Therapy in Patients with Advanced Renal Cell Carcinoma: A Retrospective Cohort Study from England

Janet Brown[1] · Brooke Harrow[2] · Anne Marciniak[2] · Christine McCarthy[2] · Aude Houchard[3] · Lori Cirneanu[4] · Andrew Protheroe[5]

Abstract

Background and Objective The tyrosine kinase inhibitors cabozantinib and axitinib have been widely used in England to treat advanced renal cell carcinoma following prior vascular endothelial growth factor-targeted therapy, but data on real-world usage remain limited. Our objective was to describe the real-world treatment patterns and outcomes of patients with advanced renal cell carcinoma who received second-line or later-line ($\geq$ 2L) cabozantinib or axitinib after vascular endothelial growth factor-targeted therapy in clinical practice in England.

Methods This retrospective cohort study used clinical practice data (collected 2011–20) from the English Cancer Analysis System database. Patient characteristics, treatment sequence and duration, and overall survival (time from initiation of cabozantinib/axitinib treatment to death) were evaluated.

Results Data from 1485 eligible adults with advanced renal cell carcinoma were analyzed: 440 received $\geq$ 2L cabozantinib (2L for 88.6% of them); 1045 received $\geq$ 2L axitinib (2L for 89.5%). The most common first-line treatments were sunitinib (2L cabozantinib subcohort, 48%; 2L axitinib subcohort, 46%) and pazopanib (46% and 54%, respectively); nivolumab was the most common third-line treatment (18% and 19%, respectively). Median (interquartile range) 2L therapy duration was 5.52 (2.73–11.74) months for cabozantinib and 4.60 (1.45–12.36) months for axitinib. Following adjustment for potential confounders using inverse probability weighting, overall survival (median [interquartile range]) was longer for $\geq$ 2L cabozantinib (11.2 [5.7–28.0] months) than for $\geq$ 2L axitinib (10.4 [4.7–22.0] months; log-rank $p = 0.0034$).

Conclusions The Cancer Analysis System database is a valuable research resource providing extensive real-world clinical data. Real-world overall survival was longer with $\geq$ 2L cabozantinib than with axitinib.

Clinical Trial Registration ClinicalTrials.gov, NCT04637204; registered November 2020.

Plain Language Summary

Cabozantinib and axitinib are anticancer drugs called tyrosine kinase inhibitors. They work by blocking the activity of proteins that cancer cells use to help them divide and grow. Cabozantinib and axitinib are treatment options for a common type of kidney cancer called renal cell carcinoma (RCC). There is evidence about how well cabozantinib and axitinib work in clinical trials, but it is less clear how well they work in standard practice outside of clinical trials. We investigated how

✉ Janet Brown
j.e.brown@sheffield.ac.uk

1 Division of Clinical Medicine, University of Sheffield, Western Bank, Sheffield S10 2TN, UK

2 Formerly Ipsen, Boulogne-Billancourt, France

3 Ipsen, Boulogne-Billancourt, France

4 IQVIA, London, UK

5 Department of Oncology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

cabozantinib and axitinib are used and how well they work as part of 'real-world' RCC care. We did this by analyzing patient data from an English cancer database. All patients in the study had advanced RCC and had been treated with at least one previous anticancer drug. This includes a type of drug that blocks new blood vessels forming, which tumors need for rapid growth. Most of the 1485 patients received cabozantinib or axitinib after receiving only one previous anticancer drug. These patients were treated for a median of 5.5 months with cabozantinib and 4.6 months with axitinib. Patients lived for a median of 11.2 months after starting cabozantinib treatment and a median of 10.4 months after starting axitinib treatment. This study provides new evidence showing how well cabozantinib and axitinib work in everyday RCC care. The results add to those from clinical trials and show the value of the English cancer registry for conducting studies of routine cancer care.

Key Points

We used the English Cancer Analysis System database to investigate treatment patterns and outcomes for patients with advanced renal cell carcinoma in England between 2011 and 2020.

For patients who had previously received vascular endothelial growth factor-targeted therapy, treatment duration was longer for cabozantinib than axitinib.

Adjusted median overall survival was longer with cabozantinib than axitinib.

1 Introduction

In 2020, the age-standardized incidence of kidney cancer was 4.6 per 100,000 people globally and 10.3 per 100,000 people in the UK [1, 2]. Of the estimated 13,300 people diagnosed with kidney cancer per year in the UK [3], most have renal cell carcinoma (RCC) [4, 5]. Approximately one-third of patients with RCC present with locally advanced or metastatic disease, usually requiring systemic anticancer therapy (SACT) [6, 7]; one-fifth of patients who experience disease recurrence after nephrectomy may also require SACT [8, 9].

The past decade has seen substantial advances in RCC treatment and the introduction of numerous targeted SACTs [10–13]. Antiangiogenic therapies target cancer-related neovascularization, commonly by inhibiting the activity of vascular endothelial growth factor (VEGF) or VEGF receptors (VEGFRs) [14, 15]. Approved VEGF-targeted treatments for advanced RCC (aRCC) include the tyrosine kinase inhibitors (TKIs) axitinib, cabozantinib, pazopanib, sorafenib, and sunitinib [14, 16].

Cabozantinib is an oral small-molecule inhibitor of multiple receptor tyrosine kinases, including VEGFRs, MET, and AXL [17], and is indicated as monotherapy for adults with aRCC following prior VEGF-targeted therapy, based on

results from the phase III METEOR trial (NCT01865747) [17–19] (European Medicines Agency authorization, September 2016; National Institute for Health and Care Excellence [NICE] recommendation for use in the National Health Service [NHS] in England and Wales, August 2017 [20]). It is also indicated for use in SACT-naive adults with intermediate-risk or poor-risk aRCC based on the CABOSUN trial (NCT01835158) [17, 21, 22] (European Medicines Agency authorization, May 2018; NICE recommendation for use in the NHS, October 2018 [23]). When cabozantinib was approved in the UK, axitinib was an established standard of care for aRCC that had progressed during prior cytokine or VEGF-targeted TKI therapy [24]. Axitinib is a selective inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3, and was authorized in Europe in 2012 based on the phase III AXIS trial (NCT00678392) [24, 25] and recommended by NICE in February 2015 for use in the NHS [26].

