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Cabozantinib for the treatment of renal cell carcinoma patients

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Oncology in Clinical Practice
2017, Vol. 13, No. 4, 147–155
DOI: 10.5603/OCP.2017.0019

ISSN 2450–1654

ABSTRACT

Anti-angiogenesis is a key target of the first-line systemic therapy in renal cell carcinoma. Resistance to this therapy ultimately occurs in almost every patient who requires subsequent treatment to manage disease progression. Cabozantinib is a tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor and additionally blocking MET and AXL kinases, which are associated with tumour growth, proliferation, invasion, and resistance. Cabozantinib has been shown to improve overall survival, progression-free survival, and objective response rate in comparison to everolimus in patients with advanced renal cell carcinoma in the phase 3 METEOR study. It resulted in the approval for use in the treatment of advanced renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy and contributed to a change of treatment guidelines, placing cabozantinib among second-line therapy options. Herein we discuss the biological and clinical rationale behind cabozantinib use in renal cell carcinoma therapy and its position in the rapidly developing renal cell carcinoma treatment landscape. We outline current research and future directions for renal cell carcinoma therapy.

Key words: anti-angiogenesis, cabozantinib, practice guidelines, renal cell carcinoma, tumour resistance

Oncol Clin Pract 2017; 13, 4: 147–155

Introduction

Clear-cell renal cell carcinoma (RCC) is one of the most challenging malignancies to treat and remains largely incurable. This most common form of kidney cancer is a cause of more than 2700 deaths every year in Poland and over 35,000 in the European Union [1]. The earliest forms of systemic therapy were based on immunotherapy. Understanding of angiogenesis mechanisms led to the development of today's first-line therapies, which inhibit the vascular endothelial growth factor (VEGF) or the mammalian target of rapamycin (mTOR) pathways. Patients frequently develop resistance to these therapies, as shown by disease progression. The median progression-free survival (PFS) was less than one year with first-line VEGFR tyrosine kinase inhibitors (TKIs) [2–4] or mTOR inhibitor [5]. Subsequent therapies with different drugs are the current standard for tumour resistance management [6–8]. Understanding of resistance mechanisms led to the development of novel therapies, which redefine the landscape of RCC treatment. In recent years, drugs with new targets have been approved.

The METEOR study of cabozantinib, an oral TKI targeting multiple distinct pathways associated with tumour angiogenesis, invasiveness, metastasis, and drug resistance, showed significant benefit in overall survival (OS), PFS, and objective response rate (ORR) over everolimus in patients with advanced RCC [9, 10]. These findings contributed to recent substantial modification of the second-line RCC treatment guidelines, [6–8] moving everolimus to the subsequent lines of treatment [11]. Most recently, in CABOSUN, involving patients with previously untreated intermediate- or poor-risk RCC, cabozantinib compared to standard-of-care sunitinib significantly increased median PFS [12].

In this review, we summarise the biology of RCC, contributing to recent developments and accumulated data about cabozantinib in the treatment of RCC patients impacting current treatment guidelines.

Renal cell carcinoma: pathophysiology, resistance, and therapeutic implications

Thanks to advances in molecular biology today, we understand, at least in part, the mechanisms responsible for the formation of cancer cells, and their proliferation and expansion in RCC. In most RCC cases we observe dysregulation of the von Hippel-Lindau (VHL) pathway [13]. The VHL protein is a tumour suppressor acting as the substrate recognition component of an E3 ubiquitin ligase, which in normoxic state targets the hydroxylated, oxygen-sensitive α-subunits of hypoxia-inducing factor (HIF) for ubiquitination and degradation [14–16]. *VHL* gene mutations and loss of its function lead to translocation and accumulation of HIF in the nucleus, where it acts as a transcription factor [17]. Transcriptional targets of HIF include a variety of pro-tumourogenic genes, leading to overproduction of growth factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor [17].

