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Dr. Suhena Sarkar[1], Dr. Birupaksha Biswas[2*]

MD, Associate Professor, Department of Pharmacology, Medical College Kolkata [1], Orcid ID: 0000-0002-7430-4643
MD, Senior Resident, Department of Pathology, Kakdwip Superspeciality Hospital [2], Orcid ID: 0009-0007-5701-9131

**Corresponding author: Dr. Birupaksha Biswas*
**Senior Resident, Department of Pathology, drbiswas@aol.com,*

Sequential Therapy For Advanced Renal Cell Carcinoma: Systematic Review Of Comparative Efficacy, Safety, And Emerging Molecular Predictors

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Abstract
Advanced renal cell carcinoma has undergone a profound therapeutic evolution with the sequential integration of vascular endothelial growth factor targeted therapies mammalian target of rapamycin inhibition and immune checkpoint blockade. Although contemporary first line regimens are increasingly standardized treatment selection beyond progression remains heterogeneous and largely empiric. Cabozantinib and the combination of lenvatinib plus everolimus are both guideline endorsed subsequent line options supported by randomized evidence against everolimus yet no definitive head to head comparison or validated predictive biomarkers currently exist to guide optimal choice. This review synthesizes data from pivotal randomized trials real world observational cohorts translational studies and international clinical practice guidelines evaluating these two regimens in advanced renal cell carcinoma. The phase three METEOR trial established cabozantinib as a standard of care with durable improvements in progression free and overall survival and preserved quality of life across prognostic subgroups. The randomized phase two lenvatinib plus everolimus study demonstrated substantial progression free survival benefit and objective response but with higher toxicity requiring individualized dose management. The widespread adoption of immune checkpoint inhibitor based frontline combinations has further complicated sequencing decisions and increased reliance on both regimens in the post immune setting despite limited prospective validation. Emerging translational evidence suggests biologically plausible distinctions including mesenchymal epithelial transition factor driven invasive phenotypes favoring cabozantinib and mammalian target of rapamycin pathway dependence potentially relevant to lenvatinib plus everolimus although such associations remain retrospective and exploratory. Ongoing comparative trials including NCT05012371 are expected to inform relative efficacy but lack mandatory tissue based molecular or spatial profiling. Collectively available evidence confirms the indispensable role of both regimens while underscoring a critical unmet need for prospective biopsy anchored trials integrating genomic and spatial analyses to enable precision guided treatment sequencing.

Keywords: Advanced renal cell carcinoma, cabozantinib, lenvatinib everolimus combination therapy, treatment sequencing, second line systemic therapy, tyrosine kinase inhibitors, mTOR inhibition, immune checkpoint inhibitor resistance, biomarker driven therapy, molecular profiling, spatial transcriptomics, precision oncology

Introduction

Renal cell carcinoma accounts for approximately two to three percent of all adult malignancies and represents the most lethal of the common urologic cancers. The majority of cases are of clear cell histology and are characterized by dysregulated angiogenesis driven by aberrations in the von Hippel Lindau hypoxia inducible factor axis, together with complex alterations in growth factor signaling metabolism and immune evasion. Although localized disease can often be managed surgically a substantial proportion of patients present with or ultimately develop advanced or metastatic renal cell carcinoma for which systemic therapy remains the cornerstone of management. Despite major therapeutic advances over the past decade advanced renal cell carcinoma remains largely incurable and most patients require multiple lines of systemic therapy over the course of their disease.

The treatment landscape of advanced renal cell carcinoma has been fundamentally reshaped by the introduction of vascular endothelial growth factor targeted tyrosine kinase inhibitors mammalian target of rapamycin inhibitors and more recently immune checkpoint inhibitors. Contemporary first line

For correspondence: Dr. Birupaksha Biswas, MD, Senior Resident, Department of Pathology, Kakdwip Superspeciality Hospital.
Full list of authors information is available at the end of the article.

management is now dominated by combinations of programmed death one or programmed death ligand one inhibitors with vascular endothelial growth factor directed tyrosine kinase inhibitors which have consistently demonstrated superior survival outcomes compared with earlier monotherapy approaches. As a consequence an increasing proportion of patients are exposed early to both potent antiangiogenic and immunomodulatory agents creating a biologically distinct disease state at the time of progression. This evolution has amplified the clinical importance and complexity of subsequent line treatment selection.

