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Research Article

Pazopanib or Sunitinib as First-Line Treatment in metastatic Renal Cell Cancers: A Retrospective Comparative Analysis of Survival and Toxicity Outcomes

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Abstract

Objectives: To evaluate and compare the real-world efficacy and safety of pazopanib and sunitinib as first-line treatments in patients with metastatic renal cell carcinoma (mRCC).

Methods: This retrospective study included 81 patients with histologically confirmed mRCC who received first-line pazopanib (n=32) or sunitinib (n=49) between 2018 and 2023. Primary endpoints were progression-free survival (PFS) and overall survival (OS). Treatment-related adverse events were assessed and graded according to CTCAE v5.0.

Results: Median PFS was 10.7 months with pazopanib and 13.6 months with sunitinib (p = 0.88). Median OS was 54.4 months and 63.3 months, respectively (p = 0.41). No statistically significant differences were found between groups. Univariate analysis showed associations between survival outcomes and nephrectomy or IMDC score, but no independent predictors were identified in multivariate models. Hand–foot syndrome was more frequent with sunitinib, whereas elevated liver enzymes were more common with pazopanib. Fatigue was equally reported in both groups. Grade ≥3 toxicities occurred in 43.7% of pazopanib patients and 36.7% of sunitinib patients.

Conclusion: Pazopanib and sunitinib demonstrated comparable efficacy in a real-world setting. Differences in safety profiles may help guide treatment selection in environments where access to immunotherapy is restricted.

Keywords: Metastatic renal cell carcinoma, Pazopanib, Sunitinib, Adverse events, First-line treatment

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Renal cell carcinoma (RCC) constitutes approximately 90% of all kidney cancers, with clear-cell RCC being the most prevalent histological subtype.[1,2] Despite advances in diagnostic imaging and surgical management, a significant proportion of patients still present with metastatic disease (mRCC) at diagnosis, and up to one-third of initially localized cases eventually develop distant metastases.[1,3]

The introduction of targeted therapies has significantly improved outcomes in mRCC. Tyrosine kinase inhibitors (TKIs) targeting the vascular endothelial growth factor (VEGF) pathway, such as sunitinib and pazopanib, were the mainstay of treatment for over a decade.[3,4] More recently, immune checkpoint inhibitors (ICIs), either as monotherapy or in combination with TKIs, have redefined first-line treatment strategies. Randomized trials such as CheckMate 214

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and JAVELIN Renal 101 demonstrated the superiority of ICI-based regimens over TKI monotherapy in intermediate- and poor-risk patients, leading to a paradigm shift in international guidelines.[4–6]

However, the benefit of ICI-based combinations in favorable-risk patients remains uncertain. Subgroup analyses from pivotal trials have shown comparable or even superior outcomes with TKI monotherapy in favorable-risk populations.[6,7] Additionally, emerging data suggests that the traditionally defined favorable-risk group is heterogeneous. Stratification into "very favorable" and "favorable" subgroups has been proposed to improve prognostic accuracy and inform treatment decisions.[8]

In Turkiye, although international guidelines recommend ICI–TKI combinations as standard first-line therapy, national reimbursement policies currently do not support routine use of immunotherapy in this setting. Consequently, TKI monotherapy, most commonly sunitinib or pazopanib remains the predominant first-line treatment option in routine clinical practice. This context underscores the importance of real-world studies evaluating the comparative effectiveness and tolerability of these agents, particularly in populations where access to immunotherapy is limited.

Methods

Patient Selection

This retrospective cohort study included patients with histologically confirmed mRCC who received either pazopanib or sunitinib as first-line systemic therapy between January 2018 and December 2023. Eligible patients were aged 18 years or older, had measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 guidelines,[9] and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 or a Karnofsky Performance Score (KPS) of ≥70% at the start of therapy.[10] Patients were also required to have adequate bone marrow, liver, and renal function as evidenced by standard laboratory parameters prior to treatment initiation.

All baseline radiological assessments were performed within four weeks before the start of therapy, and follow-up evaluations were conducted at regular intervals (every 6–12 weeks) according to institutional standards. Measurable lesions were evaluated using CT or MRI, and responses were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) per RECIST 1.0 guidelines.