Increased *VEGF* gene expression [18] and VEGF protein levels [19] have been found in RCC and correlate with microvessel density [18], as a measure of the extent of angiogenesis. Inhibition of VEGF has been pursued as a therapeutic target in RCC, and subsequently therapies directed specifically against the VEGF protein (bevacizumab) and VEGF receptor kinases (sunitinib, pazopanib, axitinib, and sorafenib) have been developed in the past decade [2, 3, 20–22] and have since remained a standard-of-care. Other treatments include mTOR inhibitors (temsirolimus and everolimus) [5, 23] and the programmed cell death 1 (PD-1) checkpoint inhibitor nivolumab [24].

However, the majority of patients become resistant and require further systemic therapy. Chronic treatment with anti-angiogenic agents may affect tumour cells leading to upregulation of alternative tumour-survival and invasion pathways. Activation of the prometastatic MET and AXL tyrosine kinase receptors seems to be one of the tumour escape pathways contributing to treatment resistance [25]. AXL expression is directly activated by HIF [16] and is clinically correlated with aggressive tumour behaviour, poor prognosis, and increased risk of patient mortality [16, 26]. Direct activation of MET through mutations in its gene has been identified in hereditary, and sporadic papillary RCC [27] and its expression was shown *in vitro* to be upregulated in the loss of VHL function and hypoxia in clear-cell RCC [28]. Dysregulation of MET is involved in tumour development, invasion, and angiogenesis [28]. Simultaneous inhibition of MET and VEGF signalling did not only decrease tumour growth but also reduced invasion and metastasis [29]. *In vitro* studies of sunitinib-induced resistance [25, 30–32] provide support for targeting of VEGFR, MET, and AXL for RCC treatment.

Cabozantinib has a novel, multi-kinase inhibition mechanism of action. By blocking VEGFR 1–3 and, unlike other VEGRF inhibitors, additionally inhibiting MET and AXL, cabozantinib targets key pathways important to tumour growth, metastasis, and angiogenesis [33] (Fig. 1). Indeed, outcomes of RCC therapy in clinical trials [9, 10, 12] suggest that the observed in vitro effects on MET and AXL may have practical relevance and are a step towards overcoming resistance to VEGFR inhibition.

Renal cell carcinoma treatment landscape

The treatment landscape for RCC is dynamic and has changed considerably in the past year. Current guidelines recommend the use of several systemic therapies to treat patients with unresectable RCC. The choice of drug always depends on the context of the clinical course of the disease, physician experience, drug availability, and patient preference [34], and in Poland it is determined by a specific procedure called the therapeutic or drug program. In such programs, the health service provider permits treatment in selected diseases to well-defined groups of patients, according to specific inclusion/exclusion criteria and the definition of the dosage regimens, mode of administration, and list of diagnostic tests needed for qualification for the program. Figure 2 summarises recently updated guidelines from the European Society of Medical Oncology (ESMO) [6], the European Association of Urology (EAU) [7], and the National Comprehensive Cancer Network (NCCN) [8]. All these guidelines refer mainly to the clear cell histology of the RCC because most of the pivotal trials have been conducted in patients with this, the most common histological subtype of RCC. Guidelines differ in how recommendations are provided, e.g. in patient's risk differentiation, reaching survival advantage outcome, categorisation of level of evidence and expert consensus, and number of lines of therapy.

Inhibitors of VEGFR-TKI/VEGF and mTOR dominate in the treatment of RCC (Fig. 2). Oral VEGFR-TKI inhibitors such as sunitinib and pazopanib are established in the first-line treatment algorithm based on the pivotal phase 3 clinical trials [2–4] (Fig. 2). Temsirolimus, the mTOR inhibitor, is reserved for patients with poor-prognosis [5] (Fig. 2).

