A Prospective Non-interventional Real-World Study of cabozantinib in Pretreated Patients With Advanced Renal Cell Carcinoma Refractory to Vascular Endothelial Growth Factor-Targeted Therapy (CASSIOPE)

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Abstract

CASSIOPE was a real-world study of cabozantinib use as a second-line or later-line therapy for advanced renal cell carcinoma after prior VEGF-targeted therapy. Of 679 patients prospectively enrolled in Europe, second-line or later-line cabozantinib use was shown to be effective and manageable in a real-world setting and had a safety profile consistent with previous studies.

Background: There is a lack of published data on real-world cabozantinib use in patients with advanced renal cell carcinoma after prior vascular endothelial growth factor (VEGF)-targeted therapy. **Methods:** CASSIOPE was a real-world, prospective, multicenter, non-interventional postauthorization safety study of cabozantinib in adult patients with advanced renal cell carcinoma in Europe following prior VEGF-targeted treatment (NCT03419572). Endpoints included cabozantinib utilization (dose modifications due to adverse events [AEs; primary endpoint], dose, dose modifications, and treatment duration), safety, effectiveness (progression-free survival [PFS], overall survival [OS], best overall response [BOR]), and healthcare resource utilization. **Findings:** Full analysis set (FAS)/safety population comprised 679 patients; 433 of these initiated cabozantinib at 60 mg/day (recommended dose) (primary safety population). Median age (FAS) was 67 (range, 29-93) years; most were male (73·0%), had clear-cell histology (85·7%), metastatic disease at cabozantinib initiation (97·8%), and prior nephrectomy (80·3%). In the primary safety population, 77·1% experienced dose modification owing to an AE. In the safety population, the median daily dose was 40·0 (range, 7·8-60·0) mg/day and the median treatment duration was 7·8 (< 0·1-15·2) months. Treatment-emergent and treatment-related AEs were experienced by 95·9% and 90·4% of patients, respectively. Median PFS (FAS) assessed by the local investigator

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using any method was 8·3 months, and 1-year OS rate was 74%. Approximately one-third of all patients had a BOR of partial response and 6 had a complete response. **Interpretation:** Second- or later-line cabozantinib was effective and manageable in a real-world setting and had a safety profile consistent with previous studies.

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Introduction

Immune checkpoint inhibitors, mammalian target of rapamycin inhibitors, and vascular endothelial growth factor (VEGF)-targeted therapies, as monotherapies and combination therapies, are available for the treatment of advanced renal cell carcinoma (aRCC).[1,2] However, few patients experience complete and long-lasting response,[3-5] and ≤ 70% of patients receive subsequent therapies.[6,7]

Cabozantinib, a multitargeted tyrosine kinase inhibitor (TKI), is approved in Europe for use in treatment-naive adults with intermediate- or poor-risk aRCC or following prior VEGF-targeted therapy.[2,8] cabozantinib is also approved in combination with nivolumab as a first-line (1L) treatment.[8]

Approval of cabozantinib as subsequent monotherapy was based on the results of the phase 3 METEOR trial, which demonstrated efficacy in patients with metastatic clear cell renal cell carcinoma (RCC) who had progressed after previous VEGF receptor-targeted TKI treatment.[9,10] In METEOR, cabozantinib significantly improved median progression-free survival (PFS) and overall survival (OS) compared with the mammalian target of rapamycin inhibitor everolimus (PFS: 7·4 vs. 3·9 months, respectively; OS: 21·4 vs. 16·5 months, respectively).[10]

Although a gold standard for establishing the efficacy and safety of novel therapies and informing clinical decision-making, randomized controlled trials (RCTs) typically occur under highly regulated conditions at specialist centers, and only 43-68% of patients with aRCC are eligible for inclusion.[11-13] Real-world study data can complement RCT data helping to understand treatment performance in patient populations managed in standard clinical practice.[14] However, prospective real-world data on cabozantinib use in aRCC are limited. Here we report results from CASSIOPE, a prospective real-world study conducted in Europe that investigated cabozantinib use in patients with aRCC following prior VEGF-targeted therapy.

Methods

Study Design

CASSIOPE was a real-world, prospective, multicenter, noninterventional, voluntary, postauthorization safety study to assess cabozantinib utilization in patients with aRCC after prior VEGF-targeted treatment (conducted between April 2018 and May 2022) (Figure S1). Data were collected from the medical records of eligible patients for a maximum of 12 months from cabozantinib initiation. CASSIOPE is registered in the European Union Electronic Register of Post-Authorisation Studies (EU PAS Register; EUPAS19464) and on ClinicalTrials.gov (NCT03419572).

Eligibility Criteria

Eligible patients were aged ≥ 18 years, with a diagnosis of aRCC, and had received ≥ 1 prior VEGF-targeted therapy. The decision to start cabozantinib treatment was made prior to and independent from study enrollment. Prior cabozantinib treatment and concurrent involvement in another interventional study were not permitted. Patients provided their consent. There were no exclusion criteria (patients with brain metastases were not excluded). Consenting patients were enrolled consecutively and treated according to local routine clinical practice.

Study Endpoints

The primary endpoint was the proportion of patients with ≥ 1 dose modification (reduction, interruption, or discontinuation) due to adverse events (AEs), based on the investigator's decision, in the second-line (2L) or third-or-later-line (≥ 3L) cabozantinib settings. If treatment was interrupted and restarted at a reduced dose, it was recorded as both a dose interruption and a dose reduction; if it was restarted at the same dose, it was recorded as a dose interruption only.

Secondary endpoints were to describe: real-world cabozantinib use (including median daily dose, duration of treatment, dose modifications due to any reason, time to first dose modification); treatment-emergent adverse events (TEAEs; classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4·0); the effectiveness of cabozantinib (clinical and radiographic PFS, OS rate, and radiographic best overall response [BOR], based on Response Evaluation Criteria in Solid Tumors [RECIST] 1·1 or by other standard-of-care method) as assessed by the local investigator; and healthcare resource utilization associated with TEAE management during the treatment period (including concomitant medications, emergency room visits, hospitalizations, intensive care unit (ICU) stays, physician visits and homecare visits by nurses, and concomitant surgeries).

The severity of TEAEs was classified as mild (grade 1), moderate (grade 2), severe and undesirable (grade 3), life-threatening or disabling (grade 4), and death related to TEAE (grade 5).

