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ADIS DRUG EVALUATION

Cabozantinib: A Review in Advanced Renal Cell Carcinoma

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Abstract The multiple tyrosine kinase inhibitor (TKI) cabozantinib (Cabometyx™) is approved in the USA for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior antiangiogenic therapy. In the EU, cabozantinib is indicated for the treatment of advanced RCC in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy. In adults with advanced or metastatic clear-cell RCC who had previously received VEGF receptor (VEGFR) TKIs, progression-free survival (PFS) and overall survival (OS) were significantly prolonged in patients who received oral cabozantinib versus oral everolimus in the pivotal METEOR trial. Objective response was achieved in a significantly higher proportion of patients receiving cabozantinib than those receiving everolimus. Cabozantinib had a manageable adverse events profile in patients with advanced RCC. Thus, cabozantinib is an important new option for use in patients with advanced RCC who have previously received antiangiogenic therapy.

Cabozantinib: clinical considerations in advanced renal cell carcinoma
Inhibits multiple tyrosine kinases, including VEGFR, MET and AXL
Significantly prolonged PFS and OS versus everolimus
Significantly higher objective response rate versus everolimus
Manageable adverse events profile

1 Introduction

Renal cell carcinoma (RCC) is the most common form of kidney cancer [1]. In adults, clear-cell RCC is the most common histological subtype responsible for 70–85% of RCC cases, followed by papillary and chromophobe subtypes [2]. In clear-cell RCC tumours, the von Hippel-Lindau tumour-suppressor proteins are inactivated, consequently triggering the upregulation of genes encoding vascular endothelial growth factor (VEGF), MET and AXL [3]. The tyrosine kinase VEGF receptor (VEGFR) drives angiogenesis in clear-cell RCC, and expression of other receptor tyrosine kinases such as MET and AXL can be associated with an invasive tumour phenotype and poor prognosis [3].

Among the various agents recommended for use in the first-line treatment of advanced clear-cell RCC are agents targeting the VEGF pathway, including the VEGFR tyrosine kinase inhibitors (TKIs) (e.g. axitinib, sorafenib, pazopanib, sunitinib) [4]. Most patients eventually develop acquired resistance to VEGFR TKIs, which is associated

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with upregulation of alternative angiogenesis pathways, such as MET [5]. Thus, administering a multikinase inhibitor that targets both the VEGF and MET pathways represents a rational approach to subsequent therapy in advanced clear-cell RCC [6].

Cabozantinib (Cabometyx™) tablets are approved in the USA for the treatment of patients with advanced RCC who have received prior antiangiogenic therapy [7], and in the EU for the treatment of advanced RCC in adults following prior VEGF-targeted therapy [8]. This narrative review discusses the clinical efficacy and tolerability of cabozantinib in patients with advanced RCC who have received prior antiangiogenic therapy. The pharmacological properties of the agent are also discussed. The use of cabozantinib capsules (Cometriq®) in patients with metastatic medullary thyroid cancer is beyond the scope of the current review, and has been reviewed elsewhere [9].

2 Pharmacodynamic Properties of Cabozantinib

Cabozantinib inhibits multiple tyrosine kinases implicated in oncogenesis, tumour angiogenesis, tumour cell survival, tumour invasion and/or metastasis, including VEGFR-1, -2 and -3, MET, AXL, RET, KIT, FLT3, ROS1, MER, TYRO3, TRKB and TIE-2 [6, 7, 10]. It demonstrates potent activity against MET, which is implicated in tumour survival, growth and metastasis, as well as cellular invasion and angiogenesis [6]. Cabozantinib potently inhibits VEGFR (specifically VEGFR2), which plays a key role in tumour development. AXL, RET, KIT and FLT3, which are implicated in tumour pathobiology, are also inhibited by cabozantinib [6].

In vitro, cabozantinib inhibited tumour cell line migration, invasion and proliferation [6], including in clear-cell RCC lines [10]. Cabozantinib also reduced migration and invasion in a clear-cell RCC line pretreated with sunitinib [11]. In xenograft murine models, cabozantinib inhibited VEGFR-2 and MET phosphorylation, disrupted tumour vasculature, induced tumour cell apoptosis and did not promote metastasis [6]. In addition, cabozantinib inhibited tumour growth in a dose-dependent manner in xenograft murine models [6].