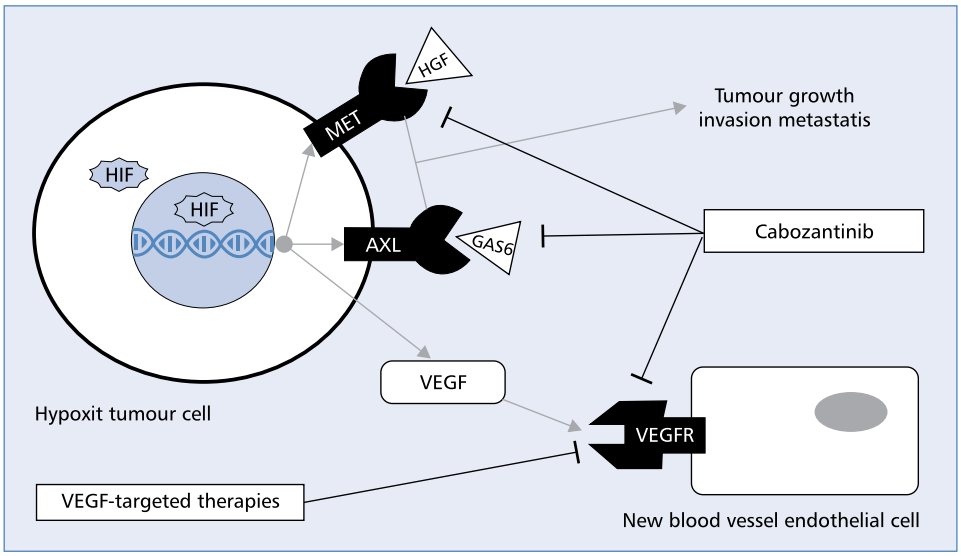

Figure 1. Cabozantinib mechanism of action. VHL dysregulation promotes accumulation of HIF, resulting in expression of hypoxia-response genes, including *VEGF*, *MET*, and *AXL*. MET and AXL signalling supports tumour growth, survival, invasion, and metastasis also in response to VEGFR inhibition. Cabozantinib, as well as VEGFR inhibition, also blocks MET and AXL tyrosine kinase receptors affecting tumour escape and survival signalling pathways [24, 30]. AXL — AXL receptor; GAS6 — growth arrest-specific 6; HGF — hepatocyte growth factor; HIF — hypoxia-inducing factor; MET — hepatocyte growth factor receptor; VEGF — vascular endothelial growth factor; VEGFR — vascular endothelial growth factor receptor

The availability of drugs with different mechanisms of action provides multiple options for second-line and subsequent therapies (Fig. 2). Recently, the PD-1 immune checkpoint inhibitor nivolumab and the multi-kinase inhibitor cabozantinib showed significant improvement in the OS over everolimus when used after one or two lines of VEGF-targeted therapy(-ies) [9, 10, 35]. PFS was significantly improved only in the cabozantinib study [9, 10]. These studies significantly impacted the current therapeutic landscape and increased the number of options for patients with advanced RCC.

In consequence, ESMO has recently provided modified recommendations for the second-line treatment of RCC after initial therapy with TKIs [6]. The EAU recommended both cabozantinib and nivolumab after initial VEGFR-targeted therapy [7]. Also, based on the results of the CheckMate 025 [35] and the METEOR [9, 10] studies, the NCCN panel has included cabozantinib and nivolumab as category 1 (high-level evidence where there is uniform NCCN consensus that the intervention is appropriate) subsequent therapy options in patients who previously have been treated with a TKI [8] (Fig. 2). As shown in phase III clinical trials, patients should preferentially receive one of these agents over everolimus.

Cabozantinib in the second-line therapy of renal cell carcinoma

Cabozantinib has been approved by the European Commission in September 2016 for the treatment of advanced RCC in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy [36], based on results of the phase III METEOR randomised, open-label, multicentre study [9, 10].

Study design

The study enrolled 658 adult patients with advanced or metastatic clear cell RCC, who had received at least one previous VEGFR-TKI and had documented disease progression on the most recent drug within six months before randomisation. Patients were randomly assigned to receive either cabozantinib (n = 330) or everolimus (n = 328). Everolimus was chosen as the comparator for cabozantinib because it was an accepted standard of care for the second-line treatment of advanced RCC. There was no limit to the number and type of previous therapies but patients previously treated with an mTOR inhibitor were not eligible for participation. Randomisation was stratified by number of prior VEGFR-TKIs and Memorial Sloan Kettering Cancer Centre (MSKCC) risk groups, commonly used in clinical trials design and interpretation [37].