Sample Size

Assuming that 75% of patients require dose modification, based on the pivotal METEOR trial,[9,10] a sample size of 289 patients per therapy line subgroup was required to estimate a 2-sided 95% confidence interval (CI) of the dose modification proportion with a precision of ± 5%. Assuming that ≤ 15% of patients would start cabozantinib using regimens different from the recommended

initiation regimen (60 mg/day),[15,16] in total ≥ 680 patients were required, 340 each in the 2L and ≥ 3L subgroups.

Analysis Populations

The full analysis set (FAS) included all patients who provided informed consent and received ≥ 1 dose of cabozantinib. Baseline characteristics and effectiveness outcomes were assessed in the FAS. Safety outcomes were assessed in the safety population (all patients from the FAS population who had a safety follow-up). The primary endpoint was assessed in the primary safety population (all patients from the safety population who started cabozantinib at the recommended dose [60 mg/day]).

Statistical Analysis

All analyses were primarily descriptive in this non-interventional study. The Clopper–Pearson method was used to calculate 2-sided 95% CIs for the primary endpoint analysis, BOR, and overall response rate (ORR). Median PFS, OS, and median time to first dose modification were analyzed using the Kaplan–Meier method.

Statistical analyses were performed using Statistical Analysis System (SAS®) version 9·4 or higher (SAS Institute Inc., Cary, NC, USA).

Results

Patient Disposition and Baseline Characteristics

Enrollment occurred between April 24, 2018 and May 19, 2022 across 91 centers in 11 European countries (Austria, Belgium, Czech Republic, France, Germany, Greece, Italy, the Netherlands, Poland, Spain, and the United Kingdom). Of 689 patients enrolled, 679 were eligible and included in the FAS and safety populations (Figure S2). In total, 335 patients received 2L cabozantinib and 343 received ≥ 3L cabozantinib. One patient receiving 1L cabozantinib (protocol deviation) was included in the overall FAS and safety populations and the subgroup of patients who initiated cabozantinib at 40 mg/day. The primary safety population comprised 433 patients (2L subgroup, $n = 237$; ≥ 3L subgroup, $n = 196$) who initiated cabozantinib at 60 mg/day (recommended dose). In total, 221 patients initiated cabozantinib at 40 mg/day (1L, $n = 1$; 2L, $n = 90$; ≥ 3L, $n = 130$). In the safety population, 296/679 patients had previously received nivolumab treatment; 285/296 (96·3%) received ≥ 3L cabozantinib.

Baseline characteristics are presented in Table 1. Briefly, median (range) age was 67 (29-93) years (aged < 65 years, 286 [42·1%]; ≥ 65 years, 393 [57·9%]), most patients were male (73·0%), had clear cell RCC (85·7%), had metastatic disease at cabozantinib initiation (97·8%), and had prior nephrectomy (80·3%). Most patients reported prior TKI therapy (96·9%), most commonly sunitinib (57·3%) or pazopanib (34·5%) monotherapies. Almost half had received prior programmed death receptor-1/programmed death ligand-1 therapy (PD1/PDL1; 44·8%), most commonly nivolumab monotherapy (39·6%) (Table S1).

Demographic and baseline characteristics were generally similar between the 2L and ≥ 3L subgroups. That proportionately fewer patients in the 2L subgroup had received prior PD1/PDL1 immunotherapy (2·7%) compared with patients in the ≥ 3L subgroup (86·0%) reflects that cabozantinib is not approved after immunotherapy alone (Table S1).

Patterns of Cabozantinib Use

Dose Modifications Due to AEs. The overall median (range) study exposure for the FAS population was 8.7 (< 1-15.4) months and was similar between the 2L and ≥ 3L subgroups (8.5 [0.2-15.4] months and 9.3 [< 1-15.0] months, respectively). Of the 433 patients in the primary safety population, 77.1% experienced a dose modification (reduction, interruption, or discontinuation) owing to an AE (primary endpoint) (Figure 1**A**). Approximately half of this population experienced a dose reduction, about half experienced a dose interruption, and approximately a quarter discontinued treatment owing to an AE. Findings were similar between the 2L and ≥ 3L subgroups.

Similar trends were observed among 221 patients in the safety population who initiated cabozantinib at 40 mg/day (Figure 1**B**). However, dose reduction and any modification rates were lower with an initial dose of 40 mg/day (43·9% and 70·6%, respectively) versus 60 mg/day (56·8% and 77·1%, respectively) cabozantinib. With 2L cabozantinib, the dose interruption rate was lower in patients initiating at 40 mg/day (38·9%) versus 60 mg/day (53·2%).

In subgroup analyses, proportionately fewer patients aged < 65 years than ≥ 65 years experienced dose modifications due to AEs (71·7% vs. 77·6%) (Table S2). Experience of dose reductions and treatment discontinuations due to AEs was also higher in patients aged ≥ 65 years (55·5% and 30·5%, respectively) than patients aged < 65 years (46·5% and 17·8%, respectively). Approximately half of each age subgroup experienced dose interruptions. The proportion of patients aged ≥ 65 years who experienced dose reductions was interestingly lower than the 91·4% of patients aged ≥ 70 years in the ZEBRA/MEET-URO 9 study (a tolerability study of cabozantinib in elderly real-world patients).[17]

In the safety population, median (95% CI) time to first dose modification, reduction, interruption, or discontinuation due to AEs was 60 (57-68) days, 135 (113-179) days, 136 (104-173) days, and 457 (457-not calculable) days, respectively (Table 2). Times to dose modification, reduction, or interruption were numerically longer with 2L than ≥ 3L cabozantinib (68·0 vs. 56·0 days, 141·0 vs. 120·0 days, and 173·0 vs. 99·0 days, respectively), suggesting better health in 2L patients. Median time to discontinuation was not reached owing to limited numbers of discontinuation events.

Of 296 patients with prior nivolumab, 78·0% experienced dose modifications due to AEs (52·7% experienced reduction; 54·1% experienced interruption; 27·4% experienced discontinuation).

