Review article

Cabozantinib in monotherapy and combination therapy for first-line renal cell carcinoma: Patient profiles

Piotr Tomczak

Oncology Clinic, Poznan University of Medical Sciences
Head: prof. Rodryg Ramlau, MD, PhD

ABSTRACT

Systemic treatment of metastatic kidney cancer is continuously evolving, which leads to the need to choose between monotherapy with tyrosine kinase inhibitors or the use of one of the dual therapy regimens.

Cabozantinib, a tyrosine kinase inhibitor of VEGFR, MET, and AXL receptors, is registered for monotherapy and in combination with nivolumab as a first-line treatment for patients with metastatic kidney cancer. The drug is characterized by a good profile of efficacy and side effects, as demonstrated in both clinical trials and the results of real-world data analyses. Cabozantinib also has specific pharmacokinetic features, which may be a consideration when choosing treatment.

Cabozantinib represents a valuable treatment option in the first line for patients with metastatic kidney cancer and a defined clinical profile.

Key words: kidney cancer, cabozantinib, first line systemic treatment

Correspondence:
Piotr Tomczak, MD, PhD
Oncology Clinic, Poznan University of Medical Sciences
60-514 Poznań, Szamarzewskiego 84

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INTRODUCTION

Primary renal cell carcinoma (RCC) constitutes approximately 3% of all adult malignancies, with the clear cell subtype (ccRCC) accounting for about 80% of cases. The incidence peaks in the 6th to 7th decades of life, with a male-to-female ratio of 1.5 : 1. According to the National Cancer Registry, 5,234 new cases of kidney cancer were diagnosed in Poland in 2017, including 3,144 men and 2,088 women. In the same year, 2,464 patients died of the disease (1,525 men and 938 women). Epidemiological projections estimate that by 2030, the annual number of new cases in Poland may reach approximately 7,000, with nearly half of patients expected to present with advanced-stage disease and a poor prognosis. In approximately 15–30% of cases, kidney cancer is diagnosed at an advanced stage, with distant metastases already present. Moreover, in about 30% of patients who undergo radical treatment (radical or partial nephrectomy), disease progression occurs, typically within 2–3 years after surgery, necessitating further systemic therapy. Despite significant advances in therapeutic options, the median overall survival for patients with metastatic disease rarely exceeds 3.5 years, with 5-year survival rates ranging from 15% to 60%, depending on prognostic factors. The 5-year survival rate for patients with organ-confined kidney cancer approaches 90%, whereas for those with metastatic disease it decreases dramatically to only 10–15%. Management of localized disease is primarily surgical and remains within the domain of urology, involving either radical nephrectomy (removal of the entire kidney) or partial nephrectomy (tumor excision with renal preservation). Performing cytoreductive nephrectomy may be recommended in patients with metastatic disease, but is no longer the current standard, and eligibility is related to both disease and patient profiles. On the other hand, it is always worth considering surgical removal of metastatic lesions, which often has clear benefits. This is particularly relevant for patients with isolated or localized metastases confined to a single organ, as well as for those with late recurrences. The introduction of adjuvant therapy with pembrolizumab in patients at high risk of recurrence – following radical nephrectomy, metastasectomy, or radiotherapy for metastatic lesions performed within one year of nephrectomy – has improved the effectiveness of surgical management in this setting. If low-grade metastatic disease (oligometastatic disease) with indolent dynamics is identified, active surveillance may be considered instead of immediate systemic treatment [1].

TREATMENT OF KIDNEY CANCER

Renal cell carcinoma is a chemo-resistant tumor, and improvements in the efficacy of systemic treatment have been brought about by the introduction of molecularly targeted drugs, which act mainly by inhibiting neoangiogenesis, and immunocompetent therapies. Renal cell carcinoma is inherently resistant to conventional chemotherapy. Advances in systemic therapy have been achieved through the introduction of molecularly targeted agents, primarily inhibiting tumor neoangiogenesis, **and through immunotherapy with immune checkpoint inhibitors.** In approximately 2% of patients, RCC is associated with a mutation in the von Hippel–Lindau (VHL) tumor suppressor gene. This alteration leads to the accumulation of hypoxia-inducible factor 1 (HIF-1), resulting in increased expression of angiogenic and growth factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF). The consequence of these molecular alterations is the development of highly vascularized tumor tissue, which underlies the susceptibility of RCC to anti-angiogenic therapies. Moreover, RCC is recognized as a highly immunogenic tumor, and the advent of immune checkpoint inhibitors (ICIs) has further improved the efficacy of systemic treatment.