Several real-world studies have examined TKI use following other SACTs such as checkpoint inhibitors [27–37], but data specific to the real-world use of cabozantinib and axitinib after VEGF-targeted therapy in England remain limited [38, 39]. We therefore conducted a retrospective observational cohort study of patients receiving ≥ second-line (2L) cabozantinib or axitinib following prior VEGF-targeted therapy for aRCC in routine care in England.

2 Methods

2.1 Study Design

This retrospective cohort study used clinical practice data from the Cancer Analysis System (CAS) database (NCT04637204). The objective of this study was to describe real-world use of cabozantinib and axitinib after VEGF-targeted therapy in patients with aRCC, and real-world treatment patterns and outcomes. The study included an identification period during which patients received an initial diagnosis of RCC or aRCC (1 January, 2011–31 December, 2018) and a follow-up period from cabozantinib or axitinib treatment initiation to data extraction (31 January, 2020).

2.2 Data Sources

The CAS database facilitates analysis of all patients with a cancer diagnosis in England (other UK countries are not included). It comprises linked retrospective data (at patient level [typically by NHS number] and tumor level) from the SACT dataset (treatment data, e.g., traditional chemotherapy drugs, biologics, immunotherapy, hormonal therapies, investigational agents from inpatient/outpatient/community settings) [40] and the Cancer Outcomes and Services Dataset (clinical data, e.g., cancer morphology, histology, staging, grade, tumor/node/metastasis status, surgery, date of death) [41]. The retrospective data extracted for analysis included demographic data (year of diagnosis, sex, age at diagnosis, ethnicity), clinical data at the time of diagnosis (prior nephrectomy status, tumor/node/metastasis stage, histology type, morphology code, metastatic status), and clinical data relating to treatment (Eastern Cooperative Oncology Group performance status [ECOG PS] score at index treatment initiation, time from aRCC diagnosis to SACT initiation, duration of follow-up). Data on some components of the International Metastatic RCC Database Consortium (IMDC) risk categorization, including hemoglobin, calcium, neutrophil, and platelet levels, were not available in the database.

2.3 Patient Population

The study included adults (aged ≥ 18 years) with an initial diagnosis of aRCC (International Classification of Diseases, Tenth Revision, code C64 or C65, and stage III/IV disease; confirmed cases), and those with an initial diagnosis of RCC (International Classification of Diseases, Tenth Revision code C64 or C65, and stage I/II disease or missing staging data) who initiated SACT indicative of aRCC during the study period (proxy cases, for whom metastatic or advanced disease was not confirmed). Eligible patients received cabozantinib or axitinib monotherapy after at least one VEGF-targeted therapy in any treatment line.

Patients were excluded if they had been diagnosed with a concomitant tumor other than nonmelanoma skin cancer in the year before aRCC diagnosis, had a prescription for SACT > 30 days before initial aRCC diagnosis, or were receiving treatment via the Cancer Drugs Fund (owing to restricted availability of outcomes data). Participation in clinical trials was not an exclusion criterion.

2.4 Endpoints and Evaluations

Demographic and clinical characteristics of patients at ≥ 2L cabozantinib or axitinib initiation were recorded, and real-world overall survival (OS) was evaluated. Duration of therapy (DoT) and treatment sequencing were also described for patients who received 2L cabozantinib or axitinib.

Time from diagnosis to treatment initiation was based on the time between RCC/aRCC diagnosis and index prescription start date. Duration of therapy was estimated from initiation until the projected index treatment end date (the start date of the last cycle plus the median cycle length for intravenous SACT, the date of the last prescription plus 30 days for oral SACT, or death, deregistration/loss to follow-up, or study end) or the start of subsequent therapy. Censoring events were loss to follow-up or death, and instances when index treatment was initiated too close to the study end to permit subsequent therapy. For patients who did not start a subsequent therapy or did not have a record of death within the study period, the end of follow-up was the earliest of loss to follow-up or the end of the follow-up period (31 January, 2020). Overall survival was the time between the patient's index treatment start date and their date of death during the study period.

2.5 Statistical Analysis

The primary analyses of patient characteristics, cabozantinib and axitinib treatment patterns, and OS were descriptive. The study population was divided into four prespecified cohorts: ≥ 2L cabozantinib after VEGF-targeted therapy excluding patients who received prior axitinib (the cabozantinib cohort); ≥ 2L axitinib after VEGF-targeted therapy excluding those who received prior cabozantinib (the axitinib cohort); cabozantinib following axitinib; and axitinib following cabozantinib. Only results from the cabozantinib and axitinib cohorts are reported here owing to the small sizes of the other cohorts.

Treatment sequencing patterns for the subcohorts who received 2L cabozantinib or axitinib were visualized using Sankey diagrams. For time-to-event analyses (duration of follow-up, DoT, and OS), medians and interquartile ranges (IQRs) were reported. Overall survival was estimated for the cabozantinib and axitinib cohorts using Kaplan–Meier curves. An exploratory analysis was performed to compare median OS between cohorts. This analysis used inverse probability weighting (IPW) to account for differences in baseline characteristics between the cohorts. The method used propensity score matching to create a pseudo-population, different from the original population, in which confounding was accounted for and treatment (cabozantinib or axitinib) was independent of measured confounders (age, sex, tumor stage, index treatment year, and prior nephrectomy). To increase the power of the analysis and the precision of comparative estimates, this method used oversampling, with unequal weights to increase the sample size (i.e., to base estimates on more events and more censored patients), and the medians and quartiles remaining

approximately the same. Median OS for cabozantinib versus axitinib was assessed using the standard log-rank test with a significance threshold of <0.05 for exploratory purposes only. Two-sided 95% confidence intervals (CIs) were reported for the 1-year landmark survival analysis.

3 Results

3.1 Population Characterization

In total, 77,305 patients in the CAS database received an initial RCC diagnosis during the recruitment period, among whom 26,418 had confirmed aRCC (stage III/IV disease) and 2194 had proxy aRCC (stage I/II disease, or stage missing, but initiated SACT for aRCC). Overall, 2502 patients with aRCC received cabozantinib or axitinib. After exclusion of ineligible individuals (including those receiving adjunct/

combination therapies), the cabozantinib cohort comprised 440 patients who received ≥ 2L cabozantinib following prior VEGF-targeted therapy (other than axitinib), and the axitinib cohort comprised 1045 patients who received ≥ 2L axitinib following prior VEGF-targeted therapy (other than cabozantinib). In addition, 91 patients received ≥ 2L cabozantinib following axitinib and 30 patients received ≥ 2L axitinib following cabozantinib; these cohorts were not included in this analysis owing to their small sample sizes. Patient disposition is reported in Fig. 1.