Cabozantinib Exposure and Dose Modifications for Any Reason. In the safety population (ie, irrespective of starting dose), the median (range) daily dose across all patients was 40·0 (7·8-60·0) mg/day, and the median (range) duration of cabozantinib treatment was 7·8 (< 0·1-15·2) months (Table 2). Findings were similar for both subgroups; however, proportionately more patients in the 2L subgroup initiated cabozantinib at 60 mg/day (70·7%) than in the ≥ 3L subgroup (57·1%). Most patients experienced a dose modification owing to any reason (93·8%), with a mean of 2·7 (standard deviation [SD], 2·3) dose modifications per patient. The median

Table 1 Baseline Demographics and Clinical Characteristics (Full Analysis Set)

Characteristics	2L cabozantinib ($n = 335$)	≥ 3L cabozantinib ($n = 343$)	All Patients ($n = 679$)[a]
Age, years, median (range)	66 (29-93)	67 (36-89)	67 (29-93)
Age category, *n* (%)			
< 65 years	142 (42·4)	143 (41·7)	286 (42·1)
≥ 65 years	193 (57·6)	200 (58·3)	393 (57·9)
Sex, male, *n* (%)	243 (72·5)	252 (73·5)	496 (73·0)
Time since diagnosis, months, median (range)	30·1 (1·9-311·3)	44·5 (5·4-341·3)	36·6 (1·9-341·3)
Cancer predominant history at diagnosis, *n* (%)			
Clear cell RCC	281 (84·4)	298 (86·9)	580 (85·7)
Nonclear cell RCC	52 (15·6)	45 (13·1)	97 (14·3)
Papillary carcinoma Type I	10 (3·0)	8 (2·3)	18 (2·7)
Papillary carcinoma Type II	15 (4·5)	10 (2·9)	25 (3·7)
Chromophobe RCC	8 (2·4)	7 (2·0)	15 (2·2)
Collecting duct RCC	0	1 (0·3)	1 (0·1)
Renal medullary carcinoma	2 (0·6)	0	2 (0·3)
Unclassified RCC	17 (5·1)	19 (5·5)	36 (5·3)
RCC histology not reported	2	0	2
ECOG performance status, *n* (%)			
0-1	275 (89·0)	236 (78·9)	512 (84·1)
≥ 2	34 (11·0)	63 (21·1)	97 (15·9)
Missing	26	44	70
RCC stage at diagnosis, *n* (%)			
Localized (I/II)	119 (35·7)	104 (31·1)	223 (33·4)
Locally advanced (III)	66 (19·8)	69 (20·7)	135 (20·2)
Metastatic (IV)	148 (44·4)	161 (48·2)	310 (46·4)
Missing	2	9	11
RCC stage at start of cabozantinib treatment, *n* (%)			
Locally advanced (III)	10 (3·0)	5 (1·5)	15 (2·2)
Metastatic (IV)	325 (97·0)	338 (98·5)	664 (97·8)
Prior surgery, n (%)			
Nephrectomy	257 (76·7)	287 (83·7)	545 (80·3)
Other	89 (26·6)	123 (35·9)	212 (31·2)
Metastasis site, *n* (%)			
Any site	325 (97·0)	338 (98·5)	664 (97·8)
Brain	30 (9·0)	37 (10·8)	67 (9·9)
Bones	138 (41·2)	138 (40·2)	276 (40·6)
Liver	74 (22·1)	103 (30·0)	177 (26·1)
Lungs	193 (57·6)	214 (62·4)	408 (60·1)
Lymph nodes	137 (40·9)	168 (49·0)	306 (45·1)
Other visceral metastasis	57 (17·0)	86 (25·1)	143 (21·1)
Other	98 (29·3)	116 (33·8)	214 (31·5)
Number of sites with metastasis, *n* (%)			
0	10 (3·0)	5 (1·5)	15 (2·2)
1	94 (28·1)	69 (20·1)	163 (24·0)
2	105 (31·3)	106 (30·9)	212 (31·2)
≥ 3	126 (37·6)	163 (47·5)	289 (42·6)
IMDC/Heng score for metastasis RCC prognosis, *n* (%)			
Favorable	35 (17·9)	34 (19·0)	69 (18·4)
Intermediate	133 (67·9)	106 (59·2)	239 (63·6)

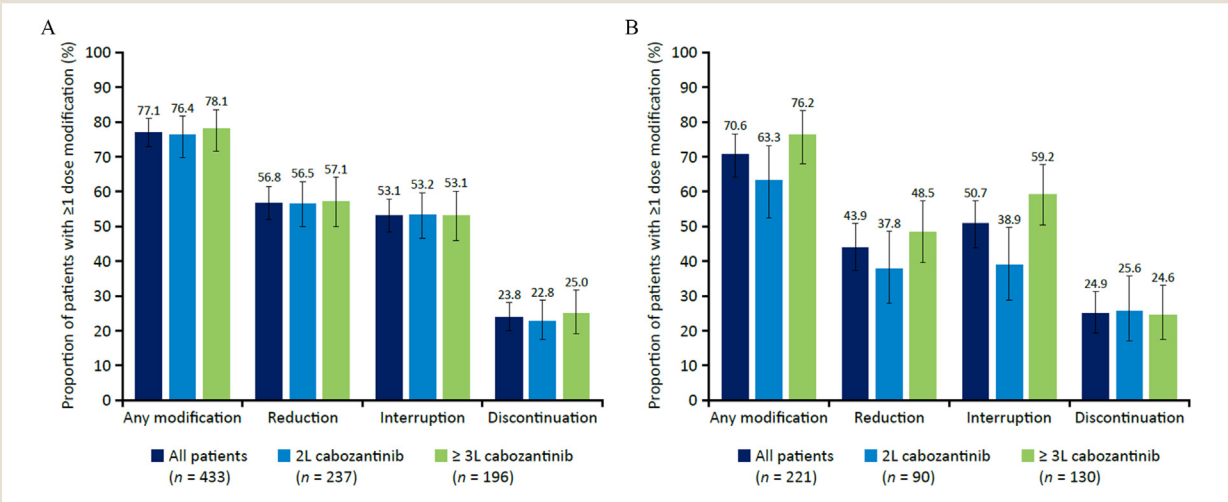
(*continued on next page*)

Table 1 (*continued*)

Characteristics	2L cabozantinib ($n = 335$)	≥ 3L cabozantinib ($n = 343$)	All Patients ($n = 679$)[a]
Poor	28 (14·3)	39 (21·8)	68 (18·1)
Missing	139	164	303
Number of prior systemic therapies, *n* (%)			
1	335 (100·0)	0	335 (49·3)
2	0	258 (75·2)	258 (38·0)
3	0	58 (16·9)	58 (8·5)
4	0	16 (4·7)	16 (2·4)
> 4	0	11 (3·2)	11 (1·6)
Class of prior systemic therapy			
TKI	319 (95·2)	339 (98·8)	658 (96·9)
PD1/PDL1	9 (2·7)	295 (86·0)	304 (44·8)
mTOR inhibitors	0	36 (10·5)	36 (5·3)
Cytokines	0	3 (0·9)	3 (0·4)
Other	7 (2·1)	30 (8·7)	37 (5·4)

Percentages are based on the number of patients in the FAS population with nonmissing value.
Abbreviations: ≥ 3L = third- or later-line; 2L = second-line; ECOG = Eastern Cooperative Oncology Group; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; mTOR = mammalian target of rapamycin; PD1/PDL1 = programmed death receptor-1/programmed death ligand-1; RCC = renal cell carcinoma; SD = standard deviation; TKI = tyrosine kinase inhibitor.
[a] Includes 1 patient who received cabozantinib as first-line therapy.