Cabozantinib was given orally once a day at 60 mg, and everolimus was given once a day at 10 mg. Treatment modification was allowed, including interruptions and dose reductions to manage adverse events (AEs). Dose reductions were permitted to 40 and then to 20 mg for cabozantinib and to 5 and then to 2.5 mg for everolimus. Patients could continue treatment beyond progression at the investigator's discretion, but crosso-

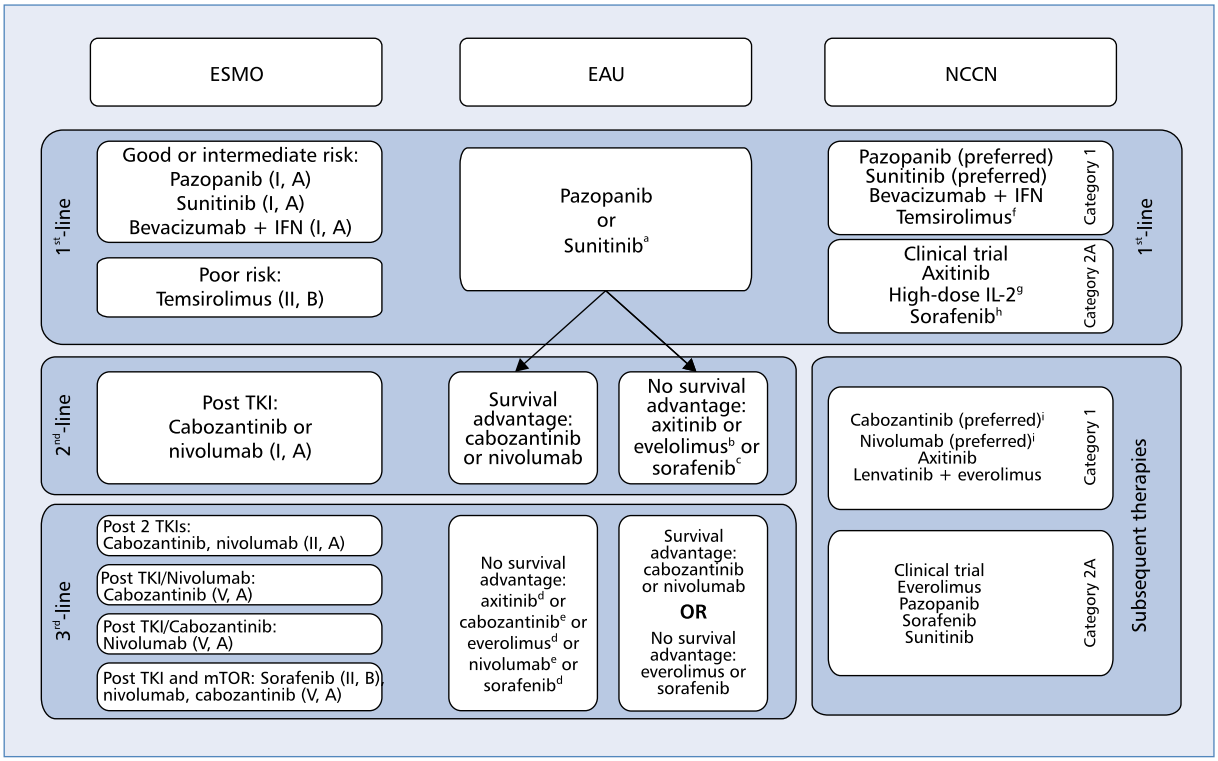

Figure 2. Summary of the renal cell carcinoma systemic therapy practice guidelines

ESMO, adopted from the European Society of Medicinal Oncology Guidelines for the systemic therapy for metastatic RCC with clear cell histology [6]. Only standard therapy choices with highest available levels of evidence and grades of recommendation are presented. Levels of evidence (I–V) and grades of recommendation provided in brackets. Recommendations for therapy post-cytokines are not included. mTOR — mammalian target of rapamycin; TKI — tyrosine kinase inhibitor