Cabozantinib overcame sunitinib resistance in a murine RCC model of acquired sunitinib resistance [11]. Tumour size was rapidly reduced with the administration of cabozantinib, and MET and AXL signalling and tumour angiogenesis were inhibited [11].

3 Pharmacokinetic Properties of Cabozantinib

Following single-dose oral administration of cabozantinib 20, 40 and 60 mg tablets in healthy volunteers, there was a dose-proportional increase in cabozantinib area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) values [12]; the median time to reach C_{max} for cabozantinib was 3–4 h [12].

Following administration of a single 140 mg oral dose of cabozantinib tablets or capsules in healthy volunteers, the difference in AUC values between the cabozantinib formulations was <10%; however, bioequivalence was not shown for C_{max}, which was 19% higher for the tablet formulation [12]. Therefore, cabozantinib tablets should not be substituted with cabozantinib capsules [7, 8] (Sect. 6). Administration of a single oral dose of cabozantinib 140 mg following a high-fat meal resulted in an increase in C_{max} and AUC values compared with fasting conditions in healthy subjects [7, 8]; therefore, cabozantinib should not be administered with food (Sect. 6). Cabozantinib has an oral volume of distribution of ≈319 L and is highly plasma protein bound (≥99.7%) [7, 8].

Cabozantinib is a substrate of cytochrome P450 (CYP) 3A4 [7, 8]. Following administration of a single radiolabelled dose of cabozantinib 140 mg, ≈54% of radioactivity was recovered in the faeces and 27% was recovered in the urine, with the parent drug accounting for 43% of total radioactivity in faeces [7]. Cabozantinib had an estimated apparent plasma clearance at steady state of 2.2 L/h, with an estimated terminal elimination half-life of ≈99 h [7, 13].

The effects of hepatic and renal impairment on the pharmacokinetics of single-dose cabozantinib (60 mg) have been studied in two clinical pharmacology investigations [14], with findings from these studies reflected in the US prescribing information (PI) [7] and the EU summary of product characteristics [8]. In the USA and the EU, dose reduction to 40 mg once daily in patients with mild or moderate hepatic impairment is necessary [7, 8]; in the EU, monitoring of adverse events is recommended with dose adjustments or treatment interruptions as needed [8]. No dose adjustments are needed when cabozantinib is used in patients with mild or moderate renal impairment [7, 8], although caution is recommended in these patients in the EU [8]. There is no experience with the use of cabozantinib in patients with severe renal or hepatic impairment [7, 8]. In the USA and the EU, the use of cabozantinib is not recommended in patients with severe hepatic impairment [7, 8]. Cabozantinib is not recommended in patients with severe renal impairment in the EU [8].

Given that cabozantinib is a CYP3A4 substrate, there is potential for drug interactions with strong CYP3A4 inducers and inhibitors [9]. Concomitant administration of cabozantinib with strong CYP3A4 inducers [e.g. rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital, hypericum perforatum (St. John's wort)] reduces exposure to cabozantinib and may subsequently reduce efficacy [7]. Conversely, exposure to cabozantinib is increased

following coadministration with CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole, itraconazole, indinavir, nelfinavir, ritonavir, saquinavir, grapefruit juice), which may lead to exposure-related toxicity [7]. Therefore, the US PI recommends dose adjustments of cabozantinib when coadministration of strong inducers or inhibitors of CYP3A4 cannot be avoided, with resumption of the previous cabozantinib dosage 2–3 days after discontinuation of the strong CYP3A4 inducer or inhibitor [7]. In the EU, caution is recommended when cabozantinib is coadministered with strong CYP3A4 inhibitors and chronic coadministration of cabozantinib with strong CYP3A4 inducers should be avoided [8].

4 Therapeutic Efficacy of Cabozantinib

The efficacy of oral cabozantinib in the treatment of adults with advanced RCC who had progressed after prior VEGFR-targeted therapy was compared with oral everolimus in the randomized, open-label, multinational, phase III METEOR trial [15]. Patients in METEOR were aged ≥18 years, had advanced or metastatic RCC (including adequately treated and stable patients with brain metastases) with a clear-cell component, measurable disease, adequate organ and marrow function and a Karnofsky performance status score of ≥70%. Eligible patients must have previously received at least one VEGFR TKI with radiographic progression during treatment or within 6 months of the most recent dose of the VEGFR TKI [15]. There were no limitations with regard to the number of previous antineoplastic therapies, which could include cytokines, chemotherapy and monoclonal antibodies; however, patients previously treated with a mammalian target of rapamycin inhibitor (e.g. everolimus) or cabozantinib were excluded [15].