Figure 1 Cabozantinib dose modifications due to adverse events in patients initiating cabozantinib at (A) 60 mg/day (primary safety population) and (B) 40 mg/day. Error bars represent 95% confidence interval. Any dose modification was defined as a dose reduction, interruption, or discontinuation.



Abbreviations: ≥ 3L = third- or later-line; 2L = second-line.

(range) duration of dose interruptions due to any reason was 21·0 (1·0-225·0) days (2L cabozantinib, 21·0 [2·0-123·0] days; ≥ 3L cabozantinib, 19·5 [1·0-225·0] days). Of the 221 patients who initiated cabozantinib at 40 mg/day, 36 had ≥ 1 dose increase documented during the study period. For 23 of these 36 patients, 60 mg/day was the documented increased dose. In patients with prior nivolumab, the median (range) daily dose was 39·9 (13·8-60·0) mg/day.

AEs were the main reason for all dose reductions and interruptions in the safety population (reductions: 351/384 patients, 91·4%; interruptions 349/396 patients, 88·1%) and in patients with prior nivolumab (reductions: 156/168 patients, 92·9%; inter-

Table 2 Cabozantinib Treatment and Time to Dose Modification (Safety Population, Unless Otherwise Stated)

Pattern of Treatment	2L cabozantinib ($n = 335$)	≥ 3L cabozantinib ($n = 343$)	All Patients ($n = 679$)[a]
Cabozantinib dosing and modification			
Starting dose, *n* (%)			
60 mg/day	237 (70·7)	196 (57·1)	433 (63·8)
40 mg/day	90 (26·9)	130 (37·9)	221 (32·5)
20 mg/day	7 (2·1)	11 (3·2)	18 (2·7)
Other	1 (0·3)	6 (1·7)	7 (1·0)
Median (range) daily dose, mg/day	40·7 (17·0-60·0)	39·2 (7·8-60·0)	40·0 (7·8-60·0)
Median (range) daily dose in the primary safety population, mg/day	47·8 (17·7-60·0)	44·2 (7·8-60·0)	46·2 (7·8-60·0)
Median (range) duration of treatment, months	7·3 (< 0·1-15·2)	8·2 (< 0·1-15·0)	7·8 (< 0·1-15·2)
Patients with dose modifications due to any reason			
n (%)	317 (94·6)	320 (93·3)	637 (93·8)
95% CI	91·6-96·8	90·1-95·7	91·7-95·5
Number of dose modifications due to any reason			
Mean (SD)	2·5 (1·9)	3·0 (2·6)	2·7 (2·3)
Missing, *n*	18	23	42
Dose modification due to AE related to cabozantinib			
n (%)	221 (66·0)	237 (69·1)	458 (67·5)
95% CI	60·6-71·0	63·9-73·9	63·8-71·0
Time to event due to adverse event			
First dose modification			
Median (95% CI), days	68·0 (58·0-84·0)	56·0 (49·0-61·0)	60·0 (57·0-68·0)
Patients with events, *n*	245	263	508
First dose reduction			
Median (95% CI), days	141·0 (108·0-217·0)	120·0 (99·0-170·0)	135·0 (113·0-179·0)
Patients with events, *n*	171	177	348
First dose interruption			
Median (95% CI), days	173·0 (131·0-260·0)	99·0 (81·0-136·0)	136·0 (104·0-173·0)
Patients with events, *n*	163	184	347
First dose discontinuation			
Median (95% CI), days	NC (NC-NC)	457·0 (NC-NC)	457·0 (457·0-NC)
Patients with events, *n*	81	90	171
Time to event due to any reason			
First dose modification[b]			
Median (95% CI), days	57·0 (52·0-62·0)	44·0 (39·0-50·0)	51·0 (45·0-56·0)
Patients with events, *n*	316	317	633
First dose reduction[c]			
Median (95% CI), days	112·0 (97·0-145·0)	106·0 (91·0-126·0)	110·0 (99·0-124·0)
Patients with events, *n*	188	193	381
First dose interruption[d]			
Median (95% CI), days	118·0 (98·0-162·0)	78·0 (63·0-91·0)	93·0 (83·0-112·0)
Patients with events, *n*	185	206	391
First dose discontinuation			
Median (95% CI), days	231·0 (193·0-267·0)	255·0 (224·0-309·0)	245·0 (221·0-278·0)
Patients with events, *n*	219	218	437

Patients were considered not evaluable when the date of event was unknown. Dose modification was defined as a dose reduction, interruption, or discontinuation. Clopper–Pearson method was used to calculate 95% CIs.

Abbreviations: ≥ 3L = third- or later-line; 2L = second-line; CI = confidence interval; NC = not calculable; SD = standard deviation.

[a] Includes 1 patient who received cabozantinib as first-line therapy.

[b] 4 patients were not evaluable.

[c] 3 patients were not evaluable.

[d] 5 patients were not evaluable.

Table 3 Summary of Treatment-Emergent Adverse Events (Safety Population)

Patients with Adverse Event, *n* (%)	2L cabozantinib (*n* = 335)	≥ 3L cabozantinib (*n* = 343)	All Patients (*n* = 679)[a]
AEs	320 (95·5)	331 (96·5)	652 (96·0)
Any TEAEs	320 (95·5)	330 (96·2)	651 (95·9)
TEAEs related to treatment	301 (89·9)	313 (91·3)	614 (90·4)
Serious TEAEs	150 (44·8)	163 (47·5)	313 (46·1)
AEs leading to treatment discontinuation	81 (24·2)	90 (26·2)	171 (25·2)
AEs leading to dose modification	245 (73·1)	265 (77·3)	510 (75·1)
AEs leading to dose interruption	163 (48·7)	186 (54·2)	349 (51·4)
AEs leading to dose reductions	171 (51·0)	180 (52·5)	351 (51·7)
Serious TEAEs leading to death	60 (17·9)	69 (20·1)	129 (19·0)
TEAEs by intensity			
Grade 1	254 (75·8)	273 (79·6)	528 (77·8)
Grade 2	252 (75·2)	281 (81·9)	534 (78·6)
Grade 3	160 (47·8)	162 (47·2)	322 (47·4)
Grade 4	26 (7·8)	20 (5·8)	46 (6·8)
Grade 5	60 (17·9)	69 (20·1)	129 (19·0)
TEAEs related to treatment by intensity			
Grade 1	230 (68·7)	253 (73·8)	483 (71·1)
Grade 2	226 (67·5)	251 (73·2)	477 (70·3)
Grade 3	118 (35·2)	119 (34·7)	237 (34·9)
Grade 4	10 (3·0)	8 (2·3)	18 (2·7)
Grade 5	4 (1·2)	9 (2·6)	13 (1·9)
Common TEAEs (reported in ≥ 20% of patients)			
Diarrhea	194 (57·9)	179 (52·2)	374 (55·1)
Decreased appetite	86 (25·7)	113 (32·9)	199 (29·3)
PPE	86 (25·7)	103 (30·0)	189 (27·8)
Asthenia	74 (22·1)	100 (29·2)	174 (25·6)
Hypertension	69 (20·6)	93 (27·1)	162 (23·9)
Fatigue	69 (20·6)	87 (25·4)	157 (23·1)
Nausea	68 (20·3)	87 (25·4)	156 (23·0)
Weight decrease	64 (19·1)	72 (21·0)	137 (20·2)
Common grade 3 TEAEs (reported in ≥ 2% of patients)			
Diarrhea	20 (6·0)	21 (6·1)	41 (6·0)
Hypertension	23 (6·9)	17 (5·0)	40 (5·9)
PPE	18 (5·4)	12 (3·5)	30 (4·4)
Asthenia	12 (3·6)	14 (4·1)	26 (3·8)
Fatigue	6 (1·8)	10 (2·9)	16 (2·4)
General physical health deterioration	4 (1·2)	8 (2·3)	12 (1·8)
Mucosal inflammation	3 (0·9)	9 (2·6)	12 (1·8)
Weight decrease	7 (2·1)	4 (1·2)	11 (1·6)
Pleural effusion	7 (2·1)	2 (0·6)	9 (1·3)

Abbreviations: ≥ 3L = third- or later-line; 2L = second-line; AE = adverse event; *n* = number of patients; PPE = palmar-plantar erythrodysesthesia; TEAE = treatment-emergent adverse event.
[a] Includes 1 patient who received cabozantinib as first-line therapy.

ruptions: 160/179 patients, 89·4%). Discontinuations were primarily due to disease progression (safety population: 197/437 patients, 45·1%; prior nivolumab subgroup: 79/193 patients, 40·9%), or AEs (171/437 patients, 39·1%; 81/193 patients, 42·0%, respectively).

Safety

Of the 679 patients included in the safety population, 95·9% experienced ≥ 1 TEAE and 90·4% experienced ≥ 1 treatment-related TEAE (Table 3). TEAEs and treatment-related TEAEs were mostly mild (77·8% and 71·1% of patients, respectively) or moderate (78·6% and 70·3%, respectively) in intensity. Serious TEAEs and grade 3 TEAEs were each reported in approximately half of patients. The frequency of grade 4 TEAEs was 6·8% of patients. Serious TEAEs leading to death occurred in 129 patients (19·0%), and treatment-related serious TEAEs occurred in 124 (18·3%). The most common TEAEs were diarrhea (55% of patients),

decreased appetite (29%), and palmar-plantar erythrodysesthesia (PPE) syndrome (28%) (Table 3). The most common grade 3 TEAEs were diarrhea (6·0% of patients) and hypertension (5·9%). Safety data were similar for the 2L and ≥ 3L cabozantinib subgroups (Table 3). The most common treatment-related TEAEs were diarrhea (52% of patients), PPE syndrome (27%), and decreased appetite (26%). The top 4 most common serious TEAEs were general physical health deterioration (5.4%), disease progression (5.2%), pneumonia (2.2%), and pulmonary embolism (2.2%). The 3 most common TEAEs leading to dose interruption were diarrhea (16.8%), PPE syndrome (10.0%), and asthenia (6.5%). The 3 most common TEAEs leading to dose reduction were diarrhea (19.3%), PPE syndrome (10.3%), and asthenia (7.1%). The 3 most common TEAEs leading to treatment discontinuation were diarrhea (2.7%), decreased appetite (2.4%), and asthenia (2.1%).

Of patients in the primary safety population ($n = 433$; initiating cabozantinib at 60 mg/day), 96·3% experienced a TEAE, 91·0% experienced a treatment-related TEAE, and 47·3% experienced a serious TEAE (rates were similar in patients initiating cabozantinib at 40 mg/day [94·6%, 90·0%, and 43·4%, respectively] and those with prior nivolumab [96·3%, 91·2%, and 47·6%, respectively]).

Effectiveness of Cabozantinib

In the FAS, median (95% CI) PFS assessed by the local investigator using any method (RECIST v1·1 or another standard-of-care method) was 8·3 (7·4-8·8) months (Figure 2**A**). Median (95% CI) PFS assessed by RECIST v1·1 ($n = 313$), was 8·7 (7·9-9·7) months (2L therapy, 8·1 [6·3-9·4] months; ≥ 3L therapy, 9·2 [8·0-10·9] months). If PFS was not assessed using RECIST v1·1, other standard-of-care methods were used (according to local routine practice). Median (95% CI) PFS assessed using these other standard-of-care methods ($n = 366$) was 7·8 (6·5-8·8) months (2L therapy, 7·0 [5·4-8·8] months; ≥ 3L therapy, 8·1 [6·5-9·6] months). Median (95% CI) PFS (by any method) was 7·6 (6·3-8·7) months and 8·6 (7·6-9·4) months in patients who initiated cabozantinib at 40 mg/day and 60 mg/day, respectively (Table S3). In the 296 patients with prior nivolumab, the median (95% CI) PFS (by any method) was 8·6 (7·6-9·5) months.

At study completion, there were only 144 deaths, and therefore mOS calculations were not robust. The Kaplan–Meier estimate for 1-year OS rate was 74% (95% CI: 70-78%) overall and was similar between the 2L (76% [70-81%]) and ≥ 3L (72% [66-78%]) subgroups (Figure 2**B**). Median 1-year OS rate was also similar between patients initiating cabozantinib at 60 mg/day (75% [95% CI: 69-79%]) compared with 40 mg/day (74% [66-81%]) (Table S3). Interestingly, patients aged < 65 years had a numerically higher 1-year OS rate (82% [95% CI: 76-87%]) than those aged ≥ 65 years (69% [63-74%]). The 1-year OS rate for patients with prior nivolumab was 71% (95% CI: 64-77%).

