ORIGINAL ARTICLE

DOI: 10.37047/jos.galenos.2025.2024.107988

J Oncol Sci 2025;11(1):30-35

Second Line Therapies After Tyrosine Kinase Inhibitory in Metastatic Renal Cell Carcinoma

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ABSTRACT

Objective: Controversy exists over the choice of 2nd-line drugs after the progression of 1st-line tyrosine kinase inhibitors (TKIs) for patients unable to receive 1st-line immunotherapy. We compared the efficacy of 2nd-line treatments after the progression of 1st-line TKI therapy and determined the factors predictive of its efficacy for the treatment of metastatic renal cell carcinoma (RCC).

Material and Methods: Patients were divided into 3 groups according to 2nd-line treatments: axitinib, everolimus, and nivolumab. The progression-free survival (PFS) rates for 2nd-line treatments (PFS2) and overall survival (OS) rates were calculated. Cox regression analyses were conducted to determine the associations between PFS2 and OS rates and other explanatory variables. In addition, PFS2 was compared in patients whose PFS on 1st-line TKI (PFS1) was ≥6 months (mn) with a <6-mn response for each of the 3 groups.

Results: This study included 82 patients who were diagnosed with metastatic RCC. Fourty-one patients received axitinib, 30 patients received everolimus, and 11 patients received nivolumab as a 2nd-line treatment. PFS2 and OS were statistically similar for all 3 groups. Patients who had PFS1 ≥6 months responded significantly to 2nd-line axitinib treatment compared with those with PFS1 <6 months. Multivariate analyses revealed that only PFS1 <6 months was correlated with poor OS.

Conclusion: PFS2 and OS were statistically similar among second-line axitinib, everolimus, and nivolumab treatments. PFS1 <6 mn was correlated with poor PFS2 and OS.

Keywords: Renal cell carcinoma; axitinib; nivolumab; everolimus

INTRODUCTION

Approximately 1/3 of patients with renal cell carcinoma (RCC) present with metastatic disease at their 1st hospital admission.[1] Metastatic RCC has a poor overall survival (OS) rate, with a 5-year OS rate of 12% in the metastatic stage.[1] Despite current treatments for metastatic RCC, the tumors mostly progress, and only 60% of patients can receive 2nd-line treatments.[2]

RCCs are resistant to cytotoxic chemotherapeutic agents.[3] For example, inactivation of the Von Hippel Lindau gene by the deletion of chromosome 3p causes an accumulation of hypoxy inducible factors.[4] This activates angiogenesis due to increased levels of vascular endothelial growth factor (VEGF).[5] In addition, RCCs are considerably hyperinflamed tumors; high levels of proinflammatory cytokines induce an immune response.[6] