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Original Research Article

Cabozantinib for the Treatment of Advanced Renal Cell Carcinoma in Treatment-Naive Adults

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Abstract: Cabozantinib, a potent oral tyrosine kinase inhibitor, has redefined the therapeutic landscape of advanced renal cell carcinoma (RCC), particularly for treatment-naive patients. By targeting multiple key pathways involved in tumor proliferation and angiogenesis, cabozantinib has demonstrated significant efficacy in prolonging progression-free survival and improving objective response rates compared to standard therapies. This article reviews the pharmacologic characteristics, pivotal clinical trials, efficacy, safety, and practical considerations of cabozantinib in the first-line management of advanced RCC, summarizing current evidence from clinical and real-world studies.

Keywords: Cabozantinib, Advanced renal cell carcinoma (RCC), Tyrosine kinase inhibitor (TKI), First-line therapy, Progression-free survival.

INTRODUCTION

Renal cell carcinoma is a prevalent malignancy with a rising global incidence, and a substantial portion of patients present with advanced or metastatic disease. Historically, treatment options for advanced RCC were limited and offered modest improvements in survival. The introduction of targeted therapies, such as cabozantinib, has markedly shifted first-line treatment paradigms, particularly for patients with intermediate and poor risk.

Mechanism of Action

Cabozantinib is an oral agent that inhibits multiple tyrosine kinases, including:

- VEGF receptors (primarily VEGFR2)
- MET
- AXL

By restricting both VEGF-mediated angiogenesis and MET/AXL-driven tumor progression and resistance, cabozantinib exerts robust anti-tumor and anti-metastatic effects[1][2].

CLINICAL EVIDENCE

Pivotal Trials

CABOSUN Phase II Trial

- **Population:** 157 previously untreated patients with advanced or metastatic clear cell RCC of intermediate or poor risk.

- **Design:** Randomized, open-label, comparing cabozantinib (60mg daily) versus sunitinib (50mg daily; 4 weeks on, 2 weeks off).
- **Results:**
  - **Progression-Free Survival (PFS):**
    - Median PFS: 8.6 months (cabozantinib) vs. 5.3 months (sunitinib)
    - Hazard ratio (HR): 0.48 (95% CI: 0.31–0.74)[1][3]
  - **Objective Response Rate (ORR):**
    - 33% with cabozantinib vs. 12% with sunitinib
  - **Overall Survival (OS):**
    - Trend favoring cabozantinib (HR: 0.80), but not statistically significant.

Meta-Analyses & Comparative Studies

Systematic reviews confirm cabozantinib's superiority in progression-free survival and ORR over other tyrosine kinase inhibitors (TKIs), notably in intermediate-/poor-risk subgroups[4][2][5]. Network meta-analyses show favorable hazard ratios for PFS and OS when compared with sunitinib, sorafenib, and other agents in these risk categories[4].

Real-World Data

Observational cohorts confirm cabozantinib's effectiveness in clinical practice, with therapy persistence and tolerability matching that observed in trials[6][7].

Efficacy Summary Table

Endpoint	Cabozantinib	Sunitinib	HR (Cabozantinib vs. Sunitinib)
Median PFS (months)	8.6	5.3	0.48
ORR (%)	33	12	—
Median OS (months)	26.6	21.2	0.80 (NS)

Safety and Tolerability

Cabozantinib demonstrates a side effect profile in line with other TKIs. Common adverse events include[8][9][3]:

- Diarrhea
- Fatigue
- Hypertension
- Hand-foot syndrome (palmar-plantar erythrodysesthesia)
- Nausea or anorexia
- Mucositis

Most toxicities are grade 1/2 and manageable with symptomatic measures, temporary interruptions, or dose reductions (recommended stepwise reductions in 20mg increments when needed). Proactive management and regular monitoring are essential for optimal adherence and outcomes.

Patient Selection

Guidelines support cabozantinib as:

- **First-line therapy** for intermediate-/poor-risk untreated advanced RCC, especially when immunotherapy is contraindicated or not feasible[3].
- **Second-line option** post-immunotherapy or TKIs.

Current data are strongest for the intermediate and poor prognostic groups, determined by standardized risk stratification tools (e.g., IMDC/Heng criteria)[3].

Practical Considerations

- **Administration:** Cabozantinib is administered orally, once daily, on an empty stomach.
- **Monitoring:** Regular assessment of blood pressure, electrolytes, and signs of hand-foot syndrome is recommended.
- **Drug Interactions:** Caution with CYP3A4 modulators.

Cost-Effectiveness

While associated with higher drug acquisition costs, cabozantinib delivers longer periods of disease control and may reduce resource utilization related to disease progression compared to older agents[3].

Future Directions

Ongoing research explores cabozantinib as part of combination regimens, particularly with immunotherapies (checkpoint inhibitors), and in special populations.

Figure 1. Progression-Free Survival: Cabozantinib vs. Sunitinib (CABOSUN Study)

![A Kaplan-Meier curve could depict separation in PFS favoring cabozantinib over sunitinib, as observed in pivotal phase II data.]

Figure 2. Most Frequent Grade 3–4 Adverse Events with Cabozantinib

Adverse Event	Cabozantinib (%)	Sunitinib (%)
Hypertension	28	23
Diarrhea	10	11
Fatigue	6	8
Hand–Foot Syndrome	8	4

DISCUSSION

Cabozantinib addresses key escape pathways implicated in TKI resistance, providing enhanced efficacy in both systemic disease control and bone metastasis. Its manageable safety profile and oral route offer convenience, whereas toxicity management and patient education remain critical. The ideal positioning of cabozantinib within the evolving RCC treatment landscape is as a potent targeted agent for patients unable to receive or tolerate immunotherapy, but its role may continue to expand with ongoing trials.

CONCLUSION

Cabozantinib is a highly active first-line targeted therapy for treatment-naive adults with advanced RCC, with robust evidence for improving progression-free survival and response rates over standard TKIs. Safe, tolerable, and convenient, it occupies a central place in RCC management, particularly among patients with intermediate and poor prognosis. Individualized, risk-adapted therapy selection and supportive care are fundamental for optimizing outcomes.

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