Inclusion Criteria:

1. Age ≥18 years
2. Histologically or cytologically confirmed metastatic renal cell carcinoma
3. Received pazopanib or sunitinib as first-line treatment
4. At least one measurable lesion as per RECIST v1.0
5. Karnofsky Performance Score ≥70%
6. Adequate hematologic (e.g., hemoglobin >9 g/dL, ANC $>1.5 \times 10^9$/L, platelets $>100 \times 10^9$/L), hepatic (e.g., bilirubin ≤1.5× ULN, AST/ALT ≤2.5× ULN), and renal function (e.g., serum creatinine ≤1.5× ULN or creatinine clearance ≥60 mL/min)

Exclusion Criteria:

1. Prior systemic therapy for metastatic disease
2. Presence of another active malignancy within the past 5 years (except for adequately treated basal cell or squamous cell carcinoma of the skin, or in situ cervical cancer)
3. Uncontrolled hypertension (≥150/100 mmHg despite optimal medical management)
4. Significant cardiovascular events within the past 6 months (e.g., myocardial infarction, unstable angina, NYHA class III/IV heart failure)
5. Active infection or serious medical or psychiatric condition interfering with protocol adherence
6. Pregnant or breastfeeding women

This study was approved by the institutional review board, and all patient data were anonymized prior to analysis.

Study Design

This was a single-center, retrospective cohort study conducted at the Department of Medical Oncology. The study included patients with histologically confirmed mRCC who received first-line treatment with either pazopanib or sunitinib between January 2018 and December 2023.

Pazopanib was administered orally at a continuous once-daily dose of 800 mg. All patients who received sunitinib were treated with the standard 4/2 schedule (4 weeks on treatment followed by 2 weeks off). Alternative schedules, such as the 2-weeks-on/1-week-off regimen, were not used in this cohort. Both regimens were continued until disease progression or unacceptable toxicity. Dose modifications, interruptions, or discontinuations were performed at the discretion of the treating physician according to individual patient response and tolerability.

Outcomes

Treatment responses were assessed radiologically every three months using computed tomography or magnetic resonance imaging and were evaluated according to the RECIST.[11] Assessments continued until radiologically confirmed disease progression, death, or loss to follow-up in cases where treatment was discontinued for other reasons.

The primary endpoints of the study were PFS and OS. PFS was defined as the time from the initiation of first-line treatment to the date of radiological or clinical disease progression, or death from any cause, whichever occurred first. OS was defined as the time from the start of first-line therapy to the date of death from any cause. Patients who were alive and progression-free at the time of data cutoff were censored at their last known follow-up date.

Due to limitations in standardized radiological response documentation in this retrospective cohort, objective response rate and disease control rate were not assessed as secondary endpoints.

In addition, treatment-related adverse events (AEs) were recorded and graded based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.[9] The incidence and severity of AEs were compared between the pazopanib and sunitinib groups.

Statistical Analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Survival outcomes, including progression-free survival (PFS) and overall survival (OS), were analyzed using the Kaplan–Meier method, and differences between treatment groups were assessed using the log-rank test.

To identify independent predictors of PFS and OS, univariate Cox proportional hazards regression analyses were first performed. Variables with a p-value <0.10 in univariate analysis or considered clinically relevant were included in multivariate Cox regression models. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were reported.

A p-value <0.05 was considered statistically significant in all analyses. Due to the retrospective nature of the study, no sample size calculation was performed; all treated patients were included in the study. Patients with incomplete or missing survival data were excluded from time-to-event analyses.

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

A total of 81 patients with mRCC were included in the study, of whom 49 (60.5%) received sunitinib and 32 (39.5%) received pazopanib as first-line therapy. The median age of the overall cohort was not specified; however, patients were stratified into two age groups: ≤60 years and >60 years. Among sunitinib-treated patients, 67.3% were aged ≤60 years, whereas most of the patients receiving pazopanib (68.8%) were older than 60 years.