Eligible patients were stratified by prognostic risk category (favourable, intermediate or poor) [as per the Memorial Sloan Kettering Cancer Center (MSKCC) criteria] [16] and the number of previous VEGFR TKIs (one or at least two). Patients were randomized to receive cabozantinib 60 mg or everolimus 10 mg once daily, with subsequent dosage reduction (to a minimum of 20 mg/day for cabozantinib and 2.5 mg/day for everolimus) or interruption as required to manage adverse events [15]. Treatment was continued until no clinical benefit was observed or until unacceptable toxic effects developed.

At baseline, an MSKCC prognostic risk of favourable, intermediate and poor was seen in 46, 42 and 13% of patients, respectively, and 71 and 29% of patients had previously received one or at least two VEGFR TKIs; previous systemic therapies included sunitinib (63% of patients), pazopanib (43%) and axitinib (16%) [15].

The primary endpoint was progression-free survival (PFS) as assessed by an independent radiology review committee (IRC) [15]. The primary PFS analysis was conducted in the first 375 patients to be randomized, with PFS also assessed in all 658 randomized patients (both PFS analyses were conducted at a data cut-off of 22 May 2015). Key secondary endpoints were the IRC-assessed objective response rate (ORR) and overall survival (OS). A prespecified interim OS analysis was conducted at the time of the primary PFS analysis (after 202 deaths had occurred; data cut-off 22 May 2015) [15] and an unplanned second interim OS analysis was conducted after 320 deaths had occurred (data cut-off 31 December 2015), representing 78% of the planned 408 deaths in the prespecified final OS analysis [17]. Efficacy endpoints were assessed in the intent-to-treat population.

In previously-treated patients with advanced RCC, the risk of disease progression or death (primary endpoint) was 42% lower with cabozantinib than with everolimus (primary PFS analysis), with a significantly longer median PFS in recipients of cabozantinib versus everolimus (Table 1) [15]. These results were supported by an investigator-assessed PFS analysis which indicated that the risk of progression or death was significantly reduced by 40% and median PFS was significantly longer in cabozantinib versus everolimus recipients (Table 1) [15]. Furthermore, a supportive analysis among all randomized patients indicated a significant improvement in IRC-assessed PFS and a significantly longer median PFS in recipients of cabozantinib versus everolimus (Table 1) [17].

Hazard ratios (HRs) for IRC-assessed PFS favoured cabozantinib versus everolimus in prespecified subgroups at the data cut-off of 22 May 2015 [e.g. regardless of prior treatment with programmed death-1 (PD-1) or PD-L1 immune checkpoint inhibitors, location of tumour metastases, tumour MET status, MSKCC risk group, duration of the first VEGFR TKI used, number or type (sunitinib or pazopanib) of previous VEGFR TKIs] [17]. Furthermore, in a post hoc analysis of a subgroup of patients ($n = 153$) who only received sunitinib as their prior VEGFR TKI, the HR for PFS favoured cabozantinib and the estimated median PFS was 9.1 months compared with 3.7 months in everolimus recipients [15].

The prespecified interim OS analysis yielded an OS HR of 0.67 (95% CI 0.51–0.89; $p < 0.005$) for cabozantinib therapy versus everolimus; the p value of ≤0.0019 required to achieve statistical significance at this time point was not reached [15].

At the time of the unplanned second interim OS analysis, median OS was significantly longer with cabozantinib than with everolimus (Table 1) [17]. In cabozantinib-treated patients, the risk of death was significantly reduced by 34% compared with everolimus recipients (Fig. 1; Table 1).