The selection of first-line therapy depends on both disease- and patient-related factors, which together determine the overall prognosis. Currently, the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk model is most commonly used, incorporating six clinical and laboratory parameters to stratify patients into favorable, intermediate, or poor prognostic groups. The introduction of combination regimens has significantly transformed not only treatment efficacy but also the eligibility criteria and therapeutic approach. Patients classified as having a favorable prognosis may still be considered for first-line monotherapy with sunitinib or pazopanib. Both agents are non-selective tyrosine kinase inhibitors (TKIs) targeting the vascular endothelial growth factor receptor (VEGFR) pathway. Their efficacy is comparable, with median progression-free survival (mPFS) of approximately 11.0 months for sunitinib and 9.2 months for pazopanib, and both demonstrate a similar overall tolerability profile. In contrast, patients classified into the intermediate- and poor-risk groups may be treated with cabozantinib monotherapy or, more commonly, with one of the available combination regimens. The introduction of dual immune checkpoint blockade with ipilimumab plus nivolumab in the first-line setting has markedly improved clinical outcomes, providing durable responses in a subset of patients and offering a more manageable toxicity profile compared with older therapies. Results from pivotal clinical trials have demonstrated that first-line combination regimens, such as axitinib with pembrolizumab or avelumab, lenvatinib with pembrolizumab, and cabozantinib with nivolumab, offer a significant advantage over traditional TKI monotherapy. The selection of systemic therapies available for subsequent treatment includes

tyrosine kinase inhibitors (TKIs) such as axitinib, sunitinib, and cabozantinib; mTOR inhibitors such as everolimus; and immune checkpoint inhibitors such as nivolumab. However, the widespread shift toward combination regimens in the first-line setting has created an urgent need to redefine treatment algorithms for second- and later-line therapies [2–4].

EFFICACY STUDIES OF TWO-DRUG REGIMENS

The introduction of two-drug regimens has raised the question of whether stand-alone TKI molecules, including cabozantinib, remain a valid and accepted treatment option for patients with advanced RCC with intermediate or unfavorable prognosis. Cabozantinib is a small-molecule TKI that targets VEGFR, as well as MET and AXL, which are involved in the growth, migration, and metastatic potential of kidney cancer cells. Both MET and AXL also represent alternative pathways driving neoangiogenesis, contributing to resistance against more selective TKIs such as sunitinib or tivozanib. The open-label, randomized phase II CABOSUN trial compared cabozantinib with sunitinib in terms of efficacy and safety as first-line treatment for patients with metastatic renal cell carcinoma (mRCC) and intermediate or poor prognosis.

The study enrolled 157 patients, of whom 81% had an intermediate prognosis and 19% had a poor prognosis, with an ECOG performance status of 0–2. Bone metastases were present in 30% of patients. Following randomization, 97 patients received cabozantinib at a starting dose of 60 mg once daily, while 78 patients received standard sunitinib in the 4/2 regimen. The protocol did not allow crossover between treatment arms in the event of disease progression or treatment intolerance. The median progression-free survival (PFS) was 8.2 months with cabozantinib (95% CI: 6.2–8.8) compared to 5.6 months with sunitinib (95% CI: 3.4–8.1), corresponding to a 52% reduction in the relative risk of progression or death (HR = 0.48; 95% CI: 0.31–0.75). Cabozantinib also demonstrated a higher overall response rate (ORR), a secondary endpoint, at 30% compared with 12% for sunitinib. The cabozantinib arm showed a lower rate of early progression compared with the sunitinib arm (19% vs. 26%, respectively). Median overall survival (mOS) was 26.0 months with cabozantinib (95% CI: 14.4–not reached) compared to 21.2 months with sunitinib (HR = 0.80; 95% CI: 0.53–1.21), although the difference did not reach statistical significance. Both groups reported comparable rates and severity of adverse events, with grade 3–4 toxicities observed in 67% of cabozantinib-treated patients and 68% of those receiving sunitinib, resulting in a similar overall quality of life [5, 6].