Key demographic and clinical characteristics were broadly balanced between the cabozantinib and axitinib cohorts (Table 1). Most patients were male (76.4% and 70.2%, respectively), and median age was 62.5 and 63.0 years, respectively. These cohorts differed, however, in the distribution of RCC diagnosis year: 80.1% of patients in the axitinib cohort were diagnosed before 2016, whereas 64.8% of those in the cabozantinib cohort were diagnosed
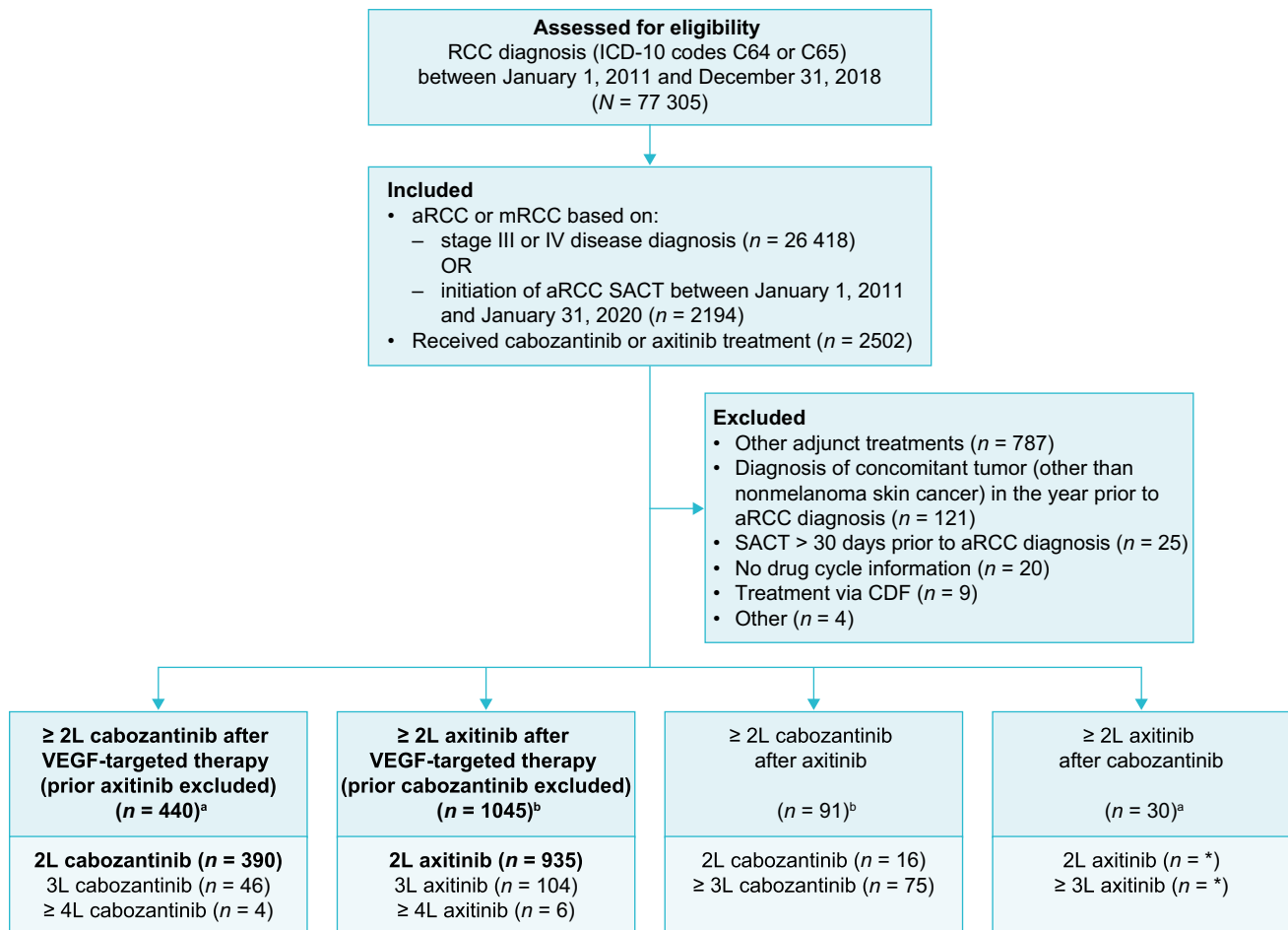
Fig. 1 Patient disposition. [a]Ten patients were in both the cabozantinib cohort and the axitinib after cabozantinib cohort. [b]Sixty patients were in both the axitinib cohort and the cabozantinib after axitinib cohort. *Subcohort sizes based on small numbers of patients (1–5) have been replaced with an asterisk to ensure patient anonymity. *1L* first-line, *2L*

second-line, *3L* third-line, *4L* fourth-line, *aRCC* advanced RCC, *CDF* Cancer Drugs Fund, *d* days, *ICD-10* International Classification of Diseases, Tenth Revision, *mRCC* metastatic RCC, *RCC* renal cell carcinoma, *SACT* systemic anticancer therapy, *VEGF* vascular endothelial growth factor

Table 1 Patient characteristics

	≥ 2L cabozantinib (n = 440)	≥ 2L axitinib (n = 1045)
Male, n (%)	336 (76.4)	734 (70.2)
Age at diagnosis, median (IQR), years	62.5 (54.0–69.0)	63.0 (55.0–69.0)
Ethnicity[a], n (%)		
White	396 (90.0)	970 (92.8)
Asian[b]	16 (3.6)	32 (3.1)
Black/Chinese/mixed/other	28 (6.4)	43 (4.1)
Year of diagnosis, n (%)		
2011–15	155 (35.2)	837 (80.1)
2016–18	285 (64.8)	208 (19.9)
Time from aRCC diagnosis to SACT initiation, n (%)		
< 1 year[d]	260 (59.1)	612 (58.6)
≥ 1 year	89 (20.2)	170 (16.3)
Missing	91 (20.7)	263 (25.2)
ECOG PS score at time of index treatment initiation, n (%)		
0–1	312 (70.9)	553 (52.9)
2–3	31 (7.0)	50 (4.8)
Missing	97 (22.1)	442 (42.3)
TNM staging at diagnosis, n (%)		
Stage I	19 (4.3)	36 (3.4)
Stage II	26 (5.9)	52 (5.0)
Stage III	81 (18.4)	176 (16.8)
Stage IV	269 (61.1)	606 (58.0)
Missing	45 (10.2)	175 (16.8)
Histology type at diagnosis, n (%)		
Clear cell	402 (91.4)	944 (90.3)
Papillary	19 (4.3)	48 (4.6)
Missing	19 (4.3)	53 (5.1)
Morphology codes at diagnosis, n (%)		
8000/3 (Neoplasm malignant)	8 (1.8)	35 (3.4)
8010/3 (Carcinoma, NOS)	7 (1.6)	8 (0.8)
8260/3 (Papillary adenocarcinoma, NOS)	19 (4.3)	48 (4.6)
8310/3 (Clear-cell adenocarcinoma, NOS)	290 (65.9)	577 (55.2)
8312/3 (Renal cell carcinoma, NOS)	112 (25.5)	367 (35.1)
Metastasis at diagnosis, n (%)	258 (58.6)	556 (53.2)
Missing/unknown	51 (11.6)	193 (18.5)
Duration of follow-up from diagnosis, months		
Mean (SD)	31.0 (22.1)	35.5 (21.9)
Median (Q1–Q3)	25.8 (13.2–45.1)	30.8 (17.3–49.7)
Min–Max	0.4–95.8	0.8–97.0

Records of prior nephrectomy were also collected. Data are, however, not included here because they are likely to be incomplete (recorded for 31 patients [7.1%] in the cabozantinib cohort and 57 patients [5.5%] in the axitinib cohort)

2L second line, *aRCC* advanced renal cell carcinoma, *ECOG PS*, Eastern Cooperative Oncology Group performance status, *IQR* interquartile range, *Max* maximum, *Min* minimum, *NOS* not otherwise specified, *Q* quartile, *SACT* systemic anticancer therapy, *SD* standard deviation, *TNM* tumor/node/metastasis

[a]Ethnicity categorization was based on the Office for National Statistics ethnic group classifications

[b]Asian comprises Indian, Pakistani, Bangladeshi, and any other Asian background groups [d]Proxy for International Metastatic Renal Cell Carcinoma Database Consortium intermediate/poor risk

after cabozantinib was approved in Europe for the treatment of aRCC in 2016. Accordingly, the median (IQR) duration of follow-up was longer for axitinib than cabozantinib: 30.8 (17.3–49.7) months versus 25.8 (13.2–45.1) months (Table 1).

In both cohorts, most patients had clear-cell RCC (90.6%, 1346/1485) and a diagnosis of stage IV disease (58.9%, 875/1485); over half had metastasis at the time of RCC/aRCC diagnosis (54.8%, 814/1485). Most patients had an ECOG PS score of 0–1 at index treatment initiation (58.2%, 865/1485; 70.9% of the cabozantinib cohort vs 52.9% of the axitinib cohort), but the ECOG PS score was not documented for a considerable proportion of patients (36.3%, 539/1485; 22.1% and 42.3% of the two cohorts, respectively; Table 1). Only a minority (5.9%, 88/1485; 7.1% and 5.5% of the two cohorts, respectively) had a record of prior nephrectomy status.

3.2 Treatment Patterns

Time from aRCC diagnosis to SACT initiation was recorded for 76% of patients. For most of these individuals, it was < 1 year (74% and 78% in the cabozantinib and axitinib cohorts, respectively).

Most patients in the cabozantinib and axitinib cohorts (88.6% and 89.5%, respectively) received these agents as 2L therapy following first-line (1L) VEGF-targeted therapy. For the subcohorts receiving 2L cabozantinib ($n = 390$) or 2L axitinib ($n = 935$), median (IQR) DoT was 5.5 (2.7–11.7) months and 4.6 (1.5–12.4) months, respectively (Fig. 2A). A larger proportion of the 2L cabozantinib subcohort than the 2L axitinib subcohort had a DoT of > 3 months (70% and 60%, respectively). For third-line (3L) cabozantinib ($n = 46$), the median (IQR) DoT was 6.5 (2.1–11.0) months; for 3L axitinib ($n = 104$), it was 4.7 (1.6–10.4) months (Fig. 2B).

In the 2L cabozantinib subcohort, the most common treatment sequence was 1L sunitinib (48%) or pazopanib (46%) followed by 2L cabozantinib monotherapy (97%) and 3L nivolumab (18%; Fig. 3A). There was, however, no record of ≥ 3L therapy for most patients in this subcohort (62%). In those with available records, the most commonly recorded 3L therapies, other than nivolumab, were everolimus and denosumab (a supportive therapy for patients with metastatic disease; 4% each); 2% received 3L axitinib. Death was recorded after 2L therapy for 12% of patients (Fig. 3A).

In the 2L axitinib subcohort, the most common treatment sequence was 1L pazopanib (54%) or sunitinib (46%) followed by 2L axitinib monotherapy (99%) and 3L nivolumab (19%), everolimus (7%) or cabozantinib (6%; Fig. 3B). As with the 2L cabozantinib subcohort, there was no record of ≥ 3L therapy for a substantial proportion of the 2L axitinib

subcohort (50%). For 17% of patients, death was recorded after 2L therapy (Fig. 3B).

For the small proportions of patients shown as receiving 2L cabozantinib or axitinib with an additional agent (3% and 1%, respectively), agents were grouped together within one treatment line by the prespecified line of treatment algorithm. Although these are presented as combination therapies, they are based on monotherapies.

3.3 Survival

Median OS was significantly longer with cabozantinib than with axitinib in both the unweighted (Fig. 4A) and exploratory IPW (Fig. 4B) analyses (log-rank test, $p = 0.0034$). In the unweighted analysis, median (IQR) OS was 11.4 (5.6–27.3) months with cabozantinib and 9.6 (4.5–20.3) months with axitinib (Fig. 4A). In the IPW analysis, median (IQR) OS estimates were 11.2 (5.7–28.0) months with cabozantinib (effective sample size after oversampling, $n = 816$) and 10.4 (4.7–22.0) months with axitinib (effective sample size after oversampling, $n = 1483$; Fig. 4B).