Table 1 Efficacy of cabozantinib vs. everolimus in adults with advanced renal cell carcinoma that had progressed after prior VEGFR-targeted therapy: results of the METEOR trial [15, 17]

Endpoint [data cut-off]	Cabozantinib	Everolimus	HR (95% CI)
Median PFS (months) [22 May 2015]			
IRC-assessed primary PFS analysis[a,b]	7.4	3.8	0.58 (0.45–0.75)*
Inv-assessed PFS analysis[b]	7.4	5.3	0.60 (0.47–0.76)*
IRC-assessed PFS analysis in overall popn[c]	7.4	3.9	0.51 (0.41–0.62)**
ORR (% of pts) [22 May 2015]			
IRC-assessed ORR in primary PFS analysis popn[b]	21*	5	
IRC-assessed ORR in overall popn[c]	17**	3	
Median OS (months) [31 December 2015]			
Unplanned second interim OS analysis in overall popn[c]	21.4	16.5	0.66 (0.53–0.83)*

HR hazard ratio, *IRC* independent radiology review committee, *Inv* investigator, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *popn* population, *pts* patients

* $p < 0.001$, ** $p < 0.0001$ vs. everolimus

[a] Primary endpoint

[b] Analysis included 187 cabozantinib recipients and 188 everolimus recipients

[c] Analysis included 330 cabozantinib recipients and 328 everolimus recipients

Furthermore, the HRs for OS across various subgroups were consistent with results for the overall population and favoured cabozantinib versus everolimus [17].

The proportion of patients estimated to be alive at 6, 12, 18 and 24 months was 91, 73, 58 and 48%, respectively, in cabozantinib recipients and 81, 63, 47 and 31%, respectively, in everolimus recipients [17].

At the time of the prespecified interim and unplanned second interim OS analyses, treatment discontinuation because of disease progression (as per RECIST 1.1) occurred in 37 and 48% of cabozantinib recipients (at the respective timepoints) versus 48 and 58% of everolimus recipients, and was the most frequent reason for discontinuation in both groups (Sect. 5) [15, 17].

Among patients in the primary PFS analysis population ($n = 375$) and all randomized patients ($n = 658$), a significantly higher proportion of those receiving cabozantinib than everolimus achieved an IRC-assessed objective response (Table 1); all objective responses were partial responses [15, 17]. In the primary PFS analysis population, the best response for 14% of cabozantinib recipients and 27% of everolimus recipients was progressive disease, and for 62% of patients in each group it was stable disease [15]. Similarly, in the overall population, 12% of cabozantinib recipients and 27% of everolimus recipients had progressive disease as best response, while stable disease was achieved in 65 and 62% of cabozantinib and everolimus recipients [17].

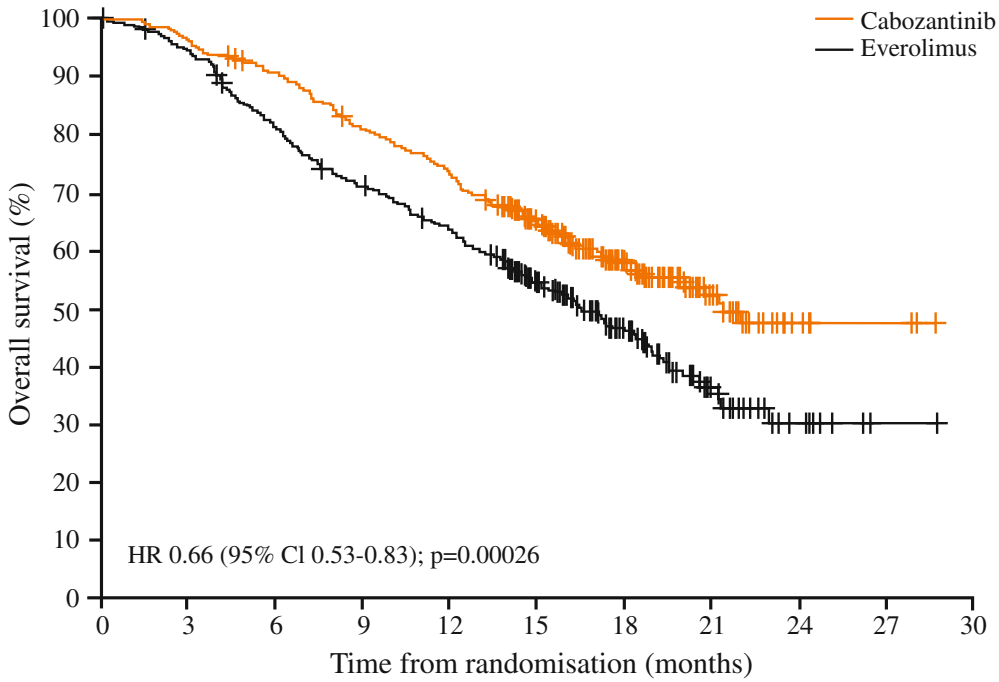
In a subgroup analysis ($n = 153$) of patients who only received sunitinib as their prior VEGFR TKI, the ORR was 22% in cabozantinib recipients and 3% in everolimus recipients [15].