Male patients predominated in both treatment groups, with men comprising 81.6% of the sunitinib group and 68.8% of the pazopanib group. Overall, 76.5% of patients were male, and 23.5% were female.

Clear-cell histology was the most common subtype, observed in 85.2% of the entire cohort. The proportion of patients with clear-cell RCC was similar across treatment arms (sunitinib: 83.7%, pazopanib: 87.5%).

A history of nephrectomy was recorded in 77.8% of patients. Among those treated with sunitinib, 89.8% had undergone prior nephrectomy, compared with 59.4% in the pazopanib group.

IMDC risk stratification revealed a distribution of 17.3%, 45.7%, 32.1%, and 4.9% for 0, 1, 2, and 3 risk factors, respectively. Notably, patients receiving pazopanib had a slightly higher proportion of poor-risk features (IMDC score = 3, 9.4%) compared to those on sunitinib (2.0%). All patients' characteristics are summarized in Table 1.

Progression-Free Survival

PFS was assessed using the Kaplan–Meier method and compared between treatment groups via the log-rank test. The median PFS was 13.6 months (95% CI, 9.0–18.1) in the sunitinib group and 10.7 months (95% CI, 9.4–12.0) in the pazopanib group. The difference between the two treatment arms was not statistically significant (p = 0.88) (Fig. 1).

No statistically significant difference was observed between the two treatment arms (log-rank p=0.88).

Univariate Cox regression analysis confirmed the absence of a significant association between treatment type and risk of progression. The HR for pazopanib compared to sunitinib was 1.04 (95% CI, 0.66–1.64; p=0.878), suggesting comparable efficacy of the two TKIs in terms of disease control.

Overall Survival

The median OS was 63.3 months (95% CI, 25.6–101.0) in the sunitinib group and 54.4 months (95% CI, 10.0–98.7) in the pazopanib group. Despite a numerically longer

Table 1. Baseline demographic and clinical characteristics of the study population

Characteristic	Sunitinib (n=49)	Pazopanib (n=32)	Total (n=81)
Age group, n (%)			
≤ 60 years	33 (67.3)	10 (31.3)	43 (53.1)
> 60 years	16 (32.7)	22 (68.8)	38 (46.9)
Sex, n (%)			
Male	40 (81.6)	22 (68.8)	62 (76.5)
Female	9 (18.4)	10 (31.3)	19 (23.5)
Histological subtype, n (%)			
Clear cell RCC	41 (83.7)	28 (87.5)	69 (85.2)
Non-clear cell RCC	8 (16.3)	4 (12.5)	12 (14.8)
Nephrectomy history, n (%)			
Yes	44 (89.8)	19 (59.4)	63 (77.8)
No	5 (10.2)	13 (40.6)	18 (22.2)
IMDC risk score, n (%)			
0	10 (20.4)	4 (12.5)	14 (17.3)
1	22 (44.9)	15 (46.9)	37 (45.7)
2	16 (32.7)	10 (31.3)	26 (32.1)
3	1 (2.0)	3 (9.4)	4 (4.9)

RCC: Renal cell carcinoma; IMDC: International Metastatic RCC Database Consortium.

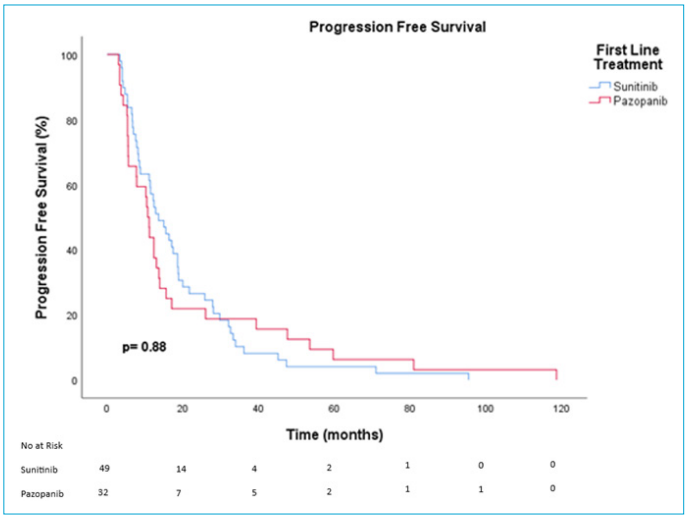

Figure 1. Kaplan–Meier curves for PFS according to first-line treatment with sunitinib or pazopanib.