EAU, adopted from the European Association of Urology Guidelines for clear cell renal cancers that are resistant to vascular endothelial growth factor receptor targeted therapy [7]. In each VEGF-resistant disease therapy line switches should be to options not given previously. Recommended switches are indicated by arrows between options providing or not providing survival advantage. [a] — sunitinib and pazopanib can be recommended in all Memorial Sloan Kettering Cancer Centre risk groups. Bevacizumab/interferon (favourable and intermediate-risk) and temsirolimus (poor-risk) have not been widely used as first-line therapy in the pivotal VEGF-resistant trials, and therefore recommendations are not possible; [b] — nivolumab and cabozantinib have not been given after everolimus and thus cannot be recommended above other agents; [c] — sorafenib has an inferior progression-free survival to axitinib; [d] — these drugs have shown a survival advantage in VEGF-resistant disease but not in this specific setting; [e] — these drugs were given after progression in the pivotal cabozantinib or nivolumab trials

NCCN, adopted from the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Kidney Cancer version 1.2017 [8]. Systemic therapy guidelines for patients with relapse and surgically unresectable cancer with predominant clear cell histology. NCCN believes that the best management of any patient with cancer is in a clinical trial. All recommendations include best supportive care. Recommendations of category 1 (high-level evidence, uniform NCCN consensus that the intervention is appropriate) and 2A (lower-level evidence, uniform NCCN consensus that the intervention is appropriate) are presented and listed alphabetically by category and preference. [f] — for poor-prognosis patients; [g] — for patients with excellent performance status and normal organ function; [h] — for selected patients; [i] — eligible patients should preferentially receive this agent over everolimus

ver between treatment groups was not allowed in the study [9, 10].

The primary endpoint of the study was PFS measured as the time from randomisation to radiographic progression according to the Response Evaluation Criteria in Solid Tumours (RECIST) or death from any cause. PFS and ORR were assessed by an independent radiology review committee. The secondary endpoints were OS — the time from randomisation to death from any cause, and objective response rate defined as the percentage of patients with complete or partial response per RECIST criteria evaluated by an independent radiology review. The total sample size of 650 patients required to evaluate OS was much larger than needed to assess the primary endpoint of PSF. To provide adequate power for all endpoint analyses and limit overrepresen-

tation of patients with early/rapid onset of progression, the primary endpoint analysis (PFS) was pre-specified to occur when 259 PFS events had occurred in the first 375 randomised patients (PFS population). The OS, ORR and also PFS were to be tested in all randomised patients, comprising the intention-to-treat (ITT) population (OS population).

Clinical efficacy of cabozantinib

Patient baseline characteristics were well balanced in the two treatment groups in terms of demographic and clinical variables. Around 70% of patients had only one prior therapy with VEGFR-TKI inhibitor. The most frequently used treatments before randomisation were sunitinib (64%) and pazopanib (44%). Most patients were categorised as having favourable (46%) or intermediate risk (42%) by MSKCC criteria. The median duration of follow-up for survival and safety was 18.7 months in the cabozantinib group and 18.8 months in the everolimus group [9].

The PFS population analysis among the first 375 randomised patients revealed PFS benefit (HR = 0.58, 95% CI: 0.45–0.75, $p < 0.001$) of cabozantinib (median PFS 7.4 months, 95% CI: 5.6–9.1) over everolimus (median PFS 3.8 months, 95% CI: 3.7–5.4). In the planned interim analysis for OS, the boundary of significance was not reached [10]. However, follow-up for OS was continued to the planned final analysis [9]. In the PFS analysis including all 658 patients, cabozantinib significantly improved PFS in comparison to everolimus with median PFS 7.4 *vs*. 3.9 months, respectively (HR = 0.51, 95% CI: 0.41–0.62, $p < 0.0001$, ITT population) [9] (Tab. 1). PFS reported for everolimus was similar to that reported in earlier trials [38]. The benefit of cabozantinib over everolimus was maintained regardless of the number of prior therapies (Tab. 1). The PFS improvements were demonstrated over everolimus across multiple subgroups, e.g. in patients with favourable and intermediate MSKCC risk, patients with bone metastases, and patients treated with the sunitinib or pazopanib as the only VEGFR TKI, and by prior treatment with a PD-1/PD-L1 checkpoint inhibitor (Tab. 1).