BOR among the 555 patients with a radiological assessment in the FAS is presented in Figure 2**C**. Approximately one-third of all patients had partial response (PR) as their BOR. The proportion of patients with a PR in the ≥ 3L subgroup (43·6%) was almost double that in the 2L subgroup (24·1%). Six patients had a complete response (2L cabozantinib, $n = 4$; ≥ 3L cabozantinib, $n = 2$). ORR (95% CI) assessed by the local investigator using any method was 34·9% (30·9-39·0) in all patients and was higher with ≥ 3L (44·1% [38·2-50·1]) than with 2L cabozantinib (25·5% [20·5-31·1]) (Figure 2**C**). Findings were similar between patients assessed using RECIST v1·1 and those assessed using another standard-of-care method. ORR (by any method) was similar between patients initiating cabozantinib at 40 mg/day (38·0%) and 60 mg/day (33·7%) (Table S3). The ORR (95% CI) was numerically higher in patients with clear cell RCC (36·9% [32·6-41·4]) than those with nonclear cell RCC (23·5% [14·8-34·2]). Of the 237 patients with evaluable data who received prior nivolumab, the ORR was 47·9% (41·4-54·4).

Healthcare Resource Utilization

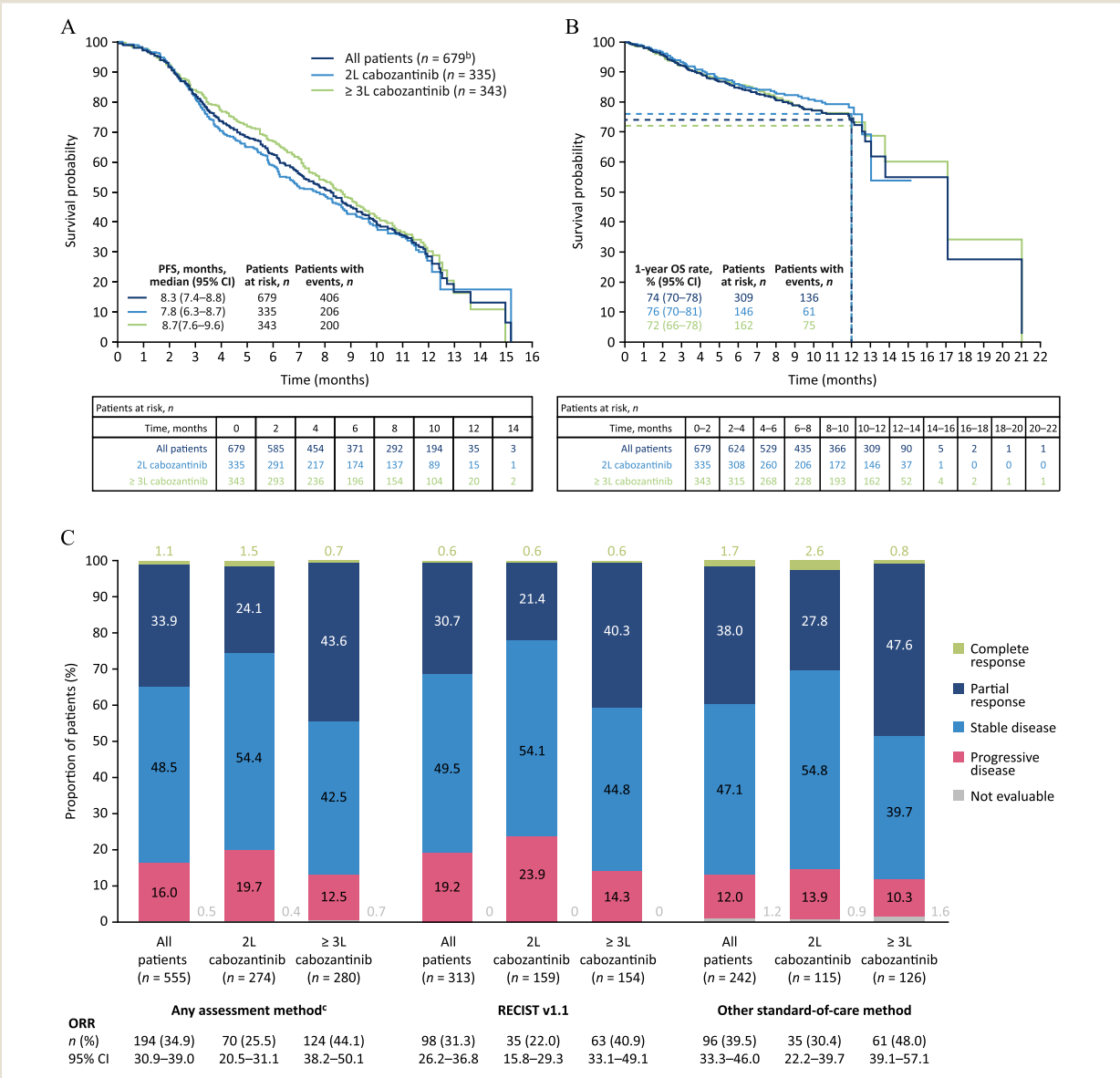
Approximately 40% of patients in the safety population experienced ≥ 1 hospitalization owing to treatment-related AEs (TRAEs) (Table S4). TRAEs led to ≥ 1 homecare visit by a nurse, ≥ 1 ICU visit, or ≥ 1 emergency room visit in approximately 3%, 4%, and 17% of patients, respectively. Less than 10% of patients overall had a surgical procedure owing to TRAEs. Approximately one-quarter of patients had ≥ 1 unplanned physician visit due to TRAEs, and rates were numerically higher with ≥ 3L than 2L cabozantinib. Concomitant medication was used to manage AEs in the majority of patients.

Discussion

This prospective, non-interventional study provides valuable information on the use of cabozantinib in patients with aRCC after prior VEGF-targeted therapy who receive treatment in real-world clinical practice in Europe. Patients included in CASSIOPE were considered representative of the real-world population of patients with aRCC; patient characteristics were similar to those in several other real-world studies.[18-22] However, differences of note included the proportion of patients with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0-1, which was slightly higher in CASSIOPE than in other real-world studies (84·1% vs. 60·7-80·9%, respectively), and the proportion of patients with lung metastasis, which was slightly lower (60·1% vs. 65·0-76·3%, respectively). Patient characteristics in CASSIOPE were also similar to those in the phase 3 clinical METEOR trial.[10] However, a higher proportion of patients had bone and brain metastasis in CASSIOPE than METEOR (40·6% vs. 23·3%; and 9·9% vs. 0·6%, respectively), a higher proportion were previously treated with nivolumab (43·6% vs. 5%), and a lower proportion had lymph node metastasis (45·1% vs. 62·4%). In addition, all patients in METEOR were required to have an ECOG performance status of 0 or 1 and a clear cell histology, but only 84·1% and 85·7% of patients in CASSIOPE met these parameters, respectively. Lastly, while the proportion of patients with poor risk in CASSIOPE was similar to that in METEOR, proportionately fewer patients had favorable and more had intermediate risk in CASSIOPE.