Unweighted survival estimates at the 1-year landmark were 48% (95% CI 43–54) and 42% (95% CI 39–45), respectively. By the end of the study period, 57.4% of patients in the cabozantinib cohort and 82.9% in the axitinib cohort had died.

4 Discussion

This study responded to a need for real-world data on commonly prescribed TKIs for patients with aRCC in England [39]. It described treatment patterns and outcomes for patients receiving ≥ 2L cabozantinib or axitinib following prior VEGF-targeted SACT between January 2011 and January 2020. It should be noted that the study period pre-dates major therapeutic changes associated with the approval of combination TKI-CPI regimens for aRCC in England; most patients had therefore received prior 1L VEGF-targeted monotherapy. Although 1L CPI-based combination therapy has become the standard of care for aRCC, the data we report remain relevant to the subset of patients for whom 1L CPI-based therapy is contraindicated or unavailable, and for patients in countries and healthcare settings where access to and/or affordability of such therapies remain limited [14, 42, 43].

Overall, the baseline characteristics were generally consistent with other real-world studies of cabozantinib use in RCC [28, 33, 34, 37, 39, 44, 45], and key clinical and demographic characteristics were broadly balanced between treatment cohorts. Some relevant data, however, were incompletely recorded in the CAS database, limiting the ability to characterize the population in terms of, for example, time
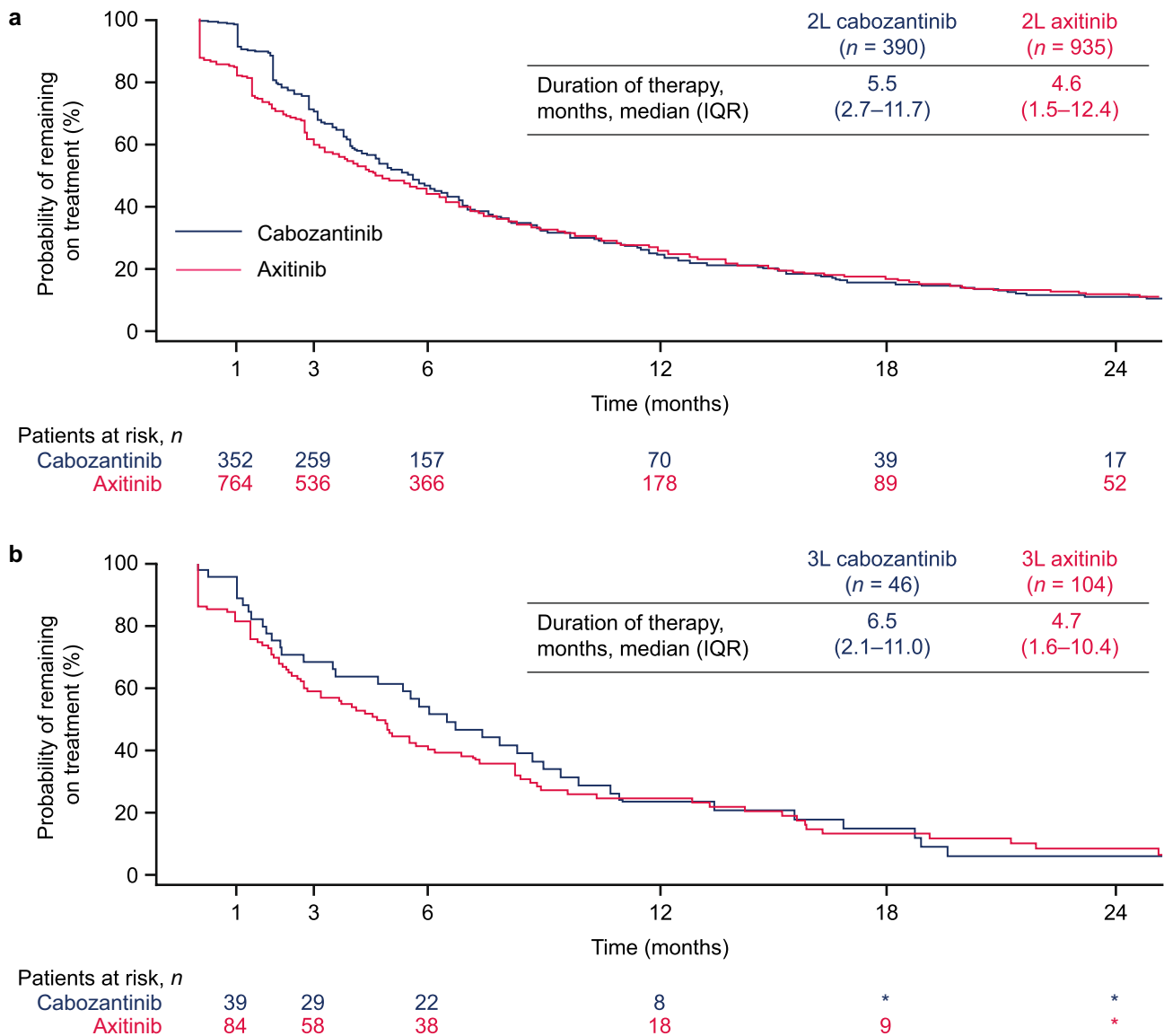
Fig. 2 Duration of therapy from the start of index treatment until the projected end date of index treatment or start of subsequent therapy for second-line (2L) treatment (**a**) and third-line (3L) therapy (**b**).