In a subsequent analysis with longer follow-up, treatment with cabozantinib increased OS in comparison to treatment with everolimus, demonstrating a 34% reduction in the rate of death vs. comparator. The median OS was 21.4 months in the cabozantinib and 16.5 months in the everolimus group (HR = 0.66, 95% CI: 0.53–0.83, $p = 0.00026$) (Tab. 1). At each time point of the Kaplan-Meier landmark estimates at 6, 12, 18, and 24 months, the proportion of patients estimated to be alive was greater in the cabozantinib than in the everolimus group [9]. It is worth noting that none of the previously approved VEFGR-TKI inhibitors [2, 3, 15, 39] or everolimus [23] showed OS benefit over comparators or placebo in second-line RCC treatment.

Assessment of the ORR showed partial responses in 17% of patients in the cabozantinib and 3% in the everolimus group ($p < 0.0001$). Progression as best

Table 1. Overall survival and progression-free survival results of the METEOR study comparing cabozantinib *vs.* everolimus in the treatment of patients with advanced or metastatic RCC [9]

Outcome	Cabozantinib	Everolimus	HR (95% CI)
	no. of patients/events		
Overall survival	330/140	328/180	0.66 (0.53–0.83)
Progression-free survival	330/180	328/214	0.51 (0.41–0.62)
Progression-free survival depending on no. prior VEGFR-TKIs			
1	235/131	229/155	0.52 (0.41–0.66)
≥ 2	95/49	99/59	0.51 (0.35–0.74)
Progression-free survival depending on type of previous VEGFR-TKI			
Only sunitinib	135/74	132/97	0.43 (0.32–0.59)
Only pazopanib	88/51	83/49	0.67 (0.45–0.99)
PD-1 or PD-1L	18/6	14/11	0.22 (0.07–0.65)
Progression-free survival depending on MSKCC risk group			
Favourable	66/34	62/37	0.47 (0.30–0.76)
Intermediate	210/107	214/137	0.48 (0.37–0.62)
Poor	54/39	52/40	0.67 (0.48–1.04)

MSKCC — Memorial Sloan Kettering Cancer Centre; HR — hazard ratio (value below 1 favours cabozantinib; value above 1 favours everolimus); VEGFR-TKI — vascular endothelial growth factor tyrosine kinase inhibitor

response was observed in 12% of patients treated with cabozantinib and 27% treated with everolimus, which indicates lower incidence of refractory disease in patients treated with cabozantinib [9]. In the case of PFS and ORR, the results of assessments performed by masked independent review committee and by investigators were similar [9].

The METEOR study results support the hypothesis that inhibition of MET and AXL targets by cabozantinib might overcome tumour progression and resistance to VEGFR-directed therapies. The question whether high MET expression was associated with favourable outcomes was addressed in the study [9]. Archival or recent biopsied tumour tissue was obtained from around 2/3 of patients treated with cabozantinib or everolimus for immunochemistry analysis of MET protein levels. Every third patient had high MET expression status. The results suggest that the MET expression level might not affect outcomes with cabozantinib. One limitation of this analysis is that archival tissue samples were mainly used rather than obtaining biopsies during treatment [9]. Further investigation of biomarkers may help to define the roles of all the individual molecular targets in the clinical activity of cabozantinib. Finding biomarkers predictive of response to therapy is an unmet need in the RCC treatment landscape.

Quality of life and safety profile

Cabozantinib improved PFS, OS, and ORR [9] and resulted in quality of life (QoL) similar to everolimus in patients with advanced or metastatic RCC [40]. The QoL data were collected from ≥ 75% of patients using Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19) and EuroQol EQ-5D-5L instruments. No treatment arm differences in the FKSI-19 total score over time were observed and scores at the end of treatment were around seven points lower than at baseline in both arms. This was mainly due to disease progression.