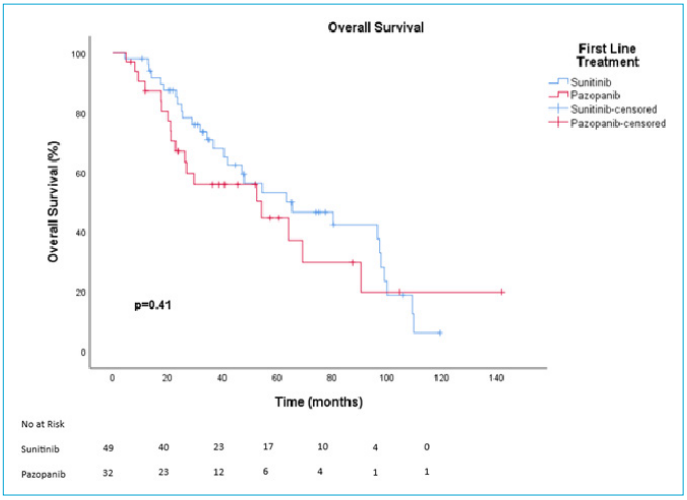

Figure 2. Kaplan–Meier curves for OS according to first-line treatment with sunitinib or pazopanib.

OS observed with sunitinib, the difference between the two treatment arms did not reach statistical significance (p=0.41) (Fig. 2).

The corresponding mean OS was 66.2 months (95% CI, 54.6–77.7) for sunitinib and 61.3 months (95% CI, 41.1–81.4) for pazopanib. Univariate Cox regression analysis demonstrated that the choice of first-line TKI (sunitinib vs. pazopanib) was not a significant predictor of overall survival (HR, 1.28; 95% CI, 0.71–2.31; p = 0.415).

Univariate and Multivariate Analysis for PFS

In univariate analysis, prior nephrectomy was significantly associated with longer PFS (HR: 0.45; 95% CI: 0.26–0.77; p=0.004). Other factors, including age group (>60 vs. ≤60 years; HR: 1.46; 95% CI: 0.94–2.28; p=0.096), IMDC risk score (HR: 1.25; 95% CI: 0.94–1.67; p=0.130), sex (HR: 1.14; 95% CI: 0.68–1.91; p=0.626), and histological subtype (HR: 1.14; 95% CI: 0.61–2.14; p=0.676) were not significantly associated with PFS but were retained in the multivariate analysis due to clinical relevance.

Table 2. Univariate and multivariate analysis for PFS

Variable	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Age group (>60 vs. ≤60 years)	1.55 (0.86–2.79)	0.141	1.20 (0.59–2.46)	0.608
Sex (Male vs. Female)	1.36 (0.69–2.69)	0.379	1.38 (0.64–2.99)	0.417
Histology (Clear cell vs. Non-clear cell)	1.40 (0.59–3.32)	0.449	1.36 (0.55–3.35)	0.506
Nephrectomy history (Yes vs. No)	0.32 (0.16–0.66)	0.002	0.47 (0.19–1.13)	0.089
IMDC risk score (per point increase)	1.49 (1.00–2.20)	0.048	1.47 (0.97–2.24)	0.069

HR: Hazard ratio; CI: Confidence interval; IMDC: International Metastatic RCC Database Consortium.

In the multivariate Cox regression model, none of the variables were independently associated with PFS. Age group (HR: 1.20; 95% CI: 0.69–2.08; p=0.511), sex (HR: 1.12; 95% CI: 0.64–1.96; p=0.689), histology (HR: 0.98; 95% CI: 0.51–1.89; p=0.954), IMDC risk score (HR: 1.15; 95% CI: 0.84–1.57; p=0.395), and nephrectomy history (HR: 0.56; 95% CI: 0.28–1.13; p=0.107) did not reach statistical significance.

These findings suggest that while prior nephrectomy may be associated with improved PFS in univariate analysis, its independent prognostic value diminishes after adjusting for other clinical factors. All univariate and multivariate results are summarized in Table 2.

Univariate and Multivariate Analysis for OS

Univariate Cox regression analysis identified nephrectomy status and IMDC risk score as significant predictors of OS. Patients with a prior nephrectomy had significantly better survival outcomes compared to those without (HR: 0.32; 95% CI: 0.16–0.66; p=0.002). Additionally, increasing IMDC risk score was associated with worse survival (HR: 1.49; 95% CI: 1.00–2.20; p=0.048).

Other variables—including age group (>60 vs. ≤60 years), sex (male vs. female), and histological subtype (clear cell vs. non-clear cell)—did not show statistically significant associations with OS in univariate analysis.

In the multivariate Cox regression model, neither nephrectomy (HR: 0.47; 95% CI: 0.19–1.13; p=0.089) nor IMDC score (HR: 1.47; 95% CI: 0.97–2.24; p=0.069) retained statistical significance, though both exhibited trends toward independent prognostic relevance. Age, sex, and histological subtype also remained nonsignificant in the adjusted model. All results are summarized in Table 3.

Adverse Events

Treatment-related adverse events (AEs) were common in both treatment groups. Fatigue was the most frequently reported AE, occurring in 55% of patients in both the pazopanib and sunitinib groups. Grade 3–4 fatigue was more common in the sunitinib arm (17%) compared to the pazopanib arm (10%).

Hand–foot syndrome was reported in 29% of patients receiving pazopanib, with no grade 3–4 events, whereas it was more frequent and severe in the sunitinib group, occurring in 50% of patients with 12% experiencing grade 3–4 toxicity. Dysgeusia, rash, and hypothyroidism were more frequent in patients treated with sunitinib than pazopanib, although none resulted in grade 3–4 events.

Liver function abnormalities were observed in both groups. Increased AST and ALT levels were reported in over half of pazopanib-treated patients (61% and 60%, respectively), with grade 3–4 elevations in 11% and 15%. In comparison, sunitinib was associated with slightly lower rates of AST (60%) and ALT (43%) elevation, with 3% and 4% of patients experiencing grade 3–4 elevations, respectively.

Yellow skin discoloration and increased bilirubin were more prominent in the pazopanib group; however, severe hyperbilirubinemia was rare in both groups. Overall, adverse events were manageable and generally consistent with known toxicity profiles of VEGF-targeted therapies. A detailed summary of treatment-related adverse events is presented in Table 4.

Table 3. Univariate and multivariate Cox regression analysis for overall survival

Variable	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Age group (>60 vs. ≤60 years)	1.46 (0.94–2.28)	0.096	1.20 (0.69–2.08)	0.511
Sex (Male vs. Female)	1.14 (0.68–1.91)	0.626	1.12 (0.64–1.96)	0.689
Histology (Clear cell vs. Non-clear cell)	1.14 (0.61–2.14)	0.676	0.98 (0.51–1.89)	0.954
Nephrectomy history (Yes vs. No)	0.45 (0.26–0.77)	0.004	0.56 (0.28–1.13)	0.107
IMDC risk score (per point increase)	1.25 (0.94–1.67)	0.130	1.15 (0.84–1.57)	0.395

HR: hazard ratio; CI: Confidence interval; IMDC: International Metastatic RCC Database Consortium.

Table 4. Treatment-related adverse events in patients receiving first-line pazopanib or sunitinib

Adverse Event	Pazopanib All Grades n (%)	Pazopanib Grade 3–4 n (%)	Sunitinib All Grades n (%)	Sunitinib Grade 3–4 n (%)
Fatigue	18 (55)	3 (10)	27 (55)	8 (17)
Hand–foot syndrome	9 (29)	0 (0)	24 (50)	6 (12)
Dysgeusia	8 (26)	0 (0)	18 (36)	0 (0)
Rash	6 (18)	1 (4)	11 (23)	0 (0)
Hypothyroidism	4 (12)	0 (0)	12 (24)	0 (0)
Yellow skin	0 (1)	0 (0)	7 (15)	0 (0)
Increased AST	20 (61)	4 (11)	29 (60)	1 (3)
Increased ALT	19 (60)	5 (15)	21 (43)	2 (4)
Increased total bilirubin	12 (36)	1 (3)	13 (27)	1 (2)