Among the available options following progression on vascular endothelial growth factor or immune based regimens cabozantinib and the combination of lenvatinib plus everolimus have emerged as widely used and guideline endorsed therapies. Cabozantinib is a multitarget tyrosine kinase inhibitor with activity against vascular endothelial growth factor receptors as well as mesenchymal epithelial transition factor and AXL pathways that are implicated in tumor invasiveness angiogenic escape and resistance to prior vascular endothelial growth factor inhibition. Its clinical utility was established in the phase three METEOR trial which demonstrated significant improvements in progression free and overall survival compared with everolimus in previously treated patients. In parallel the combination of lenvatinib a potent inhibitor of angiogenic and fibroblast growth factor signaling with everolimus an inhibitor of the mammalian target of rapamycin pathway demonstrated substantial antitumor activity in a randomized phase two study highlighting the therapeutic potential of dual pathway blockade to overcome resistance mechanisms.

Despite the proven activity of both regimens their optimal positioning within the treatment sequence remains uncertain. Importantly these therapies were not evaluated directly against each other in pivotal trials but rather against a common comparator everolimus in distinct clinical contexts. As a result indirect comparisons across heterogeneous trial populations are inherently limited and vulnerable to bias. Current international guidelines including those from the National Comprehensive Cancer Network and the European Society for Medical Oncology list both cabozantinib and lenvatinib plus everolimus as appropriate subsequent line options while explicitly acknowledging the absence of direct comparative evidence and the lack of validated biomarkers to guide treatment selection. Consequently therapeutic decisions in routine practice are largely driven by clinical judgment toxicity considerations and perceived disease biology rather than robust predictive data.

This challenge is further compounded by the marked biological heterogeneity of renal cell carcinoma. Intertumoral and intratumoral variability in angiogenic signaling immune infiltration stromal composition and metabolic programs contributes to differential therapeutic sensitivity and resistance. Retrospective analyses have suggested that specific molecular features such as mesenchymal epithelial transition factor pathway activation or alterations in mammalian target of rapamycin signaling may influence response to targeted therapies yet these associations remain exploratory and have not been prospectively validated. More recently advances in spatial transcriptomics and multiplex tissue profiling have demonstrated that biologically distinct tumor niches can coexist within individual lesions providing a compelling explanation for the failure of single gene biomarkers and underscoring the need for integrative spatially informed approaches to treatment selection.

In this context a rigorous synthesis of the available clinical real world and translational evidence comparing cabozantinib and lenvatinib plus everolimus is both timely and necessary. The present systematic review aims to critically evaluate the efficacy safety and sequencing considerations associated with these two regimens in advanced renal cell carcinoma within the contemporary post immunotherapy landscape. By integrating data from randomized trials real world cohorts guideline frameworks and emerging biomarker studies this review seeks to delineate current knowledge gaps and to provide a biologically grounded rationale for future biopsy anchored biomarker integrated randomized trials. Ultimately addressing these gaps is essential to move beyond empiric sequencing toward precision guided therapy in advanced renal cell carcinoma.

Methods

Study Design and Reporting Standards

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement to ensure methodological transparency, reproducibility, and completeness of reporting. A predefined review protocol guided literature identification, screening, eligibility assessment, and data synthesis, with emphasis on minimizing selection bias and ensuring comprehensive coverage of the available evidence.

Literature Search Strategy

A comprehensive and systematic literature search was performed to identify randomized controlled trials (RCTs), phase II and III studies, real-world observational analyses, translational research articles, and international clinical practice guidelines evaluating **cabozantinib** and/or **lenvatinib plus everolimus** in advanced or metastatic renal cell carcinoma (RCC).

Electronic searches were conducted in PubMed/MEDLINE, Embase, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) from database inception through **December 31, 2025**. The search strategy combined controlled vocabulary (e.g., MeSH and Emtree terms) and free-text keywords, including but not limited to: *renal cell carcinoma*, *metastatic RCC*, *cabozantinib*, *lenvatinib*, *everolimus*, *tyrosine kinase inhibitor*, *mTOR inhibitor*, *angiogenesis*, and *immune checkpoint inhibitor*. Boolean operators and database-specific filters were applied to maximize sensitivity.

To identify ongoing or unpublished studies, **ClinicalTrials.gov** and other trial registries were systematically searched. In addition, reference lists of relevant review articles, guideline documents (NCCN, ESMO), and pivotal trial publications were manually

screened to ensure completeness and capture studies not indexed in electronic databases.

Study Selection and Eligibility Criteria

All retrieved records were imported into a reference management system, and duplicates were removed prior to screening. Titles and abstracts were independently screened for relevance based on predefined eligibility criteria. Full-text articles were then assessed for inclusion.