In the METEOR study, reflecting the differing safety profile of each drug, there were differences in the adverse events reported for each treatment: diarrhoea and nausea were more frequent for those treated with cabozantinib, whereas shortness of breath was worse for everolimus. No differences between treatments were observed for the other three FKSI subscales (disease-related symptom index physical, emotional, function/well-being) or for the EQ-5D-5L questionnaire. The median time to deterioration defined as earlier death, progression, or ≥ 4-point decrease in FKSI disease-related symptom index, was longer in the cabozantinib arm than in everolimus group (5.5 *vs*. 3.7 months, $p < 0.0001$) [40].

Cabozantinib demonstrated a safety profile similar to other VEGFR-TKIs used in advanced RCC patients [41]. In the METEOR study, all patients in both groups reported adverse events (AEs). Grade 3 or 4 AEs occurred in 71% of patients treated with cabozantinib and 60% of patients using everolimus. The most common grade 3 or 4 AEs (as per Common Terminology Criteria for Adverse Events) reported in the METEOR study were hypertension (15%), diarrhoea (13%), and fatigue (11%) in the cabozantinib group and anaemia (17%), fatigue (7%), and hyperglycaemia (5%) in the everolimus group. Grade ≥ 3 serious adverse events occurred in 39% and 40% patients in the cabozantinib and everolimus groups, respectively [9].

AEs were managed with dose modifications and supportive care. The open-label study design allowed for the appropriate management of AEs in both study groups. In the cabozantinib arm 62% of the patients had at least one dose reduction (median daily dose 43 mg) and in the everolimus arm 25% of patients had dose reductions (median daily dose 9 mg). Treatment discontinuation because of AEs not related to disease progression occurred in 12% of cabozantinib patients and 11% of everolimus patients, suggesting that dose modifications in both treatment groups, however frequent, adequately addressed the management of AEs, allowing a substantial number of patients to remain on study treatment for an extended period and preventing treatment-associated discontinuations. Deaths during the study, irrespective of causality, occurred in 8% of patients in the cabozantinib group and 8% of patients in the everolimus group. Most of these were related to disease progression [9].

Based on favourable OS, PFS, and ORR of cabozantinib in comparison to everolimus, it was authorised as treatment for advanced RCC in Europe [36] and the United States [41] for the treatment of advanced RCC in adults following prior VEGF-targeted therapy. Oncology and urology associations recommended cabozantinib for the treatment of RCC in the second-line setting [6–8]. Future research on the optimal use of cabozantinib and other available treatments aims to provide optimal care to patients with RCC.

Changes in the renal cell carcinoma treatment landscape: future implications

As described earlier, recent guidelines of RCC treatment will need continuous revision over the coming years because a range of targeted agents are in development. However, guidelines do not provide universal sequencing of treatments, since the presence of prognostic factors affecting OS always need careful sequencing of all treatments to ensure that individual patients receive optimum care. Further studies will

reveal new data on the optimal sequencing of current treatment options and also will allow introduction of new therapies. Precision treatment may become a reality in future therapy of RCC.

In April 2016, nivolumab, a programmed death receptor-1 (PD-1) blocking antibody, received European approval for the second-line treatment of advanced RCC. In the CheckMate 025 study, the median OS was significantly longer with nivolumab vs. everolimus (25.0 months *vs.* 19.6 months, respectively), while the median PFS was similar in both treatment groups; 4.6 months (95% CI 3.7–5.4) in the nivolumab group and 4.4 months (95% CI 3.7–5.5) in the everolimus group (HR 0.88; 95% CI 0.75–1.03; p = 0.11) [35]. In May 2016, lenvatinib, a VEGFR and FGF TKI inhibitor, in combination with everolimus was approved by the Food and Drug Administration for the treatment of advanced RCC following one prior VEGF-targeted therapy [42]. The EMA gave its approval with the same indication in August 2016 [43]. The combination of lenvatinib with everolimus significantly prolonged investigator-assessed PFS *vs.* everolimus alone (HR 0.40, 95% CI 0.24–0.68; p = 0.0005). Patients treated with single-agent lenvatinib had a significantly longer median PFS *vs.* those treated with single-agent everolimus (HR 0.61, 95% CI 0.38–0.98; p = 0.048), but PFS was not significantly different from the lenvatinib + everolimus combination arm (HR 0.66, 0.39–1.10; p = 0.12) [44]. The combination of targeted therapy and immunotherapy is an area of many ongoing trials in RCC. Another investigational combination therapy is ipilimumab, an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody, + nivolumab, which will be compared with sunitinib monotherapy in patients with previously untreated metastatic RCC in a large phase III clinical study [45]. Two other phase III studies are investigating anti-PD-1/PD-L1 antibodies in combination with axitinib [46] and bevacizumab [47] in advanced RCC. The hypothesis of blocking multiple pathways needed for tumour growth with agents having different modes of action inspired researchers also to combine ipilimumab with cabozantinib and nivolumab in different types of cancers, including RCC [48]. It highlights that novel therapeutic approaches are required to improve outcomes with RCC therapy.

