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Comparison of Third-Line Treatment Options in Patients with Metastatic Renal Cell Carcinoma

Ömer Faruk Kuzu[1], Nebi Batuhan Kanat[2], Dilruba İlayda Özel Bozdağ[2], Alper Topal[3], Nuri Karadurmuş[4], İsmail Ertürk[4]

[1]*Çankırı State Hospital, Clinic of Oncology, Çankırı, Türkiye*
[2]*University of Health Sciences Türkiye, Gülhane Training and Research, Hospital, Department of Internal Medicine, Ankara, Türkiye*
[3]*Tokat Gaziosmanpaşa University Faculty of Medicine, Department of Oncology, Tokat, Türkiye*
[4]*University of Health Sciences Türkiye, Gülhane Training and Research, Department of Internal Medicine and Medical Oncology, Ankara, Türkiye*

ABSTRACT

Aim: Metastatic renal cell carcinoma (mRCC) is a challenging malignancy requiring multiple lines of therapy. While tyrosine kinase inhibitors remain the standard first-line treatment, resistance often necessitates further therapeutic options. Nivolumab, everolimus, axitinib, and cabozantinib are commonly used in later-line settings, but the optimal sequencing strategy remains unclear.

Methods: This retrospective study analyzed 32 patients with mRCC treated at University of Health Sciences Türkiye, Gülhane Training and Research Hospital between January 2015 and December 2022. All patients had received at least two prior systemic therapies. Survival outcomes were assessed using Kaplan-Meier analysis. Progression-free survival (PFS) and overall survival (OS) were compared among treatment groups using the Log-Rank test.

Results: Axitinib was the most frequently used third-line therapy (50.0%), followed by everolimus (25.0%), cabozantinib (12.5%), and nivolumab (12.5%). Nivolumab showed the longest median PFS (41.0 months, p=0.034) and OS (149.0 months), although OS differences were not statistically significant (p=0.154).

Conclusion: This study highlights variation in third-line treatment patterns and outcomes among mRCC patients. Nivolumab and axitinib demonstrated promising efficacy, suggesting their consideration as preferred options in this setting.

Keywords: Genitourinary cancer, metastatic renal cell carcinoma, third-line therapy

Introduction

Metastatic renal cell carcinoma (mRCC) remains a significant challenge in oncology, often requiring multiple lines of therapy to achieve sustained disease control. Tyrosine kinase inhibitors (TKIs), which target the vascular endothelial growth factor receptor (VEGFR) pathway, have long been the backbone of first-line treatment. However, the development of resistance is common, necessitating additional therapeutic options. Among patients who experience disease progression on immunotherapy, the role of titrated axitinib dosing as a subsequent therapy remains investigational, with only a single phase 2 study evaluating its efficacy [1].

The phase 3 METEOR trial compared cabozantinib and everolimus in 658 mRCC patients who had progressed after VEGF-TKI therapy, revealing that 69% had received one prior systemic therapy, while 31% had undergone two or more, underscoring the need for effective later-line treatment options [2-4]

Recent studies indicate that everolimus is increasingly being utilized in third-line and subsequent treatment lines for renal cell carcinoma**,** reflecting its evolving role in later treatment stages [5-8]. Additionally, immune checkpoint inhibitors (ICIs), such as nivolumab, have reshaped the treatment landscape, particularly in second-line and beyond settings. Nivolumab

Address for Correspondence: Ömer Faruk Kuzu MD, Çankırı State Hospital, Clinic of Oncology, Çankırı, Türkiye
E-mail: drfarukkuzu@gmail.com **ORCID ID:** orcid.org/0000-0003-3197-7861
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has demonstrated superior efficacy and tolerability compared to everolimus, leading to its widespread adoption in clinical practice [4].

Despite these advancements, the optimal sequencing of third-line therapies remains an area of active investigation, with treatment options including axitinib, everolimus, cabozantinib, and nivolumab.

This study aims to evaluate real-world treatment patterns and survival outcomes of mRCC patients receiving third-line therapy, focusing on the efficacy of available options including axitinib, everolimus, cabozantinib, and nivolumab.

Methods

We conducted an analysis of 32 patients diagnosed with mRCC who were managed at University of Health Sciences Türkiye, Gülhane Training and Research Hospital. The analyzed patients had previously received two lines of systemic therapy before initiating third-line treatment. The effectiveness of third-line therapies was assessed by comparing their impact on survival outcomes using the Kaplan-Meier analysis. Primary end points were time to progression-free survival (PFS) and overall survival (OS). OS is the duration of time from the start of treatment until death from any cause. PFS was defined as disease progression or death from any cause after third-line treatment.

Ethical approval for this study was obtained from the University of Health Sciences Türkiye, Gülhane Training and Research Hospital Ethics Committee, and the study was conducted in accordance with the principles of the Declaration of Helsinki (decision no: 2025/119, date: 12.06.2025). Due to the retrospective nature of the study, the Ethics Committee of University of Health Sciences Türkiye, Gülhane Training and Research Hospital waived the obligation to obtain informed consent.