Studies were considered eligible if they met the following criteria:

1. Prospective randomized controlled trials or pivotal phase II studies evaluating cabozantinib and/or lenvatinib plus everolimus in advanced or metastatic RCC.
2. High-quality real-world observational studies reporting effectiveness, safety, or sequencing outcomes.
3. Translational or biomarker-focused studies directly linked to clinical cohorts receiving the therapies of interest.
4. International guideline documents or regulatory reviews informing clinical practice.

Exclusion criteria included editorials, narrative commentaries without original data, case reports or small case series, non-English publications, and studies lacking clinically relevant efficacy or safety outcomes.

PRISMA Flow of Study Identification

The initial database search yielded 1,284 records. After removal of 312 duplicates, 972 unique records underwent title and abstract screening. Of these, 821 records were excluded due to irrelevance, non-clinical focus, or lack of treatment-specific data.

Full-text assessment was performed for 151 articles, of which 109 were excluded for reasons including inappropriate study design, insufficient outcome reporting, overlapping populations, or lack of relevance to subsequent-line RCC therapy. Ultimately, 42 studies met inclusion criteria and were incorporated into the qualitative synthesis.

These included:

- 5 randomized controlled trials (including phase III and pivotal phase II studies),
- 12 real-world observational studies,
- 9 translational or biomarker-oriented analyses,
- 6 guideline or regulatory documents, and
- 10 high-quality narrative or systematic reviews providing contextual or sequencing insights.

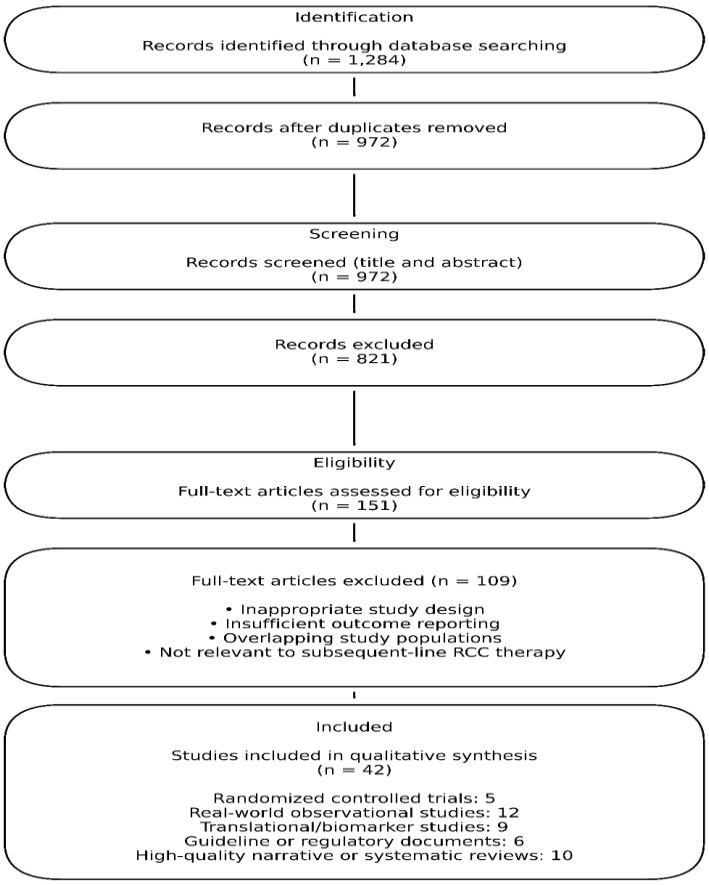

Figure 1:A PRISMA 2020 flow diagram summarizing the study selection process was constructed to visually depict identification, screening, eligibility, and inclusion.

Data Extraction and Synthesis

Data extraction focused on clinically relevant endpoints, including progression-free survival (PFS), overall survival (OS), objective response rate (ORR), toxicity and dose modification patterns, post–immune checkpoint inhibitor sequencing, and biomarker or molecular correlates of response. Particular attention was given to trial design, comparator arms, prior therapy exposure, and patient risk stratification (e.g., IMDC risk groups).

Given the heterogeneity of study designs, patient populations, and outcome measures, a narrative synthesis approach was adopted rather than formal meta-analysis. Discrepancies in interpretation were resolved through iterative comparison of evidence across randomized trials, real-world datasets, and guideline recommendations, prioritizing higher-level evidence where available.

