Cabozantinib in Renal Cell Carcinoma: Clinical Insights and Future Directions

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ABSTRACT

This roundtable discussion, featuring leading genitourinary oncologists Dr. Thomas Hutson, Dr. Marc Matrana, and Dr. Michael Serzan, delves into the multifaceted role of cabozantinib, a multi-targeted tyrosine kinase inhibitor, in the evolving treatment landscape of advanced and metastatic renal cell carcinoma (RCC). The experts provide clinical insights into cabozantinib's attractiveness as a therapy, highlighting its broad applicability across RCC histologies (including non-clear cell), established efficacy in both treatment-naïve (CABOSUN trial demonstrating superiority over sunitinib in intermediate- and poor-risk patients) and previously treated settings (METEOR trial showing improved progression-free survival compared to everolimus), and its synergistic potential in combination with immune checkpoint inhibitors (e.g., cabozantinib plus nivolumab demonstrating a median PFS of 16.6 months in CheckMate 9ER versus 8.3 months with sunitinib).

The discussion addresses the strategic question of optimal timing for cabozantinib use, with a consensus towards utilizing it earlier in the treatment course, particularly in the first-line setting for patients with aggressive disease, bulky tumors, or bone metastases, rather than reserving it solely for later lines. Practical guidance on managing cabozantinib's toxicity profile is provided, emphasizing proactive strategies such as dose reductions (observed in over 80% of patients in CheckMate 9ER, achieving high disease control despite lower average dosing), short drug holidays, and multidisciplinary supportive care to maintain tolerability and quality of life.

Furthermore, the roundtable explores real-world examples of cabozantinib's clinical impact and discusses sequencing strategies with other available therapies, including lenvatinib-everolimus and HIF inhibitors. Finally, the experts offer perspectives on the future directions of cabozantinib in ongoing and upcoming clinical trials, such as the PEDIGREE trial investigating its role following ipilimumab-nivolumab, combinations with HIF inhibitors, and potential in neoadjuvant settings, alongside the ongoing quest for reliable predictive biomarkers in RCC. The key takeaways emphasize cabozantinib's versatility, the importance of early utilization for optimal disease control, and the need for creative toxicity management to maximize its therapeutic benefit for RCC patients.

INTRODUCTION

The treatment landscape for advanced and metastatic renal cell carcinoma (RCC) has evolved dramatically over the past two decades, transitioning from limited options like interleukin-2 (IL-2) and interferon-alpha to a robust armamentarium of targeted therapies and immune checkpoint inhibitors (ICIs)[1]. Among these, cabozantinib, a multi-targeted tyrosine kinase inhibitor (TKI), stands out for its versatility, efficacy, and established role across various RCC histologies and treatment settings. Its ability to inhibit key pathways, including vascular endothelial growth factor receptor (VEGFR), MET, and AXL, has made it a cornerstone in both clear cell and non-clear cell RCC management[2].

In this roundtable discussion, hosted by the Kidney Cancer Journal, three renowned genitourinary oncologists explored cabozantinib's clinical applications, addressing critical questions about its use, toxicity management, sequencing strategies, and future potential. Thomas Hutson, DO, PharmD, PhD, Editor-in-Chief of the Kidney Cancer Journal and Director of the Texas Tech University Health Sciences Center Cancer Center, moderated the session. Dr. Hutson, a practicing oncologist with extensive experience in RCC, was joined by Marc Matrana, MD, Professor of Internal Medicine at the University of Queensland Medical School and a clinician at Ochsner Health specializing in genitourinary and gastrointestinal malignancies, and Michael Serzan, MD, a medical oncologist at the Lank Center for Genitourinary Oncology at Dana-Farber Cancer Institute and Instructor of Medicine at Harvard Medical School, with expertise in kidney, bladder, prostate, and testicular cancers. Together, they provided a comprehensive analysis of cabozantinib's role, offering practical guidance for oncologists and HCPs.

What Makes Cabozantinib an Attractive Therapy?

Dr. Hutson initiated the discussion with a foundational question: "What makes cabozantinib an attractive therapy in your clinical experience, and how do you select it for patients? Are there specific criteria?" This prompted a detailed exploration of cabozantinib's appeal, rooted in its extensive clinical evidence and practical utility.