In post hoc analyses ($n = 145$) of patients who continued on study medication for ≥2 weeks after radiographic progression (22 May 2015 data cut-off), stable disease or partial response occurred in 7% (5 of 74) of cabozantinib recipients and 8% (6 of 71) of everolimus recipients after the initial radiographic progression [17]. Moreover, the sum of target lesion diameters was lower than the pre-randomization baseline value in 46 and 21% of cabozantinib and everolimus recipients in at least one assessment.

In terms of health-related quality of life outcomes in METEOR [assessed using the Functional Assessment of Cancer Therapy-Kidney Symptom Index questionnaire (FKSI-19)], there were no between-group differences in mean total scores for FKSI-19 for the cabozantinib and everolimus treatment arms, according to an exploratory analysis (available as an abstract) [18]. The median time to deterioration (measured at the earliest occurrence of death, progression or ≥4-point decrease in FKSI disease-related symptom index) was significantly ($p < 0.0001$) longer with cabozantinib (5.5 months) than with everolimus (3.7 months) [post hoc analysis] [18].

5 Tolerability and Safety of Cabozantinib

In METEOR, the tolerability and safety analyses were conducted in the safety population, comprising 331 patients receiving cabozantinib and 322 patients receiving everolimus [15, 17]. The focus of this section will be the



Number at risk											
Cabozantinib	330	318	296	264	239	178	105	41	6	3	0
Everolimus	328	307	262	229	202	141	82	32	8	1	0
Number Censored											
Cabozantinib	0	0	3	1	0	35	57	56	32	3	3
Everolimus	0	3	2	1	2	34	42	36	20	7	1

Fig. 1 Kaplan–Meier plot of overall survival through Dec 31, 2015. All 658 randomly assigned patients were included in the analysis. The number of patients censored is summarized by interval. *HR* hazard ratio. Reproduced from Choueiri et al. [17] with permission

updated safety data (cut-off 31 December 2015) [17]. At the time of the updated safety data, patients were exposed to cabozantinib and everolimus for a median duration of 8.3 and 4.4 months, with a median daily dose of 43 mg of cabozantinib and 9 mg of everolimus [17].

The tolerability profile of oral cabozantinib in previously-treated adults with advanced or metastatic clear-cell RCC was generally manageable [15, 17]. At the time of the updated safety analysis, dose reductions were required in 62% of cabozantinib recipients [because of diarrhoea, palmar-plantar erythrodysaesthesia (PPE) syndrome and hypertension, for example] and in 25% of everolimus recipients (because of pneumonitis, fatigue and stomatitis, for example) [15, 17]. Treatment discontinuation as a result of adverse events occurred in 12% of cabozantinib recipients (because of decreased appetite and fatigue, for example) and in 11% of everolimus recipients [15, 17].

Adverse events of any grade and irrespective of causality occurred in 100 and 99.7% of cabozantinib and everolimus recipients, with grade 3 or 4 adverse events in 71 and 60% of these patients [17]. The most commonly occurring (≥25%) adverse events of any grade in cabozantinib recipients were diarrhoea, fatigue, nausea, decreased appetite, PPE syndrome, vomiting, weight decrease, constipation and hypertension. Patients receiving everolimus therapy most frequently reported diarrhoea, fatigue, nausea, decreased appetite, cough, dyspnoea, rash and anaemia [17].