The results of the CABOSUN trial have been corroborated by real-world studies demonstrating the effectiveness of cabozantinib in routine clinical practice. Although most available data concern its use in second and later lines of therapy, emerging evidence also supports its efficacy in the first-line setting. In real-world data, the reported mPFS ranges from 7.8 to 10.2 months, with an average overall response rate (ORR) of approximately 30%, and a median overall survival (OS) of 14.7 to 26.2 months. Importantly, the profile and severity of adverse effects were comparable to those observed in the CABOSUN trial, despite the fact that patients treated in routine practice generally present with poorer performance status and less favorable baseline characteristics than those typically included in clinical studies. Although TKI monotherapy remains one of the standards of care in patients with metastatic mRCC, a meta-analysis of phase II and III clinical trials was conducted to evaluate its efficacy and safety. The analysis included data from 12 trials comprising 4,243 patients for efficacy assessment and 12 trials with 4,306 patients for toxicity evaluation. The primary objectives of the meta-analysis were to evaluate mPFS and to determine the proportion of patients who experienced grade 3–4 adverse events according to CTCAE criteria while receiving first-line treatment with sunitinib, pazopanib, sorafenib, cabozantinib, or tivozanib. Among the agents analyzed, cabozantinib demonstrated the highest probability of efficacy in terms of PFS (P = 0.9481), followed by sunitinib, pazopanib, and tivozanib. In indirect comparisons, cabozantinib demonstrated similar PFS outcomes to other TKIs, except for sorafenib. Regarding treatment-related toxicity, cabozantinib was associated with favorable tolerability, with a comparatively lower likelihood of grade 3–4 CTCAE adverse events [7–9]. Further advances in the treatment of mRCC are linked to the use of cabozantinib in combination with nivolumab, as demonstrated in the CheckMate 9ER trial. This phase III study included 651 previously untreated patients (excluding those who had received perioperative adjuvant or neoadjuvant therapy), who were randomized to receive either cabozantinib (40 mg daily) plus nivolumab (240 mg every 2 weeks; n = 323) or standard sunitinib monotherapy (50 mg daily for 4 weeks followed by 2 weeks off; n = 328). Eligibility criteria included the presence of measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST), the absence of clinically significant laboratory abnormalities or brain metastases, and a Karnofsky performance status ≥70%. After a median follow-up of 32 months, mPFS was 16.6 months in the cabozantinib–nivolumab arm compared with 8.3 months in the sunitinib arm (HR = 0.51; 95% CI: 0.41–0.64; p <0.001).

An objective response was achieved in 55.7% of patients in the cabozantinib–nivolumab arm compared with 27.1% in the sunitinib group (p <0.001), including a doubling of the complete response rate (12.4% vs. 5.2%). The combination regimen also improved mOS, reaching 37.7 months versus 34.3 months with sunitinib (HR = 0.70; 95% CI: 0.55–0.90). Importantly, the benefits of combi-

nation therapy in terms of PFS, ORR, and overall survival (OS) were observed across all patient subgroups, with the most pronounced effect in those with positive PD-L1 expression. The advantage was also evident across all IMDC prognostic categories, particularly in patients with intermediate or unfavorable prognosis (tab. 1). Both treatment arms showed similar rates of adverse events, including grade ≥3 toxicities (75.5% in the combination arm vs. 70.6% with sunitinib). However, patients receiving the combination reported improved quality of life, as measured by the FKSI-19 questionnaire, along with a significantly longer time to deterioration in overall condition (HR = 0.70; 95% CI: 0.56–0.86) [10, 11].

ADDITIONAL ACTIVITIES

Cabozantinib, a small-molecule second-generation TKI, is distinguished by unique characteristics relevant to treatment selection. One notable feature is its tropism for metastatic bone lesions, observed across tumor types, which leads to inhibition of osteoclast activity and a reduction in the RANKL/osteoprotegerin ratio in osteoblasts. This mechanism may slow or even halt the progression of bone metastases and, over time, enhance overall treatment efficacy. Such benefits were confirmed in the METEOR and CABOSUN trials. In the CABOSUN study, the hazard ratio (HR) for mPFS was 0.54 (95% CI: 0.31–0.95) in patients with bone metastases, compared with 0.78 (95% CI: 0.48–1.21) in those without bone metastases. Both trials also demonstrated a trend toward improved OS in patients with bone metastases, showing a 53% reduction in the risk of death (HR = 0.47; 95% CI: 0.26–0.87; p = 0.02), compared with a 44% reduction in patients without bone involvement (HR = 0.56; 95% CI: 0.40–0.79; p = 0.001) [11, 12]. The inclusion of cabozantinib may also be considered in patients with brain metastases. Data from previous clinical trials and real-world evidence (RWE) suggest significant efficacy of the drug in this setting, leading to a multicenter study involving 88 patients with RCC and brain metastases. In cohort A, following prior local treatment (15% surgery and 70% whole-brain radiotherapy [WBRT] or stereotactic body radiotherapy [SBRT]), patients received cabozantinib monotherapy. In cohort B (55 patients), systemic cabozantinib was administered concurrently with radiotherapy for brain lesions. Promising results were observed in both cohorts: in cohort A, 55% of patients achieved a central nervous system (CNS) response and 48% a response at extracranial sites, with a mOS of 15 months. In cohort B, CNS responses were observed in 47% of patients and extracranial responses in 38%, with an mOS of 16 months. At the same time, no increase in adverse events was observed in either cohort compared with overall data, supporting both the feasibility and safety of concomitant cabozantinib therapy with radiotherapy, as well as the effectiveness of this combined approach [13, 14]. When selecting therapy for patients with advanced RCC, it is essential to consider the general condition, clinical profile, and age of the patient. Compared with first-generation TKIs, cabozantinib demonstrates higher response rates and provides better control of disease symptoms, which may ultimately translate into significant improvements in overall condition and quality of life. The prolonged duration of treatment response is also a clinically relevant feature. In the CheckMate 9ER study, the time to onset of response was significantly shorter in the combination arm (2.8 months vs. 4.4 months with sunitinib), while the duration of response was markedly longer (20.2 months vs. 11.5 months). Importantly, concomitant systemic diseases are usually not a contraindication to cabozantinib therapy; however, optimal management of comorbidities prior to treatment initiation is advisable, and multidisciplinary consultations are often beneficial in this regard. As with all TKIs, the management of hypertension, diabetes, or thyroid dysfunction is significantly more effective when overseen by the appropriate specialist. In this context, the need for a cardiology consultation prior to initiating treatment becomes particularly important. The patient's age is not a contraindication to cabozantinib use nor an indication for initial dose reduction. However, in daily practice, it may be reasonable to start treatment at 40 mg/24 h, a dose consistent with real-world experience and close to the mean dose reported in the METEOR and CABOSUN studies. The nature and severity of cabozantinib-related adverse effects are typical for TKIs, but its long half-life (120 h) results in slower resolution of toxicities after treatment discontinuation compared to other TKIs, which may pose additional challenges in elderly patients [1, 6, 15–17]. In addition to the criteria outlined above, papillary renal cell carcinoma (pRCC) should be considered in the profile of patients eligible for first-line cabozantinib therapy. Cabozantinib is regarded as the treatment of choice in this histopathological subtype. However, under current national B.10 program regulations, its use is limited to patients with intermediate or unfavorable prognostic profiles. The superiority of cabozantinib over other agents has been demonstrated in several clinical trials that included patients with papillary or other non-clear cell RCCs. In particular, the results of the PAPMET trial clearly established cabozantinib as the most effective treatment option for patients with pRCC [18, 19].