Dr. Serzan emphasized the drug's versatility and depth of experience: "Cabozantinib's appeal lies in its remarkable breadth of application. The CABOSUN trial,

Figure 1. A screenshot from roundtable webinar discussion organized by Kidney Cancer Journal.

published in 2016, established cabozantinib's efficacy as a single agent in treatment-naïve clear cell RCC, outperforming sunitinib in patients with intermediate- and poor-risk disease[3]. Since then, we've seen its role expand in combinations with nivolumab in the first-line metastatic setting. In CheckMate 9ER, cabozantinib plus nivolumab demonstrated a median progression-free survival (PFS) of 16.6 months compared to 8.3 months with sunitinib[4]. Additionally, cabozantinib has demonstrated efficacy in nonclear cell RCC as both a single agent and in combination with nivolumab[5,6]. Lastly, cabozantinib has been investigated as a component of triplet therapy with nivolumab and ipilimumab in first line metastatic ccRCC[7]" He highlighted subset analyses showing efficacy in challenging clinical scenarios, such as patients with liver, bone, and brain metastases, where cabozantinib's multi-targeted profile offers advantages over more selective TKIs[8,9]. "When selecting cabozantinib, I focus on patients needing rapid disease control—those with aggressive disease or specific metastatic patterns. Cabozantinib's therapeutic window is well-understood, and our nurse practitioners and physician assistants, are familiar with adverse effect management, making it an appealing practical choice."

Dr. Matrana echoed this enthusiasm, describing cabozantinib as "a workhorse in our treatment algorithms, used day in and day out across RCC subtypes." He pointed to its molecular profile as a key strength: "Cabozantinib targets MET, which is particularly relevant in non-clear cell histologies like papillary RCC, alongside VEGFR and AXL[2]. I often call it a 'dirty TKI'—not a drawback, but a positive attribute. In New Orleans, we love dirty rice; similarly, this broad inhibition enhances versatility and efficacy." He selects it for patients with symptomatic disease, bulky tumors, or bone metastases, noting its National Comprehensive Cancer Network (NCCN) endorsements: Category 1 in combination with nivolumab for first-line therapy and Category 2 as a single agent based on CABOSUN[10]. "Its track record, backed by significant clinical investment, makes it a go-to option," he added.

Should Cabozantinib Be Used First-Line or Reserved for Later?

Dr. Hutson then posed a strategic question: "Do you ever feel using cabozantinib upfront could be a downfall, missing its refractory-setting efficacy from the METEOR trial? Community oncologists often reserve it for later lines—what would you tell them to consider it first-line?" This sparked a debate on optimal timing, reflecting a common clinical dilemma.

Dr. Serzan advocated for early use: "The METEOR trial solidified cabozantinib's role in refractory RCC, with a PFS of 7.4 months versus 3.8 months for everolimus[11], but I'm a big believer in deploying effective drugs upfront. We've all had patients with aggressive disease experience symptomatic disease progression, limiting our ability to use cabozantninb in later lines of therapy.. I start at typically start cabozantinib at the approved doses— 60 mg as a single agent or 40 mg with nivolumab. Once we are able to achieve disease control, then dial dosing back to manage toxicity.. Later lines can leverage more targeted TKIs like tivozanib, but missing that early window may risk worse outcomes for some patients."

Dr. Matrana agreed, emphasizing the expanded therapeutic landscape: "We're not in the old days of IL-2 and interferon with limited options. Today, we have a plethora of therapies—lenvatinib-everolimus, tivozanib, belzutifan—so I'm not worried about saving cabozantinib. Data show a nearly 50% drop-off from first to third line, meaning many patients never reach later therapies. My advice to community oncologists is to prioritize the most efficacious regimen upfront, like cabozantinib-nivolumab, especially for bulky or bone-metastatic disease where its performance is unparalleled." Dr. Hutson nodded, citing prospective and retrospective data supporting this shift toward aggressive first-line strategies, including triplets or quadruplets when warranted.

How Do You Manage Cabozantinib's Toxicity Profile?

Toxicity management was a critical focus, with Dr. Hutson asking, "How does cabozantinib's 'dirty' profile tie into toxicity challenges and advantages, like

overcoming resistance?" Dr. Matrana tied this to clinical trial insights: "CheckMate 9ER showed that over 80% of patients required dose reductions, with an average of 30 mg rather than the FDA-approved 40 mg with nivolumab. Yet, the disease control rate exceeded 90%, with an objective response rate of 55.7%[4]. This 'dirty' profile drives efficacy—hitting multiple pathways—but also increases toxicity like diarrhea, fatigue, and hypertension. I tell patients reductions are expected and effective, balancing efficacy with tolerability."

Dr. Hutson followed up: "I was surprised by cabozantinib-nivolumab's tolerability at 40 mg—what's your explanation?" Dr. Serzan offered a hypothesis: "There's potential synergy with nivolumab. Debulking tumors early may reduce disease burden, making higher doses more tolerable. My approach is proactive—short holds of 2-3 days can alleviate adverse effects such as diarrhea or fatigue, avoiding prolonged interruptions. Many of my patients are understandably anxious about holding an effective therapy, so education and setting expectations from the outset if crucial." Dr. Hutson shared his evolution: "As an author on METEOR, I expected more challenges, but I've shifted to drug holidays over reductions. Pausing maintains exposure (AUC) better than lowering doses—a new mindset with second-generation TKIs versus older agents like sunitinib."

Long-term effects prompted another question: "What about sarcopenia or weight loss in patients on cabozantinib for years?" Dr. Matrana advised, "I've seen this—a slow muscle decline despite patients feeling well. A multidisciplinary approach is key: nutrition for protein support, early palliative care for symptom control—not just end-of-life—and complementary therapies like acupuncture. Disease control often improves these effects." Dr. Serzan added, "Nephrology tracks hypertension, proteinuria, and chronic kidney disease, while nutrition ensures high-protein diets. Our complementary medicine program uses exercise and wearables to preserve quality of life—vital for long-term responders."

Where Has Cabozantinib Saved the Day, and How Do You Sequence It?

Dr. Hutson sought real-world insights: "Can you share examples where cabozantinib saved the day, and how do you sequence it across lines?" Dr. Matrana recounted, "In first-line, cabozantinib-nivolumab transforms symptomatic, bulky disease—patients go from debilitated to functional. As salvage, it's rescued cases failing second- or third-line therapies, though upfront use is now more common. Sequencing-wise, I favor lenvatinib-everolimus second-line for its mTOR mechanism, distinct from prior TKI-IO exposure, then HIF inhibitors or salvage TKIs like axitinib or tivozanib third-line. The PEDIGREE trial—cabozantinib-nivolumab post-ipilimumab-nivolumab—is a clever way to optimize response and duration."

Dr. Serzan shared a dramatic case: "I always think about a patient of mine with sarcomatoid RCC who we treated with nivolumab plus ipilimumab followed by cytorductive nephrectomy. Unfortunately shortly after surgery, he experienced rapidly recurrent disease with formation of a tumor-bowel fistula which caused a symptomatic GI bleed with a hemoglobin of 7. Acknowledging the difficulty of the situation, we decided to start cabozantinib 60mg while he was inpatient with the goal of attaining disease control. Within just a few days his symptoms improved, GI bleeding resolved, and now approximately six months later, he's thriving on 60 mg—a testament to its rapid control. I sequence cabozantinib-nivolumab first-line for response-driven cases, followed by lenvatinib-everolimus, then newer agents like tivozanib or belzutifan in later lines, adjusting based on prior TKI exposure."

Where Is Cabozantinib Headed in Future Trials?

Looking forward, Dr. Hutson asked, "Where do you see cabozantinib fitting in upcoming trials at ASCO, SITC, or ESMO?" Dr. Serzan highlighted PEDIGREE: "This trial randomizes patients with stable disease or partial response after four doses of ipilimumab-nivolumab to cabozantinib-nivolumab versus nivolumab alone, asking if early cabozantinib boosts outcomes. It's a massive, multi-site effort that could

further redefine cabozantinib's role in our treatement paradigm. I'm also excited for cabozantinib-HIF inhibitor combinations—targeting several molecules within the HIF-VEGF pathway potentially leading to durable disease control and low rates of progressive disease. I'm also excited to see if cabozantinib-baded combinations can improve neoadjuvant therapy for patients with a large primary or tumor thrombi, which is an area where we are lagging behind in RCC compared to melanoma or bladder cancer."