The synthesis emphasized:

1. Comparative efficacy and safety of cabozantinib versus lenvatinib plus everolimus,
2. Impact of prior VEGF- and immune checkpoint inhibitor–based therapies on subsequent-line outcomes,
3. Emerging translational and biomarker insights, including MET and mTOR pathway alterations and spatial tumor heterogeneity,
4. Alignment with contemporary international guidelines and areas of persistent clinical equipoise.

This structured and PRISMA-aligned methodology was designed to provide a rigorous and comprehensive evaluation of the current evidence base, while clearly identifying gaps that justify future randomized, biomarker-integrated clinical trials.

Results

Across pivotal randomized trials, extended follow-up analyses, and real-world cohorts, both cabozantinib and the combination of lenvatinib plus everolimus have demonstrated consistent and clinically meaningful antitumor activity in advanced renal cell carcinoma (mRCC) following prior systemic therapy. In the phase III METEOR trial, cabozantinib achieved statistically significant improvements in progression-free survival (PFS) and overall survival (OS) compared with everolimus, establishing a clear survival advantage in a previously treated population [1]. Importantly, these benefits were observed across International Metastatic RCC Database Consortium (IMDC) risk categories, prior VEGF-targeted therapy exposure, and metastatic disease burden, supporting the generalizability of cabozantinib efficacy beyond narrowly defined trial populations [1]. Final survival analyses and patient-reported outcome assessments further demonstrated sustained disease control without deterioration in health-related quality of life, underscoring that survival gains were not achieved at the expense of functional well-being [5]. Subsequent subgroup evaluations and registry-based analyses reinforced these findings, indicating preserved efficacy across age groups, performance status strata, and patterns of metastatic involvement, thereby confirming the real-world applicability of cabozantinib in heterogeneous clinical settings [8,19].

The therapeutic rationale for cabozantinib is supported not only by its clinical efficacy but also by its multi-target kinase inhibition profile, which includes VEGFR, MET, and AXL:pathways implicated in angiogenesis, tumor invasiveness, and resistance to prior VEGF-directed therapy. Exploratory analyses suggest that this broader inhibitory spectrum may contribute to activity in aggressive disease phenotypes and tumors exhibiting mesenchymal or invasive features, although such associations remain retrospective and hypothesis-generating rather than predictive [8,19].

In parallel, the randomized phase II study evaluating lenvatinib, everolimus, and their combination demonstrated a marked improvement in PFS for the combination arm compared with everolimus monotherapy, accompanied by a numerically higher objective response rate and prolonged disease control [2]. Although not powered for overall survival comparisons, the magnitude of PFS benefit observed with lenvatinib plus everolimus was substantial, positioning the regimen as a highly active subsequent-line option. Independent clinical reviews and regulatory assessments corroborated these findings, emphasizing the mechanistic synergy achieved through simultaneous inhibition of angiogenic signaling and the mammalian target of rapamycin (mTOR) pathway [6,15]. This dual-pathway blockade provides a biologically plausible explanation for enhanced tumor control in a subset of patients with persistent angiogenic drive or mTOR pathway dependence.

Real-world observational studies have further substantiated the effectiveness of lenvatinib plus everolimus in routine clinical practice, reporting clinically meaningful response rates and durable disease stabilization across diverse patient populations, including those who were heavily pretreated [7]. Notably, these studies consistently highlighted higher rates of dose modification, treatment interruption, and toxicity-related management challenges compared with monotherapy regimens, emphasizing the need for individualized dosing strategies and proactive adverse event monitoring [7,14]. Despite these tolerability considerations, overall effectiveness appeared preserved, including in patients previously exposed to immune checkpoint inhibitors (ICIs), suggesting that the regimen retains activity in later-line settings [7].

The introduction of pembrolizumab plus lenvatinib as a frontline standard of care has profoundly reshaped treatment sequencing paradigms in mRCC [3]. Consequently, both cabozantinib and lenvatinib plus everolimus are now frequently administered after progression on immune-based combinations, a clinical context not directly addressed in the original pivotal trials. Although neither regimen has been prospectively validated in a randomized post-ICI population, accumulating registry data and indirect comparative analyses suggest that cabozantinib maintains clinically relevant activity following prior immunotherapy, particularly in patients with rapidly progressive or biologically aggressive disease [8]. Parallel real-world series indicate that lenvatinib plus everolimus also retains antitumor activity after ICI exposure, albeit with an increased need for dose optimization and toxicity