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

Discussion

The treatment landscape for mRCC has undergone a remarkable transformation over the past two decades, largely driven by the development of targeted therapies. Among these, sunitinib emerged as a standard first-line treatment following the pivotal phase III trial by Motzer et al., which demonstrated its superiority over interferon-α in terms of progression-free survival, objective response rate, and overall survival in treatment-naïve patients with mRCC. In that landmark study, sunitinib significantly extended median PFS to 11 months compared to 5 months with interferon-α, with an objective response rate of 47% versus 12%, respectively.[12] These findings established Sunitinib as the new standard of care at the time.

Following the success of sunitinib, pazopanib emerged as a novel oral angiogenesis inhibitor targeting VEGFR, PDGFR, and c-Kit. The efficacy of pazopanib was confirmed in a subsequent randomized phase III trial by Sternberg et al., in which pazopanib significantly prolonged median progression-free survival compared to placebo (9.2 vs. 4.2 months overall; 11.1 months in treatment-naive patients), with an objective response rate of 30%.[13] These results demonstrated pazopanib's clinical benefit both in treatment-naive and cytokine-pretreated populations and led to its approval as a first-line agent.

In the pivotal COMPARZ trial, pazopanib and sunitinib were directly compared as first-line therapies in patients with mRCC. The study demonstrated non-inferiority of pazopanib to sunitinib with respect to PFS, with median PFS values of 8.4 months for pazopanib and 9.5 months for sunitinib (HR: 1.05; 95% CI: 0.90–1.22). Overall survival was also similar between the two groups (median OS: 28.4 vs. 29.3 months; HR: 0.91; 95% CI: 0.76–1.08).[14]

In our study, median PFS was 10.7 months for patients treated with pazopanib and 13.6 months for those receiving sunitinib. Similarly, median OS was 54.4 months and 63.3 months for pazopanib and sunitinib, respectively. Although our study population was smaller and derived from a real-world single-center experience, the findings appear to be consistent with the COMPARZ trial.

Regarding safety, the COMPARZ study highlighted differing toxicity profiles: sunitinib was associated with a higher incidence of fatigue (63% vs. 55%), hand–foot syndrome (50% vs. 29%), and hematologic toxicities, while pazopanib was more often associated with elevated liver enzymes (ALT increase: 60% vs. 43%).[14] In our study, the most frequent adverse events in the pazopanib group included fatigue (55%), increased AST (61%), and increased ALT (60%), whereas in the sunitinib group, fatigue (55%) and hand–foot syndrome (50%) were predominant. Rates of grade ≥3 toxicities were 43.7% and 36.7%, respectively.

The PISCES study, a randomized, double-blind, cross-over trial, evaluated patient preference between pazopanib and sunitinib in treatment-naive mRCC patients. Among patients who received both treatments and completed the preference assessment, 70% expressed a preference for pazopanib, while only 22% favored sunitinib, and 8% had no preference. The most frequently cited reasons for preferring pazopanib included less fatigue and a better overall quality of life. Physicians similarly favored pazopanib in 61% of cases.[15] These findings underscore that, in the context of comparable efficacy, differences in tolerability and quality of life may substantially influence patient satisfaction and treatment adherence.