Dr. Matrana agreed on combinations: "HIF-alpha inhibitors are just beginning—we've seen belzutifan as a single agent, but paired with cabozantinib, they could shine. My frustration is weak comparator arms like sunitinib, outdated since TKI-IO became standard. I would love trials pitting cabozantinib-nivolumab against newer regimens." Dr. Hutson envisioned innovation: "Cabozantinib shrinks tumors to a nadir in 3-6 months, yet we keep patients on until progression or toxicity. I hope for designs adding T-cell engagers or CAR-T at that point, pushing complete responses beyond the minority we achieve now."

On biomarkers, Dr. Hutson asked, "What's the state of biomarkers at Dana-Farber?" Dr. Serzan noted, "Kidney injury molecule-1 (KIM-1) is an emerging soluble biomarker that was shown to be prognostic and predictive for immunotherapy benefit when evaluate retrospectively in CheckMate 214 and IMmotion010[12, 13]. RNA signatures are another fascinating area that have helped us understand RCC biology however are not validated to guide clinical decisions. We look forward to seeing results from the ongoing OPTIC RCC trial, which is utilizing RNA clusters to assign first line combination therapies." Dr. Matrana quipped, "Biomarkers are RCC's Holy Grail—my career's been a rollercoaster of hope and disappointment. We need a PSA equivalent."

Key Takeaways for Oncologists

Dr. Hutson concluded, "What practical messages should colleagues take away?"

- Dr. Matrana: "Cabozantinib's versatility and IO synergy have revolutionized RCC. Creative toxicity management—reductions, holidays—ensures tolerability and quality of life."
- Dr. Serzan: "We now have over a decade of data supporting the use of cabozantinib as monotherapy and in combination for both clear and non-clear cell subtypes. I look forward to several ongoing trials using cabozantinib-based combinations to advance the standard of care for our patients with RCC."
- Dr. Hutson: "Use it early for control, not just salvage. Future trials should leverage its tumor-shrinking power with innovative designs."

CONCLUSION

Cabozantinib - A Cornerstone and Catalyst in the Ongoing Evolution of Renal Cell Carcinoma Therapy

In conclusion, the insights shared by Drs. Hutson, Matrana, and Serzan underscore the pivotal and continuously evolving role of cabozantinib in the management of renal cell carcinoma. Its established efficacy as both a single agent and, crucially, in combination regimens, particularly with immune checkpoint inhibitors, positions it as a cornerstone of contemporary RCC therapy across various disease stages and histologies. The drug's multi-targeted approach, inhibiting key pathways like VEGFR, MET, and AXL, not only contributes to its broad activity but also provides a rationale for its effectiveness in challenging clinical scenarios, including those with bone and brain metastases.

The roundtable discussion highlights a paradigm shift towards earlier utilization of cabozantinib, particularly in the first-line setting, to leverage its potential for rapid and significant disease control in patients with high-risk features. This proactive approach, contrasting with earlier tendencies to reserve it for later lines, reflects the expanding armamentarium of available therapies and the recognition that delaying the use of highly effective agents may compromise patient outcomes. However, optimizing the benefits of cabozantinib necessitates a nuanced understanding and proactive management of its toxicity profile. Strategies such as judicious dose adjustments and short treatment

interruptions, coupled with comprehensive supportive care involving multidisciplinary teams, are crucial for maintaining tolerability, preserving patient quality of life, and ensuring sustained treatment adherence.

Looking ahead, the future of cabozantinib in RCC is dynamic and promising. Ongoing and planned clinical trials are exploring its potential in novel combinations, such as with HIF inhibitors, and in different treatment settings, including the neoadjuvant space. These investigations aim to further refine its role and potentially enhance its efficacy, pushing the boundaries of achievable responses and long-term disease control. Moreover, the persistent pursuit of reliable biomarkers holds the promise of personalizing cabozantinib-based treatments, allowing for more informed patient selection and potentially predicting treatment response and resistance mechanisms. Ultimately, cabozantinib's established efficacy, its adaptability within combination strategies, and its continued investigation in innovative clinical trials solidify its position as a vital tool for oncologists striving to improve outcomes and the lives of patients with renal cell carcinoma.

CONTRIBUTIONS

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