*Small numbers of patients (1–5) have been replaced with an asterisk to ensure patient anonymity. *IQR* interquartile range

from aRCC diagnosis to SACT initiation, other IMDC risk factors, ECOG PS scores, and prior nephrectomy status. Notably, the proportion of patients with an intermediate or poor IMDC risk profile can only be inferred from the single recorded IMDC risk factor (initiation of SACT within a year of aRCC diagnosis) to be at least three-quarters; if additional data on other IMDC risk factors had been recorded and were evaluable, this proportion may have been revealed to be larger than this. The surprisingly low proportion of patients with a record of prior nephrectomy (6%) is probably because of incomplete data. No post-nephrectomy adjuvant therapies were recommended by NICE for use in England during this period; the receipt of any prior adjuvant therapy

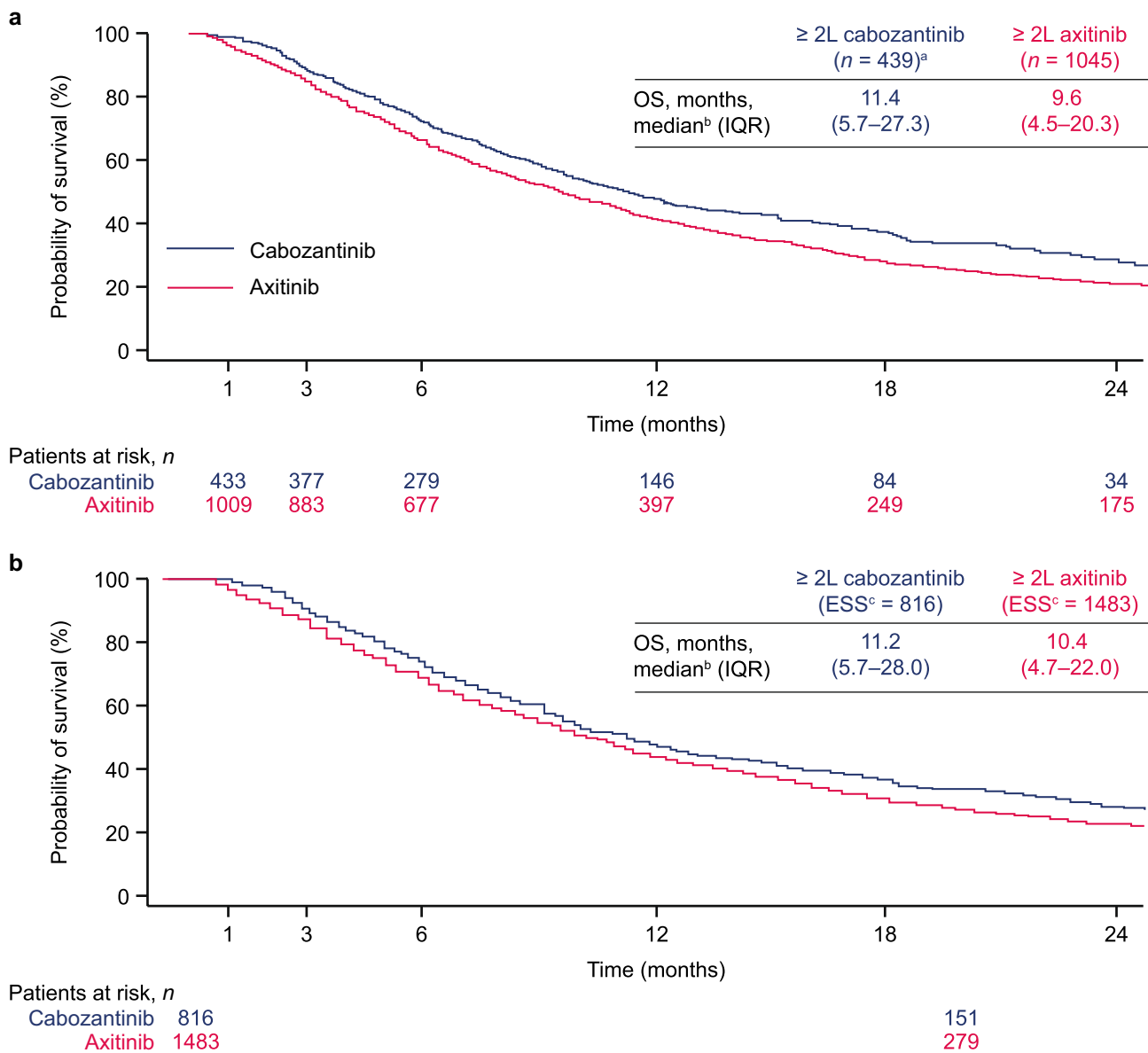is therefore likely to have been minimal and unlikely to be a meaningful confounder.

Most patients (89%) received cabozantinib or axitinib as 2L therapy; the remainder may have received other 2L therapies, such as everolimus, lenvatinib, or nivolumab. Median real-world DoT with 2L cabozantinib was notably shorter than in clinical trials: 5.5 months in the present study compared with 8.3 months in the METEOR study of patients with aRCC following VEGFR-targeted TKI therapy [19]. Similarly, median real-world DoT of 2L axitinib (4.6 months) was shorter than in the pivotal AXIS trial of patients with aRCC following SACT (6.4 months) [25]. In this study, median DoTs for 3L cabozantinib and axitinib
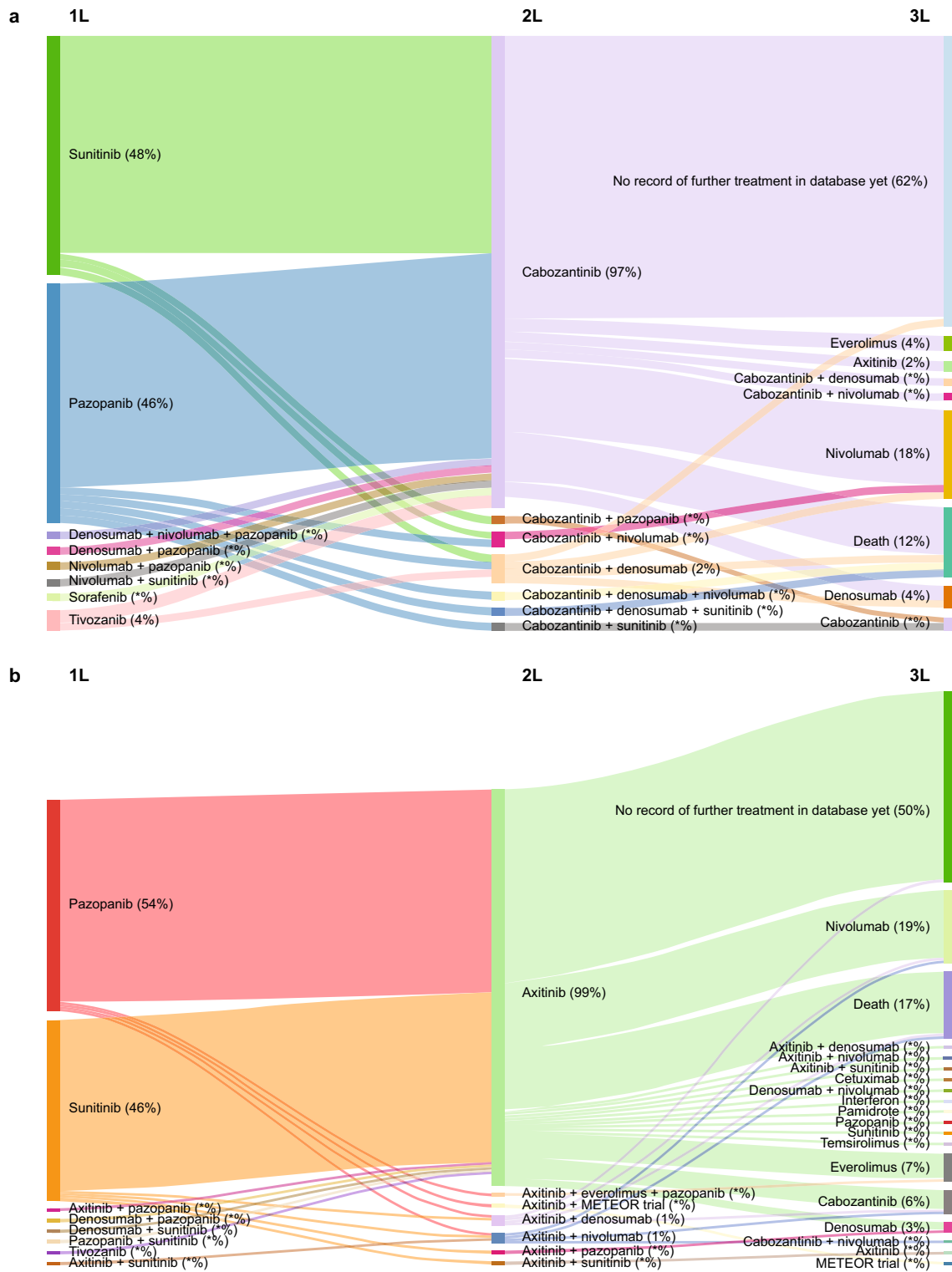
Fig. 3 Sankey diagram visualization of treatment sequences for patients who received second-line (2L) cabozantinib (**a**) or 2L axitinib (**b**). *Percentages based on small numbers of patients (1–5) have been replaced with an asterisk to ensure patient anonymity. For patients shown as receiving 2L cabozantinib or axitinib with an additional agent (3% and 1%, respectively), agents were grouped together within one treatment line by the prespecified line of treatment algorithm. *1L* first-line, *3L* third-line

a

Patients at risk, *n*

Cabozantinib	433	377	279	146	84	34
Axitinib	1009	883	677	397	249	175

b

Patients at risk, *n*

Cabozantinib	816	151
Axitinib	1483	279

Fig. 4 Overall survival (OS) for the ≥ 2L cabozantinib and axitinib cohorts in the unweighted analysis (**a**) and the inverse probability weighting analysis (**b**). Patients without a death record were censored at the date of loss to follow-up or the end of the study period. [a]One patient was removed from the cabozantinib analysis owing to missing treatment cycle data. [b]Log-rank *p*-value = 0.0034. [c]The inverse prob- ability weighting method used oversampling and selected patients in the cabozantinib and axitinib cohorts with unequal weights to increase the sample size (i.e., to base estimates on more events and more censored patients), and the medians and quartiles remained approximately the same. *ESS* effective sample size, *IQR* interquartile range

were longer than for 2L therapy (6.5 months [*n* = 46] vs 5.5 months [*n* = 390] for cabozantinib; 4.7 months [*n* = 104] vs 4.6 months [*n* = 935] for axitinib). This may reflect the small numbers receiving 3L treatment or the selection of patients with less severe clinical parameters for 3L treatment. For those who received 2L cabozantinib or axitinib, the most common 1L therapies were sunitinib and pazopanib; more than half, however, had no record of ≥ 3L therapy. The most

commonly described treatment sequences were therefore used only by a minority of patients.

Median OS was shorter in both the ≥ 2L cabozantinib and axitinib cohorts than in their respective pivotal phase III trials: for cabozantinib, 11.4 months in the present study versus 21.4 months in METEOR [19]; for axitinib, 9.6 months in this analysis versus 20.1 months in AXIS [46]. It is important, however, to note the potential impact of therapies subsequent to cabozantinib or axitinib treatment on OS, and the

potential for differing distributions of subsequent therapy use in the two treatment cohorts to confound true differences in OS estimates.

It is not possible to directly interpret the differences in DoT and OS results between this real-world study and clinical trials owing to incomplete baseline data in the present study, but it is probable that the shorter real-world DoT and survival estimates reflect the heterogeneity of patients managed in routine care, who may have more severe disease and more comorbidities than the highly selected patients eligible for clinical trials.

Recent real-world studies of TKI use for RCC, for example CABOSEQ, included substantial proportions of patients who received cabozantinib following prior checkpoint inhibitor-based treatment [27–31, 34, 37, 38]. Real-world data on TKI use and outcomes are still required to inform optimal TKI sequencing, particularly for patients for whom checkpoint inhibitor-based therapy is contraindicated. CERES was a real-world study of patients receiving cabozantinib predominantly after other TKIs via the UK managed access program in 2016–17. Treatment patterns and outcomes in the ≥ 2L cabozantinib cohort in the present study align with those from CERES: 46% and 37%, respectively, received 1L pazopanib; 48% and 44%, respectively, received 1L sunitinib; median cabozantinib DoTs were 5.5 months (2L) or 6.5 months (3L) and 6.0 months (≥2L), respectively; and median OS (unweighted) was 11.4 months and 10.8 months, respectively [39]. The outcomes of cabozantinib treatment in the present study are especially encouraging given the possibility that the study population overall may have had a poorer prognosis than was apparent from the available (incomplete) baseline data.

4.1 Strengths and Limitations

This study benefits from use of the CAS database, which is an extensive and representative source of real-world oncology data containing records for approximately 95% of patients receiving SACT in England. The present study illustrates its value as a research resource that can be harnessed in future analyses to improve the understanding of current and emerging trends in RCC management approaches and their effectiveness in real-world patient care.