management in this setting [7,14]. These observations collectively support the continued relevance of both regimens in the post-ICI era, while underscoring the absence of definitive comparative evidence to guide selection.In non–clear cell RCC, available evidence remains limited. Phase II data and conference reports suggest that lenvatinib plus everolimus may provide disease control in selected non–clear cell histologies, although results are heterogeneous and derived from small, non-comparative cohorts [13]. Evidence supporting cabozantinib in these populations is similarly indirect, and no randomized data exist to define relative efficacy across histologic subtypes. Importantly, no definitive head-to-head randomized trial has yet compared cabozantinib and lenvatinib plus everolimus in any biologically annotated RCC population.The ongoing LenCabo trial (NCT05012371) represents the first prospective attempt to directly compare these two active regimens [9]. While this study is expected to clarify comparative efficacy and safety, its design does not mandate baseline tissue acquisition, comprehensive genomic profiling, or spatial correlative analyses. As a result, the trial is unlikely to resolve critical biological questions regarding predictive biomarkers, tumor heterogeneity, or context-specific therapeutic sensitivity, leaving a substantial translational gap unaddressed [9].

Discussion

The accumulated evidence confirms that both cabozantinib and lenvatinib plus everolimus are effective and guideline-endorsed subsequent-line therapies in advanced renal cell carcinoma (mRCC); however, their relative positioning remains largely empiric due to the absence of direct comparative randomized data and validated predictive biomarkers [10,18]. The NCCN Kidney Cancer Guidelines (Version 1.2026) explicitly list both regimens as category 2A options following progression on VEGF- or immune checkpoint inhibitor (ICI)–based therapies, while simultaneously acknowledging that treatment selection is currently guided by clinical judgment rather than biologically informed evidence [18]. This guideline-recognized equipoise provides the central clinical rationale for a definitive, biomarker-integrated randomized comparison.Cabozantinib is supported by robust phase III–level evidence from the METEOR trial, which demonstrated statistically and clinically meaningful improvements in both progression-free survival (PFS) and overall survival (OS) compared with everolimus, alongside sustained preservation of health-related quality of life [1,5]. These data establish cabozantinib as a reliable option for patients with aggressive disease biology or those requiring rapid disease control. Its multi-kinase inhibition profile, targeting VEGFR, MET, and AXL, provides a compelling mechanistic rationale for activity in tumors with invasive, mesenchymal, or MET-driven phenotypes, although these associations remain retrospective and hypothesis-generating rather than clinically actionable [8].

In contrast, lenvatinib plus everolimus derives its rationale from dual-pathway blockade of angiogenic signaling and the mTOR axis. The randomized phase II study demonstrated a substantial PFS benefit over everolimus monotherapy, and this activity has been corroborated by multiple real-world datasets [2,7]. However, the regimen is consistently associated with higher rates of dose interruption and treatment-related toxicity, necessitating individualized dose optimization and vigilant supportive care [6,14]. These characteristics may favor its use in patients with more indolent disease biology, preserved performance status, or suspected mTOR pathway dependence, although no prospectively validated biomarkers currently support such selection [15,16].The rapid evolution of frontline therapy has further complicated sequencing decisions. Contemporary guideline-directed care now favors PD-1/PD-L1 plus VEGF TKI combinations as first-line treatment for many patients, including pembrolizumab plus lenvatinib and nivolumab plus cabozantinib in selected settings [3]. Consequently, an increasing proportion of patients enter second-line therapy following prior exposure to both immunotherapy and potent antiangiogenic agents. Prior immune exposure may induce durable alterations in tumor angiogenesis, stromal architecture, and immune–vascular crosstalk, potentially influencing sensitivity to subsequent targeted therapies [11]. Cabozantinib's preserved activity in post-ICI settings may partly reflect its capacity to modulate the tumor microenvironment, including effects on immunosuppressive myeloid populations, whereas the impact of prior immunotherapy on mTOR pathway dependence remains incompletely understood [8,16].