Among patients who started cabozantinib at the recommended initial dose of 60 mg/day, approximately half had their cabozantinib dose interrupted and half had their dose reduced to manage AEs. Only about a quarter of patients discontinued cabozantinib owing to AEs. This suggests that dose reductions and interruptions were a well-used and successful approach for optimizing treatment duration, and thus potential treatment response. Similar trends were

Figure 2 Effectiveness of cabozantinib (full analysis set). Kaplan–Meier plots for (A) progression-free survival,[a] according to local investigator using any assessment method and (B) overall survival. (C) Best overall response and overall response rate.



Abbreviations: ≥ 3L = third- or later-line; 2L = second-line; CI = confidence interval; ORR = overall response rate; PFS = progression-free survival; RECIST v1·1 = Response Evaluation Criteria in Solid Tumors version 1·1. [a]Clinical and radiographic. [b]Includes 1 patient who received cabozantinib as first-line therapy. [c]Excludes patients with no radiological assessment.

observed for patients who initiated cabozantinib at the lower dose of 40 mg/day. The proportion of patients receiving ≥ 2L cabozantinib who required a dose reduction due to AEs in CASSIOPE (246/433 patients [56·8%]) was similar to those reported in the phase 3 METEOR (206/331 patients [62·2%])[10] and phase 2 BREAKPOINT (14/28 patients [50·0%]) trials.[23] However, the rate of treatment discontinuation due to AEs was higher in CASSIOPE (103/433 patients [23·8%]) than in METEOR (40/331 patients [12·1%])[10] and BREAKPOINT (1/30 patients [3·3%]).[23] This may reflect the inclusion of patients in CASSIOPE with more severe disease, based on bone and brain metastasis, or other differences between the real-world patient population of CASSIOPE and the clinical population included in METEOR, or differences in patient management between typical clinical practice and the highly controlled clinical trial environment. Dose modifications due to AEs in CASSIOPE were within the range found in previous real-world

trials.[18,19,22] The proportion of patients requiring a dose reduction owing to AEs was 41·7-77·3% in real-world studies[19,22,24] compared with 56·8% in CASSIOPE, and the rate of treatment discontinuation due to AEs was 5·2-24·9% in real-world studies [18,22,24] compared with 23·8% in CASSIOPE. In general, rates of dose modifications were similar for the overall safety population and those patients who had prior nivolumab.

Overall, the safety profile of cabozantinib observed in CASSIOPE was consistent with the general known safety profile of cabozantinib; no new safety signal was identified. In CASSIOPE, almost all patients reported ≥ 1 TEAE and 90·4% reported ≥ 1 treatment-related TEAE. These findings are in line with the METEOR trial, in which 100% of patients reported TEAEs,[10] and the BREAKPOINT trial, in which 93·3% of patients reported any AE.[23] In general, there was a similar safety profile for the overall safety population and for those patients who had prior nivolumab. In addition, alternative schedules of cabozantinib dosing have been shown to be associated with lower frequency and severity of TRAEs and a longer PFS.[25]

The CASSIOPE data demonstrated that cabozantinib was clinically effective in real-world clinical practice in both the 2L and ≥ 3L settings. ORR in CASSIOPE, assessed by RECIST v1·1 (31·3%) or any method (34·9%), was similar to that reported in BREAKPOINT (37·9%),[23] and approximately double that reported in METEOR (17·3%).[10] ORRs for patients with clear cell and nonclear cell RCC were proportionately lower in CASSIOPE than those reported for the phase 2 BONSAI trial (1L cabozantinib treatment)[26] and the phase 1b COSMIC-021 trial (cabozantinib in combination with atezolizumab);[27] clear cell: 36·2% in CASSIOPE compared with 53-58% in COSMIC-021; nonclear cell: 23·5% in CASSIOPE compared with 34·8% in BONSAI and 31·3% in COSMIC-021. ORR was particularly high in the ≥ 3L cabozantinib subgroup (40·9% by RECIST v1·1 vs. 22·0% in the 2L subgroup), and was similar to that in the phase 3 CONTACT-03 trial (cabozantinib subgroup, 41%).[28] This may be explained by the high proportion of patients having received ≥ 3L cabozantinib after prior nivolumab monotherapy (77·3% in CASSIOPE and 93% in CONTACT-03),[28] because results from the CABIR study suggest that 3L cabozantinib, when administered after nivolumab, may be more effective than 3L nivolumab administered after cabozantinib.[29] Another possible explanation is that patients reaching ≥ 3L cabozantinib represent a selected population that responds to therapy.

Median PFS was also longer in CASSIOPE (8·7 months) than METEOR (7·4 months), albeit the difference was less dramatic than for ORR,[10] and similar to BREAKPOINT (8·3 months).[23] Longer PFS in the real-world setting may be explained by less frequent or irregular radiological assessments compared with those formally conducted at set intervals in the clinical trial setting. These indirect comparisons should be considered with caution, particularly in light of differences between studies in population characteristics (including differences in previous treatments) and methods of assessing responses. That the PFS was longer in the ≥ 3L subgroup (8·7 months) of CASSIOPE than the 2L subgroup (7·8 months) may again be due to the higher proportion of patients having received prior nivolumab. Indeed, PFS with 3L cabozantinib was even higher in CONTACT-03 (10·8 months) in which proportionately more patients (93%) had prior 2L nivolumab than those in CASSIOPE.[28] The 1-year OS rate in CASSIOPE (74%) was higher than CABOREAL (57%)[18] but similar to CONTACT-03 (76%).[28]

In CASSIOPE, PFS and 1-year OS rate were similar, and ORR was lower, for the overall FAS population compared with the subgroup of patients who had prior nivolumab.

To our knowledge, CASSIOPE was the largest prospective real-world study of cabozantinib use to date, which included nearly 700 patients from across 11 European countries. The design permitted the investigation of cabozantinib use and outcomes for patients with aRCC who were receiving treatment in routine clinical practice and, because there were no exclusion criteria, the study population was representative of all patients with aRCC in Europe,[18-22] including patients with more advanced/severe disease who are excluded from interventional studies. In addition, similar outcomes in this study for patients who initiated cabozantinib treatment at the recommended dose of 60 mg/day and those who initiated at 40 mg/day support the generalizability of these data to real-world cabozantinib use.