Some features of the CAS database may have influenced the characteristics of the study population. Eligible patients were identified using disease stage data (confirmed cases) or SACT data indicative of aRCC (proxy cases). Those who progressed from early-stage to advanced disease without receiving SACT would not have been included because only disease stage at diagnosis is recorded in the database. In addition, some patients with early-stage RCC may have received SACT and therefore been misclassified and included as having (proxy) aRCC. The CAS database

excludes patients receiving private healthcare, but any associated selection bias should be limited given the relatively small size of the missing population (approximately 5%).

An important consideration is the difference in index prescription date for the two cohorts (earlier for axitinib than cabozantinib), which likely reflects the earlier availability of axitinib in England. Temporal prescribing differences could introduce variations in standards of care for the two cohorts, which supports the use of descriptive (rather than comparative) analysis. A post hoc sensitivity analysis was conducted in the subgroup of patients who initiated treatment between 2016 and 2020 ($n = 430$ for cabozantinib and $n = 624$ for axitinib; median follow-up durations were not calculated). For this sensitivity analysis, unweighted median OS estimates were 11.4 months (95% CI 9.9–13.8) for cabozantinib and 10.8 months (95% CI 9.6–11.8) for axitinib (Fig. S1 of the Electronic Supplementary Material). This compared with unweighted median OS estimates of 11.4 months for cabozantinib and 9.6 months for axitinib in the primary analysis, and 11.2 months and 10.4 months for cabozantinib and axitinib, respectively, in the exploratory IPW-adjusted analysis for the full 2011–20 study period. In addition, OS estimates were not adjusted for therapies received after index cabozantinib or axitinib treatment. Another possible limitation is the use of projected treatment end dates in the DoT analysis.

Retrospective cohort studies are limited by predefined data variables. For example, because progression data are not recorded in the CAS database, an analysis of progression-free survival was not feasible or planned. Retrospective studies are also limited by the potential for confounding (e.g., by indication), and a lack of data validation. The present OS analysis may be confounded by missing data on prognostic risk factors (e.g., disaggregated components of the IMDC risk categorization) at index treatment initiation. The use of the IPW method to match some characteristics of the two cohorts in the exploratory OS analysis, however, helps to provide confidence in the evidence for significantly longer OS with cabozantinib than with axitinib. To address between-cohort differences, IPW modeling assigned weights to individual patients in the study population to create a weighted pseudo-population in which covariate distributions were balanced between the cabozantinib and axitinib treatment cohorts: larger weights were added to individuals who were under-represented in their cohort and lower weights to those who were over-represented (propensity scores near 0 or 1 yielded extreme weights). The IPW method was chosen because it could be combined with the Kaplan–Meier curve estimation of OS for presentation of the survival data. While an IPW analysis is an accepted method used to reduce confounding introduced by differences in the characteristics of comparator treatment cohorts, a limitation of our approach was that the selection of confounders was not based on

formal statistical criteria, but rather on the basis of clinical rationale and data availability. For example, histology type was not included as a weighting variable because it was not considered to be a confounder; this was because it was well balanced between treatment cohorts, and IMDC risk factors (except for time from aRCC diagnosis to SACT initiation) were not included as confounders because IMDC risk factor data were not explicitly available in the CAS database.

Real-world data sources may also be subject to incomplete data recording, as found in this study for prior nephrectomy status and ECOG PS scores, which can limit patient characterization and population comparisons as well as outcome evaluations. By their design, retrospective real-world cohort studies include a 'data lag,' with the analyzed data reflecting a prior period of clinical practice. In fast-moving disease areas like RCC, this can limit the interpretability of study findings. Nevertheless, the present analysis provides a representative picture of how cabozantinib and axitinib were being used across England at the time of the study, and the outcomes associated with those routine care practices. While this study was being conducted, international clinical practice guidelines endorsed the use of CPI-based combinations as 1L therapy for patients with aRCC [14]. The rapid uptake of CPI-based regimens as front-line therapy has changed the RCC treatment paradigm, and limits the broadscale relevance of our findings. Nevertheless, the present results remain relevant in several contexts, such as those in which cabozantinib is only recommended/eligible for reimbursement after prior VEGF-targeted therapy [20, 47], and for patients for whom 1L CPI-based combination therapy is unavailable because of contraindications or access issues. The insights from our study facilitate the benchmarking of local practices and outcomes, and also provide an important backdrop against which to consider the optimal uptake of emerging (e.g., combination) treatment approaches.

5 Conclusions

The present study demonstrates the potential of using the CAS database for clinically relevant real-world research, which can complement the results of randomized controlled trials involving more highly selected patient populations. During the study period, real-world OS was longer with ≥ 2L cabozantinib versus axitinib in patients with aRCC in England who had received prior VEGF-targeted therapy.

Declarations

Conflicts of Interest/Competing Interests Janet Brown has received research grants (to institution) from Amgen and AstraZeneca, and advisory board/speaker honoraria from Amgen, Bayer, Bristol Myers Squibb, Daiicho-Sankyo, Ipsen, MSD, Novartis, and Sandoz, and conference travel expenses from Ipsen. Brooke Harrow is a former employee of Ipsen. Anne Marciniak is a former employee (consultant) of Ipsen and an employee of Adelphi Values PROVE, and has shareholder/stockholder/stock options in Abbvie, Amgen, Pfizer, and Viatris. Christine McCarthy is a former employee (consultant) of Ipsen and an employee (consultant) for Inversago Pharma, and has shareholder/stockholder/stock options in Sanofi. Aude Houchard is an employee of Ipsen and has shareholder/stockholder/stock options in Ipsen. Lori Cirneanu is an employee of IQVIA. Andrew Protheroe has received advisory board honoraria from Astellas, Bristol Myers Squibb, Ipsen, Merck, and MSD, and speaker fees from Eisai.

Ethics Approval The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice and Good Epidemiology Practice. No specific patient consents or ethical approvals were required.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material Restrictions apply to the availability of these data because the data underlying this publication were provided by IQVIA (London, UK) under contract to Ipsen.

Code Availability Not applicable.

Authors' Contributions LC had full access to all the data in this study and takes responsibility for data acquisition, the integrity of the data, and the accuracy of the data analysis. BH contributed to the study concept and design. BH, AM, CM, AH, and LC performed the statistical analysis. All authors contributed to the analysis and interpretation of the data, drafting the manuscript, critical revision of the manuscript for important intellectual content, and read and approved the final version of the manuscript for publication.

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