Although our study did not assess formal patient preference through questionnaires, differences in adverse event profiles between treatment arms were observed. Fatigue was reported at similar rates in both groups (55%), whereas hand–foot syndrome was more common and severe in the

sunitinib group (50% vs. 29%). Conversely, elevations in liver enzymes particularly ALT and AST were more frequently observed in patients receiving pazopanib. These findings may support the notion that the more favorable tolerability profile of pazopanib observed in the PISCES trial also manifests in real-world clinical settings.[15]

This study has several limitations that should be acknowledged. First, due to its retrospective and single-center nature, inherent biases related to patient selection and data availability cannot be completely excluded. While our sample size is acceptable for a real-world observational study, the relatively modest cohort (n=81) may limit the statistical power of subgroup and multivariate analyses. Consequently, some associations may not have reached statistical significance despite potential clinical relevance. Furthermore, the lack of standardized patient-reported outcome measures, such as validated quality-of-life (QoL) assessments, restricts our ability to comprehensively compare tolerability from the patient's perspective. Finally, treatment decisions were made at the discretion of the treating physicians, potentially introducing variability in clinical practice that may not fully reflect uniform treatment protocols.

Conclusion

In this real-world, single-center retrospective study, pazopanib and sunitinib demonstrated comparable efficacy in the first-line treatment of patients with metastatic renal cell carcinoma, with no statistically significant differences in PFS or OS. Although objective response rates were numerically higher in the sunitinib group, both agents provided meaningful clinical benefit.

Differences in toxicity profiles were consistent with prior pivotal trials: while hand–foot syndrome was more common with sunitinib, elevated liver enzymes were more frequent in the pazopanib group. Fatigue was reported at similar rates in both arms. Importantly, adverse events were generally manageable and aligned with established safety expectations for VEGF-targeted therapies.

Our findings support the continued use of both pazopanib and sunitinib as viable first-line options in settings where ICIs are not accessible. Further prospective studies with larger sample sizes and quality-of-life assessments are warranted to guide personalized treatment decisions and optimize real-world outcomes in mRCC.

Disclosures

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Ethics Committee Approval: This study was approved by the Institutional Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (Decision No: 2024/010.99/2/17; Date: March 21, 2024). All patient data were anonymized prior to analysis to ensure confidentiality and privacy.

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References

1. Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. N Engl J Med 2017;376(4):354–366.
2. Heidegger I, Pircher A, Pichler R. Targeting the tumor microenvironment in renal cell cancer. Front Oncol 2019;9:490.
3. Ljungberg B, et al. EAU Guidelines on Renal Cell Carcinoma: 2022 Update. Eur Urol 2022;82(3):399–410.
4. Schmidinger M, Wittes JT. Treatment of mRCC after COMPARZ and PISCES: Lessons in trial design and interpretation. Curr Opin Urol 2015;25(5):395–402.
5. Tannir NM, et al. Nivolumab plus ipilimumab vs. sunitinib in first-line mRCC: 8-year follow-up of CheckMate 214. Ann Oncol 2024;35(7):1026–1038.
6. Choueiri TK, et al. Final results of JAVELIN Renal 101: Avelumab + axitinib vs. sunitinib in mRCC. Ann Oncol 2024.
7. Cattrini C, et al. Is there a preferred first-line therapy for mRCC? A network meta-analysis. Ther Adv Urol 2021;13:17562872211053189.
8. Altıntaş YE, et al. Very favorable vs. favorable risk groups in metastatic renal cell carcinoma: A step toward personalized treatment. Cancers (Basel) 2025;17(4):1076.
9. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92(3):205–216.
10. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, editor. Evaluation of Chemotherapeutic Agents. New York: Columbia University Press; 1949. p. 196.
11. Eisenhauer, E.A.; Therasse, P.; Bogaerts, J.; Schwartz, L.H.; Sargent, D.; Ford, R.; Dancey, J.; Arbuck, S.; Gwyther, S.; Mooney, M.; et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur. J. Cancer 2009, 45, 228–247.
12. Motzer RJ, Hutson TE, Tomczak P, et al. Overall Survival and Updated Results for Sunitinib Compared With Interferon Alfa

in Patients With Metastatic Renal Cell Carcinoma. J Clin Oncol 2009;27(22):3584-3590.
13. Sternberg CN, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28(6):1061–1068.
14. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013;369(8):722–731.
15. Escudier B, Porta C, Bono P, et al. Patient preference between pazopanib and sunitinib: results of a randomized, double-blind, cross-over study in patients with metastatic renal cell carcinoma (PISCES). J Clin Oncol 2014;32(14):1412–1418.