The most frequently (≥5%) reported grade 3 or 4 adverse events with cabozantinib or everolimus were diarrhoea (13% in the cabozantinib group vs. 2% in the everolimus group), fatigue (11 vs. 7%), anaemia (6 vs. 17%), hypomagnesaemia (5 vs. 0%), PPE syndrome (8 vs 1%), hypertension (15 vs. 4%), nausea (5 vs. 0.3%), hyperglycaemia (0.9 vs. 5%) and asthenia (5 vs. 2%) [17]. The US PI recommends monitoring of blood pressure (at baseline and regularly thereafter), with cabozantinib dose interruptions recommended in patients with blood pressure inadequately controlled with medical treatment, and subsequent dose reductions once blood pressure control is achieved [7]. In the EU, blood pressure must be controlled prior to initiating treatment with cabozantinib and all patients should be monitored for hypertension during treatment; dose reductions are recommended in patients with persistent hypertension despite the use of antihypertensive therapy [8]. Cabozantinib treatment must be permanently discontinued when there is evidence of hypertensive crisis or severe hypertension uncontrolled by

antihypertensive therapy [7, 8] or optimal medical management [7]. In the USA, cabozantinib dose interruptions and subsequent dose reductions are recommended in patients with intolerable grade 2 PPE syndrome or diarrhoea, grade 3–4 diarrhoea not managed with standard antidiarrhoeal medication and in patients with grade 3 PPE syndrome [7]. In the EU, treatment interruption should be considered in patients with severe PPE syndrome and subsequent dose reductions are recommended when PPE syndrome has resolved to grade 1 [8].

Serious adverse events of at least grade 3 severity were reported in 39% of cabozantinib recipients and 40% of everolimus recipients [17]. The most commonly reported (incidence of ≥2%) serious adverse events of at least grade 3 severity included abdominal pain (3% of cabozantinib recipients vs. 1% of everolimus recipients), pneumonia (2 vs. 4%), anaemia (2 vs. 3%), pleural effusion (2 vs. 2%), pulmonary embolism (2 vs. 0.3%) and dyspnoea (1 vs. 3%) [17]. Death, irrespective of causality, occurred in 8% of patients in each treatment group during the adverse events reporting period, with one and two deaths occurring in cabozantinib and everolimus recipients, respectively, assessed as treatment-related [17].

In terms of other adverse events of interest reported in METEOR, haemorrhage of least grade 3 severity occurred in 2.1% of cabozantinib recipients and 1.6% of everolimus recipients, fistula occurred in 1.2 and 0%, gastrointestinal (GI) perforation occurred in 0.9 and 0.6%, venous thromboembolism occurred in 7.3 and 2.5% and arterial thromboembolism occurred in 0.9 and 0.3% [7]. Fatal cases of haemorrhage, GI perforation and thromboembolism and cases of reversible posterior leukoencephalopathy syndrome (RPLS) have been reported in the cabozantinib clinical programme [7]. Cabozantinib should not be administered to patients with or at risk of severe haemorrhage, and should be permanently discontinued in patients who develop severe haemorrhage, unmanageable fistulas or GI perforations, arterial thromboembolic events (e.g. myocardial or cerebral infarction), RPLS or nephrotic syndrome [7, 8].

In subgroup analyses, the safety profile of cabozantinib across all evaluated subgroups (including patients who received sunitinib or pazopanib as their only VEGFR-TKI, patients with exposure to immune checkpoint inhibitors targeting PD-1 or PD-L1, and patients with bone metastases) was consistent with the overall safety profile in patients with advanced RCC (available as abstracts plus posters) [19, 20].

6 Dosage and Administration of Cabozantinib

Cabozantinib tablets are approved for the treatment of patients with advanced RCC who have received prior antiangiogenic therapy in the USA [7], and for the treatment of advanced RCC in adults following prior VEGF-targeted therapy in the EU [8]. The recommended regimen of cabozantinib is 60 mg once daily on an empty stomach (patients must not eat for at least 2 h before and 1 h after taking cabozantinib) until the patient no longer experiences clinical benefit or experiences unacceptable toxicity [7, 8]. Missed doses of cabozantinib should not be taken within 12 h of the next dose [7, 8].

Because of the risk of foetal harm, the US PI recommends that female patients of a childbearing age must be advised to use appropriate contraception for the duration of and for 4 months following the last dose of cabozantinib [7]. In the EU, effective contraception is recommended for male and female patients and their partners for the duration of and for 4 months after therapy completion; other methods of contraception (e.g. barrier method) should be used in addition to oral contraception [8]. Although no information is available regarding the use of cabozantinib in lactating patients, breastfeeding should stop for the duration of cabozantinib treatment and for 4 months after the last dose to avoid potential exposure in the breastfed infant [7, 8].

Tablet (Cabometyx™) and capsule (Cometriq®) formulations of cabozantinib are not bioequivalent (Sect. 3), and should not be used interchangeably [7, 8]. Local prescribing information should be consulted for detailed information regarding events for which dose adjustments are recommended, and for warnings, precautions and management of adverse reactions pertaining to cabozantinib.