Limitations of this study include the quality, and availability of data provided by different study sites varied depending on local clinical practice, reflecting the nature of real-world studies. For example, there was a high rate of missing International Metastatic Renal Cell Carcinoma Database Consortium/Heng score data at baseline, and only approximately half of patients were assessed using RECIST v1·1. The proportion of patients with an ECOG performance status > 2 reflects the condition of the patient at the start of cabozantinib in real-life conditions; however, this proportion is low and therefore these patients are underrepresented in this study. A higher number of patients than anticipated had started on cabozantinib at 40 mg/day and approximately 60% of these patients were in the ≥ 3L cabozantinib subgroup, resulting in an imbalance between therapy line groups. The proportion of evaluable patients in the ≥ 3L subgroup was lower than anticipated and therefore the precision rate for the primary endpoint was wider than planned. Patient inclusion was at the investigators' discretion and may have led to selection bias. To minimize this, the decision to start cabozantinib was made prior to and independent from enrollment and physicians were asked to include all successive eligible patients. Because cabozantinib is now recommended in combination with nivolumab in the 1L setting, real-world use of cabozantinib will continue to change, and the findings from this CASSIOPE study will only relate to a portion of the patient population. The ongoing, prospective, noninterventional CaboCombo trial is evaluating this 1L combination therapy in the real-world setting.[30] The ongoing, prospective, noninterventional, phase 2 CaboPoint study is evaluating the efficacy and safety of 2L cabozantinib following 1L checkpoint inhibitor therapy.

In conclusion, in this real-world CASSIOPE study, 2L or later-line cabozantinib was effective and the safety profile was consistent with that observed in the phase 3 METEOR trial. AEs were adequately managed using established safety guidelines, for example by using dose modifications. Treatment discontinuation rates due to AEs were higher in this study than in the METEOR trial. Further, the similarity in outcomes between patients who initiated

cabozantinib at the recommended dose of 60 mg/day and those who initiated it at 40 mg/day demonstrates the generalizability of these data to real-world cabozantinib use. Unlike the METEOR trial, CASSIOPE had no exclusion criteria and included patients with severe comorbidities such as end-stage renal failure on dialysis, ECOG performance status ≥ 2, brain metastasis, and nonclear cell RCC, and therefore provides data on the activity and tolerability of cabozantinib in the whole population of patients with aRCC. Overall, monitoring for TEAEs and managing them through dose modification can help to optimize cabozantinib use for the treatment of patients with aRCC.

Clinical Practice Points

- Cabozantinib, a multitargeted tyrosine kinase inhibitor, is approved in Europe for use in treatment-naive adults with intermediate- or poor-risk advanced renal cell carcinoma (aRCC) or following prior vascular endothelial growth factor (VEGF)-targeted therapy. Cabozantinib is also approved as first-line treatment in combination with nivolumab. Although cabozantinib approval was based on clinical data from pivotal randomized controlled trials (RCTs), the literature shows that only 43-68% of patients with aRCC are eligible for inclusion in RCTs; therefore, it is important to complement these clinical data with real-world evidence.
- CASSIOPE (NCT03419572) is a real-world, prospective, noninterventional, postauthorization safety study conducted across multiple European centers providing insight into cabozantinib use after previous VEGF-targeted therapy in patients with aRCC.
- Among 679 patients included in CASSIOPE, a large proportion (77.1%) of real-world patients experienced dose modifications due to adverse events. Treatment-emergent adverse events (TEAEs) and those related to cabozantinib treatment were experienced by 95.9% and 90.4% of patients, respectively. However, only a quarter of patients discontinued cabozantinib treatment, suggesting that dose reduction or interruption in treatment are good strategies to help manage side effects. These dose modifications were also successful in optimizing treatment duration, and thus treatment response.
- Our findings complement those reported in RCTs, supporting cabozantinib as an effective treatment in real-world second- or later-line treatment settings, with a manageable safety profile. Monitoring for TEAEs and managing them using dose modification can help to optimize treatment for patients with aRCC. These real-world insights are valuable for clinicians and patients to improve treatment of aRCC.

Contributors

All authors provided substantial contributions to study conception/design or acquisition/analysis/interpretation of data; drafting of the publication or reviewing it critically for important intellectual content. All authors have provided final approval of the publication and have given their approval of this version for publication. They have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki (Helsinki, 1964 and all subsequent amendments). This study also followed the International Society for Pharmacoepidemiology (ISPE) Guidelines for GPP, EMA guidelines for GVP, and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, when applicable. Patients' informed consent was obtained before the start of data collection.

Data Sharing Statement

Qualified researchers may request access to patient-level study data that underlie the results reported in this publication. Additional relevant study documents, including the clinical study report, study protocol with any amendments, annotated case report form, statistical analysis plan, and data set specifications may also be made available. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of study participants.

When applicable, data from eligible studies are available 6 months after the studied medicine and indication have been approved in the US and EU or after the primary manuscript describing the results has been accepted for publication, whichever is later.

Further details on Ipsen's sharing criteria, eligible studies, and process for sharing are available here (https://vivli.org/members/ourmembers/). Any requests should be submitted to www.vivli.org for assessment by an independent scientific review board.

Disclosure

MS: Consulting or advisory role—Apogepha, Bristol-Myers Squibb, Eisai, EMD Serono, EUSA Pharma, Exelixis, Ipsen, Merck Sharp & Dohme, Novartis, Oncorena, Pfizer; Speakers' bureau—Bristol-Myers Squibb, Eisai, EUSA Pharma, Ipsen, Novartis, Pfizer; Travel, accommodations, expenses—Bristol-Myers Squibb, Eisai, EMD Serono, EUSA Pharma, Ipsen, MSD Oncology, Novartis, Pfizer; Honoraria—Astellas Pharma, Bayer, Bristol-Myers Squibb, Incyte, EMD Serono, EUSA Pharma, Exelixis, Ipsen, MDS Oncology, Novartis, Pfizer, Roche; Research funding—Bayer, Bristol-Myers Squibb, Eisai, Exelixis, Novartis, Pfizer, Roche/Genentech.

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PG: Consulting or advisory role—Astellas, Bristol-Myers Squibb, Ipsen, Merck, MSD, Pfizer, Roche; Speakers' bureau—Astellas, Bristol-Myers Squibb, Ipsen, Merck, MSD, Pfizer, Roche; Travel, accommodations, expenses—Ipsen, Merck, Pfizer.

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PR: Employment—Ipsen.

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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.2024.102285.

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