CONCLUSIONS

The improved efficacy of systemic therapies for patients with mRCC necessitates greater attention to overall health status, treatment safety, and quality of life, which are closely interrelated. Most patients with renal cancer are elderly (60–70 years) and frequently present with significant comorbidities, including car-

diovascular disease (hypertension, arrhythmias, coronary artery disease), metabolic disorders (diabetes, atherosclerosis, obesity, gout), and chronic kidney disease. These conditions substantially impact both general health and treatment tolerance. Complications arising from treatment-related side effects may compromise the continuity and optimal intensity of systemic therapy. In the management of mRCC with TKIs, the therapeutic strategy emphasizes administering treatment at full intensity while striving to preserve quality of life. Evidence clearly demonstrates that maintaining higher drug doses enhances treatment efficacy; however, this benefit is frequently accompanied by a greater incidence of adverse effects. Most evidence on this relationship comes from studies involving TKIs. Notably, among the most common adverse effects of TKIs, such as hypertension, thyroid dysfunction, hematologic abnormalities, and dermatologic toxicities, a correlation has been observed between their occurrence and severity and the magnitude of response to treatment. In such cases, appropriate management focused on maintaining treatment intensity is crucial, with individualized drug selection playing a key role. This approach reduces the need for treatment delays or dose reductions, thereby prolonging the duration of active therapy and supporting a higher quality of life for patients.

Table 1. Progression-free survival, objective response rate, and overall survival outcomes in the CheckMate 9ER trial, presented for the intent-to-treat population and stratified by IMDC risk groups.

Patients/IMDCs	PFS cabozantinib + nivolumab vs sunitinib (months)	ORR/CR cabozantinib + nivolumab vs sunitinib (%)	OS cabozantinib + nivolumab vs sunitinib (months)
Beneficial	21.4 vs. 13.9 HR = 0.75 95% CI: 0.50–1.13	66% vs. 44% 9% vs 10%	NR vs. 47.6 HR = 0.94 95% CI: 0.46–1.92
Indirect	17.5 vs. 8.5 HR = 0.61 95% CI: 0,48–0,79	56% vs. 29% 11% vs. 3%	49.5 vs. 36.2 HR = 0.74 95% CI: 0.56–1.02
Unfavorable	9.9 vs. 4.2 HR = 0.36 95% CI: 0.23–0.56	38% vs. 10% 5% vs. 1%	34.8 vs. 10.5 HR = 0.45 95% CI: 0.32–0.76
All groups prognostic	16.4 vs. 8.4 HR = 0.58 95% CI: 0.29–0.58	55.8% vs. 28.4% 12.4% vs. 5.2%	46.5 vs. 36.0 HR = 0.77 95% CI: 0.65–0.95

CI – confidence interval; CR – complete response; HR – hazard ratio; IMDC – International Metastatic Renal Cell Carcinoma Database Consortium; ITT – intention-to-treat analysis; ORR – overall response rate; OS – overall survival; PFS – progression free survival; NR – not reached.

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