In parallel to the development of new treatments, there is also progress in investigating the optimal sequence of therapies. Cabozantinib and nivolumab effectiveness confirmed in trials [9, 10, 24] changed treatment guidelines in the second-line therapy of RCC [6–8]. Most recently, in the phase II CABOSUN study, cabozantinib demonstrated superiority over sunitinib in terms of PFS in patients with RCC previously not treated with systemic agents [12].

Conclusions

In the past decade, a number of agents have been approved for the first-line treatment of metastatic RCC. Drugs with anti-angiogenic activity are in the mainstream of initial treatment [6–8]. Resistance may occur when cancer cells escape from the hypoxia induced by VEGF/VEGFR-targeting drugs. They adopt alternative signalling pathways to compensate for lack of this major angiogenic factor signalling. The development of new therapies aims to act on novel mechanisms of action, and also to target multiple pathways in parallel. Cabozantinib, recently approved in the treatment of the advanced RCC, inhibits VEGFR and targets MET and AXL kinases [33]. The latter are both considered as a possible tumour escape pathways and are involved in metastatic RCC pathobiology and development of resistance [26, 27]. Cabozantinib treatment showed benefit over everolimus in patients with advanced or metastatic RCC, who had progressed after initial systemic therapy. The study met its primary endpoint — PFS improvement over the comparator, and also prolonged OS [9, 10], which is a gold standard for demonstrating clinical benefit for cancer drugs [49]. Cabozantinib and nivolumab, a PD-1 checkpoint inhibitor, became recommended second-line treatments advocated by the ESMO [6], the EUA [7], and the NCCN [8]. However, guidelines [6, 7] or indirect comparisons [48] do not provide the answer to the crucial question regarding which agent should be used over the other. Additional data, such as real-world observational data, are needed to compare survival of patients under treatment with cabozantinib *vs.* nivolumab [50].

Most recently, cabozantinib showed improvement in PFS over sunitinib in a population of treatment-naïve patients with metastatic RCC and intermediate- or poor-risk disease [12]. The CABOSUN study is the first one that showed benefit over sunitinib in the first-line setting. Ongoing trials are comparing novel strategies used in combination with PD-1 checkpoint inhibitors or VEGFR-TKIs *vs*. sunitinib [45–47].

Manuscript preparation and author contributions

This manuscript was prepared on the basis of discussions held at the "Cabozantinib in advanced RCC advisory board" meeting held in Warsaw, 29.11.2016. All authors participated in the meeting, presented and discussed the accumulated data and information on cabozantinib use in advanced RCC in the context of the treatment landscape. Maria Jessa-Jabłonska and Iwona Król-Starzomska — employees of Ipsen Poland — participated in the meeting. The meeting discussion was recorded, and based on the recording and meeting materials this manuscript has been developed. Medical writing support was provided by

Ewelina Drelich and Marcin Balcerzak of Farenta. All authors have read, commented, and approved the final version of the manuscript to be published.

Funding: This article was drafted on the basis of discussions held at the "Cabozantinib in advanced RCC advisory board" meeting held in Warsaw, 29.11.2016. The meeting was funded by Ipsen Poland. Medical writing support was provided by Ewelina Drelich and Marcin Balcerzak of Farenta with funding from Ipsen Poland.

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