7 Place of Cabozantinib in the Management of Advanced Renal Cell Carcinoma

Dysregulation of MET and VEGFR pathways has been implicated in various human malignancies [6], including RCC (Sect. 1). Although a number of VEGFR TKIs are available for the treatment of RCC [4], disease progression due to the development of resistance remains a limitation. The rationale for the use of cabozantinib as subsequent therapy in patients with advanced RCC is related to its multi-targeted mechanism of action, including its inhibition of MET (Sect. 2). Approval of oral cabozantinib in the USA for the treatment of patients with advanced RCC who have received prior antiangiogenic therapy and in the EU for the treatment of advanced RCC in adults following prior VEGF-targeted therapy was primarily on the basis of METEOR results discussed in Sects. 4 and 5 [7].

Treatment with cabozantinib was more effective than everolimus in patients with RCC who had progressed after VEGFR TKI therapy (primary PFS analysis), with a clinically relevant gain in median PFS of 3.6 months and

a 42% reduction in the risk of disease progression or death (Sect. 4) [17]. At the unplanned second interim OS analysis, the clinical activity of cabozantinib was highlighted by a significantly prolonged median OS and a 34% reduction in the risk of death in cabozantinib versus everolimus recipients. Moreover, cabozantinib was associated with a significantly higher ORR. The benefit of cabozantinib was seen across various patient subgroups.

Cabozantinib had a manageable adverse events profile in the METEOR trial, with dose reductions occurring in 62% of cabozantinib recipients, but only 12% of patients discontinuing treatment because of adverse events (Sect. 5). The tolerability profile of cabozantinib was generally consistent with that reported for other VEGFR TKIs [21], with GI and dermatological adverse events commonly reported (Sect. 5). Adverse events of special interest that have been reported in patients receiving cabozantinib (e.g. hypertension, thromboembolism, haemorrhage, fistula formation, GI perforation and RPLS; Sect. 5) may also be seen with other VEGFR TKIs [21].

Cabozantinib is recommended by the US National Comprehensive Cancer Network, preferentially over everolimus, as a subsequent targeted therapy option (category 1) in patients with advanced clear-cell RCC who have received prior antiangiogenic therapy [4]. Other subsequent treatment options (category 1) include axitinib, which is recommended for patients who have received at least one prior systemic therapy, and the immune checkpoint inhibitor nivolumab, which is also recommended preferentially over everolimus in patients with advanced RCC who have received prior antiangiogenic therapy [4].

The European Association of Eurology guidelines acknowledge the findings from METEOR [17] and recommend the use of cabozantinib or nivolumab after the failure of initial VEGFR-targeted therapy to maximize survival [22]. Data are lacking around the optimal sequence of agents in advanced RCC, including the sequential use of cabozantinib and nivolumab, and the preferential order of other agents (e.g. axinitib, everolimus and sorafenib) in the case of disease progression despite cabozantinib or nivolumab treatment [22]. Head-to-head comparisons with other second-line treatment agents, particularly nivolumab, would be beneficial.

In conclusion, cabozantinib is an important new option for use in patients with advanced RCC who have received prior antiangiogenic therapy. Cabozantinib was more effective than everolimus in patients with advanced or metastatic clear-cell RCC who had previously received VEGFR TKIs, with significantly longer median PFS and OS and a significantly higher ORR. Cabozantinib had a manageable adverse events profile.

Data Selection Cabozantinib: 247 records identified	
Duplicates removed	10
Excluded at initial screening (e.g. press releases; news reports; not relevant drug/indication)	16
Excluded during initial selection (e.g. preclinical study; review; case report; not randomized trial)	12
Excluded by author (e.g. not randomized trials; review; duplicate data; small patient number; phase I/II trials)	187
Cited efficacy/tolerability articles	6
Cited articles not efficacy/tolerability	16
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Cabozantinib, Cabometyx, BMS-907351, XL-184, renal, kidney. Records were limited to those in English language. Searches last updated 2 November 2016	

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Compliance with Ethical Standards

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Conflict of interest Z T. Al-Salama and G.M. Keating are salaried employees of Adis/Springer, are responsible for the article content and declare no relevant conflicts of interest.

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