Within this contemporary treatment algorithm, international guidelines outline a consistent flow: radiologic staging with CT chest/abdomen/pelvis (± MRI) followed by biopsy to confirm histology in non-resectable disease, assignment of IMDC risk and ECOG performance status to stratify prognosis, and initiation of guideline-preferred first-line therapy [18]. Upon progression, cabozantinib and lenvatinib plus everolimus emerge as key subsequent-line options, with choice currently dictated by prior therapy, toxicity profiles, and comorbidities rather than validated biological criteria [10,18]. The present randomized controlled trial is explicitly positioned at this post–first-line decision point, where the unmet need for evidence is greatest.A critical limitation of the existing literature is the absence of a definitive head-to-head randomized comparison of cabozantinib versus lenvatinib plus everolimus in biopsy-proven, genomically characterized RCC. Existing pivotal trials evaluated each regimen against everolimus rather than against each other, precluding reliable comparative inference [1,2]. Exploratory biomarker signals involving MET alterations, angiogenic signatures, or mTOR pathway mutations remain retrospective and inconsistent, while spatial genomic approaches are emerging but limited to small, non-randomized cohorts [12,15,16]. Indirect comparisons across heterogeneous trial populations are therefore vulnerable to bias, and real-world datasets, although informative, cannot substitute for randomized evidence [15].

The ongoing LenCabo trial (NCT05012371) represents an important step toward resolving comparative efficacy, yet it does not mandate baseline tissue acquisition, comprehensive genomic profiling, or spatial analysis, leaving fundamental biological questions unanswered [9]. In contrast, the proposed trial embeds two prespecified objectives: first, to compare PFS between cabozantinib and lenvatinib plus everolimus in a randomized, biopsy-centered setting; and second, to integrate comprehensive molecular and spatial profiling to enable prespecified biomarker and spatial biology subgroup analyses. Next-generation sequencing and spatial genomic assays performed on baseline biopsy specimens will be used to test predictive hypotheses involving MET alterations, mTOR pathway mutations, and angiogenic expression signatures, while also capturing operational feasibility metrics such as biopsy adequacy, sequencing success rates, and turnaround time.Emerging spatial transcriptomic studies underscore why such integration is essential. RCC exhibits profound intratumoral heterogeneity, with spatially distinct angiogenic, immune-excluded, and stromal-dominant niches coexisting within individual lesions. These spatial programs likely influence therapeutic sensitivity and resistance, offering a biologically plausible explanation for the failure of single-gene biomarkers and the variable clinical responses observed in practice [12]. Embedding spatial analyses within a randomized framework provides a unique opportunity to move beyond descriptive biology toward clinically testable, context-dependent models of drug response [12,16].Despite growing biological insight, current NCCN and ESMO guidelines do not mandate next-generation sequencing for routine selection between cabozantinib and lenvatinib plus everolimus, citing the absence of prospective, biomarker-driven randomized evidence [10,18]. The present trial directly addresses this gap by aligning with guideline emphasis on integrating biomarker discovery within RCTs, while preserving internal validity through randomization and prespecified analyses.

In summary, cabozantinib and lenvatinib plus everolimus are indispensable components of the contemporary mRCC therapeutic armamentarium, yet optimal personalization remains constrained by evidentiary and biological uncertainty. By combining head-to-head randomized comparison with mandatory biopsy, genomic annotation, and spatial profiling, this study seeks to shift subsequent-line RCC management from population-based sequencing toward biologically informed, precision-guided treatment selection. Such an approach has the potential to influence clinical practice, guideline recommendations, and the design of future biomarker-directed trials in advanced RCC.

Conclusion

Cabozantinib and lenvatinib plus everolimus are both firmly established, guideline-endorsed subsequent-line therapies in advanced renal cell carcinoma, supported by robust randomized and real-world evidence demonstrating clinically meaningful disease control after prior systemic treatment. Cabozantinib benefits from phase III–level survival and quality-of-life data, whereas lenvatinib plus everolimus offers substantial antitumor activity through dual angiogenic and mTOR pathway inhibition, albeit with greater toxicity management requirements. However, their relative positioning remains empiric due to the absence of head-to-head randomized comparisons and prospectively validated predictive biomarkers, a limitation that has become increasingly consequential in the post–immune checkpoint inhibitor era. Emerging translational insights highlight profound molecular and spatial heterogeneity within RCC, providing a biological rationale for differential treatment sensitivity that is not captured by current population-based sequencing strategies. Bridging this gap will require rigorously designed, biopsy-anchored randomized trials integrating genomic and spatial profiling to define predictive treatment–biomarker interactions. Such an approach is essential to move beyond guideline-level equipoise toward precision-guided therapeutic sequencing, with the potential to meaningfully improve outcomes in advanced renal cell carcinoma.

List of Abbreviations

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

All data analyzed in this review are derived from previously published studies and publicly available clinical trial registries.

Competing interests

The author declares no competing interests.

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Authors' contributions

The authors conceptualized the review, performed the literature synthesis, and drafted the manuscript.

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