Statistical Analysis

All statistical analyses were performed using the IBM Statistical Package for the Social Sciences Statistics 27.0 software package. Continuous variables were described as medians (interquartile range), and categorical variables were described as percentages. Survival curves and rates were estimated using the Kaplan-Meier method. The Log-Rank test was used to compare the survival outcomes between the groups. All reported p values were two-sided, and p values <0.05 were regarded as statistically significant

Results

A total of 32 patients were included in the study, with a median age of 55 years among them, 26 were male (81.25%) and most were diagnosed at stage 4 (68.8%). Clear cell carcinoma was the most prevalent histological subtype (84.4%), while papillary (9.4%) and chromophobe (6.3%) subtypes were less common. Additionally, sarcomatoid differentiation was identified in 9.4% of cases. Regarding metastatic involvement, lung metastases (78.1%) were the most frequently observed, followed by lymph node/soft tissue (68.8%), bone (50.0%), liver (15.6%), and brain (15.6%) metastases. The distribution of the International Metastatic RCC Database Consortium risk categories among the study cohort demonstrated that the majority of patients were classified as intermediate risk (78.1%), while 18.8% of patients were categorized as poor risk. Only 3.1% of patients were classified as having a good risk profile. In this study, all patients received TKI therapy as a first-line treatment. The most commonly used treatment among second-line treatments was nivolumab, which was administered to 27 patients (84%). Axitinib was used by 3 patients (9.4%), while sunitinib and everolimus were administered to 1 patient (3.1%). In the third-line treatment analysis, axitinib was the most frequently administered therapy, used by 16 patients (50.0%). Everolimus was the second most common option, given to 8 patients (25.0%), while cabozantinib and nivolumab were each used by 4 patients (12.5%) (Table 1).

Table 1. Clinical characteristic of patients

Variable	Category	Count (percentage)
Gender	Male	26 (81.3%)
	Female	6 (18.8%)
Diagnosis stage	Stage 1	2 (6.3%)
	Stage 2	6 (18.8%)
	Stage 3	2 (6.3%)
	Stage 4	22 (68.8%)
Histological type	Clear Cell	27 (84.4%)
	Papillary	3 (9.4%)
	Chromophobe	2 (6.3%)
Sarcomatoid features	No	29 (90.6%)
	Yes	3 (9.4%)
Metastasis status	Brain	5 (15.6%)
	Lung	25 (78.1%)
	Liver	5 (15.6%)
	Bone	16 (50.0%)
Lymph node/soft tissue	Absent	10 (31.3%)
IMDC risk	Poor	6 (18.8%)
	Intermediate	25 (78.1%)
	Good	1 (3.1%)
Second line treatments	Nivolumab	27 (84%)
	Axitinib	3 (9.4%)
	Sunitinib	1 (3.1%)
	Everolimus	1 (3.1%)
Third-line treatment	Aksitinib	16 (50.0%)
	Everolimus	8 (25.0%)
	Cabozantinib	4 (12.5%)
	Nivolumab	4 (12.5%)

IMDC: International Metastatic Database Consortium

Axitinib exhibited a median PFS of 13.0 months [95% confidence interval (CI): 5.03-20.97], whereas everolimus had a median PFS of 6.0 months (95% CI: 0.00-13.13). Cabozantinib demonstrated the shortest median PFS of 2.0 months (95% CI: 0.00-10.49). Nivolumab showed the longest median PFS of 41.0 months, though its CI could not be determined. Nivolumab provided a statistically significant PFS advantage compared to other treatment groups (p=0.034) (Figure 1).

Axitinib demonstrated a median OS of 59.0 (95% CI: 27.64-90.36), whereas everolimus had a median OS of 73.0 months (95% CI: 0.00-154.89). Cabozantinib showed a median OS of 22.0 months (95% CI: 0.00-49.44). Nivolumab exhibited the longest median OS of 149.0 months (95% CI: 106.93-358.58). No statistically significant difference in OS was observed among the treatment subgroups (p=0.154) (Figure 2).

Discussion

In this study, we evaluated the treatment patterns and outcomes of mRCC patients who received first, second, and third-line therapies. Our findings indicate that all patients received TKI therapy as a first-line treatment. While clinical trials have provided valuable insights into the efficacy of these agents, real-world data on third-line treatment choices and survival outcomes remain limited. Understanding the comparative effectiveness of these therapies in later-line settings is crucial for optimizing treatment strategies and improving patient prognosis.

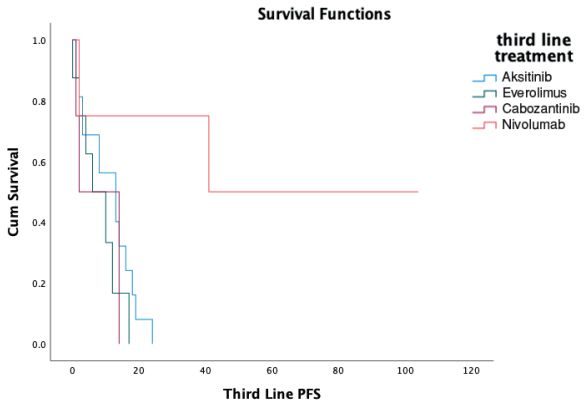

Figure 1. Third line progresyon-free survival

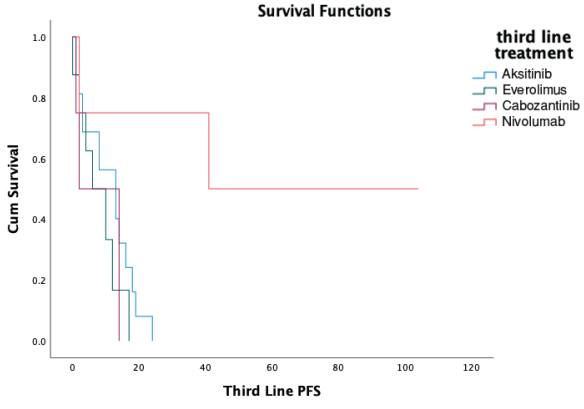

Figure 2. Overall survival

Among second-line treatments, nivolumab was the predominant choice, administered to 84% of patients, while other options such as axitinib, sunitinib, and everolimus were used less frequently. This suggests a preference for ICIs following TKI failure, consistent with the latest clinical guidelines favoring nivolumab-based regimens due to their superior efficacy and tolerability [4].

Our third-line treatment analysis revealed notable differences in PFS and OS among different therapeutic options. In our study axitinib was the most frequently administered therapy, used by 16 patients (50.0%). A study Tsironis et al. [8] demonstrated that axitinib is an effective therapeutic agent following second-line treatment. Similarly, Ishihara et al. [9] highlighted the promising efficacy of axitinib as a third-line treatment for mRCC, reporting 50.0% usage, median PFS of 12.8 months, and 1-year PFS rate of 51.3%. Additionaly, its objective response rate (29.4%) and disease control rate (94.1%) further support its effectiveness in this setting.

According to a study Rauthan et al. [10], nivolumab has demonstrated efficacy in the third-line or later setting, showing a 60% response rate and a median OS of 26 months. While median PFS was 5 months, some patients achieved long-term remission exceeding 40 months, reinforcing the treatment's role in later-line therapy for immunotherapy-sensitive cases. In our study nivolumab demonstrated the longest median PFS and a statistically significant advantage over other treatments (p=0.034), emphasizing its role as a durable treatment option. Furthermore, despite no statistically significant OS differences (p=0.15), nivolumab exhibited the longest median OS (149 months), suggesting potential long-term survival benefits. Meanwhile, the relatively limited efficacy of cabozantinib highlights the need for further investigation into optimal sequencing strategies in mRCC treatment.

Everolimus remains a third-line option for mRCC after VEGFR-TKI failure. In this study, a certain treatment was used in 25.0% of patients, showing better outcomes (PFS: 6, OS: 73 months) than cabozantinib but inferior to nivolumab (PFS: 41, OS: 149 months) and axitinib. A review conducted Buti et al. [11], which multiple studies on the efficacy of everolimus in the treatment of mRCC, demonstrated that the role of everolimus has shifted primarily to third-line and subsequent treatment options.

Study Limitations

This study has several limitations. First, the retrospective design introduces inherent risks of selection bias and incomplete data capture. Second, the relatively small sample size (n=32) limits the statistical power to detect differences in OS, and restricts the generalizability of the findings. Additionally, the single-center setting may not reflect variations in treatment practices across institutions. Finally, heterogeneity in prior lines of

therapy and patient characteristics could have influenced treatment outcomes.

Conclusion

In this retrospective single-center study evaluating third-line treatment options for mRCC, nivolumab demonstrated the longest PFS and OS among the evaluated therapies, although the difference in OS was not statistically significant. Axitinib also showed promising efficacy and remained the most frequently used third-line agent. These findings suggest that immunotherapy and VEGFR-targeted TKI continue to be relevant options in later-line settings. However, the optimal sequencing of therapies remains uncertain, underscoring the need for further prospective studies to establish individualized treatment strategies.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the University of Health Sciences Türkiye, Gülhane Training and Research Hospital Ethics Committee, and the study was conducted in accordance with the principles of the Declaration of Helsinki (decision no: 2025/119, date: 12.06.2025).

Informed Consent: Due to the retrospective nature of the study, the University of Health Sciences Türkiye, Gülhane Training and Research Hospital Ethics Committee waived the requirement to obtain informed consent.

Footnotes

Authorship Contributions

Concept: Ö.F.K., N.K., İ.E., Design: Ö.F.K., N.B.K., D.İ.Ö.B., N.K., Data Collection or Processing: Ö.F.K., N.B.K., D.İ.Ö.B., Analysis or Interpretation: Ö.F.K., A.T., Literature Search: Ö.F.K., D.İ.Ö.B., A.T., Writing: Ö.F.K., N.B.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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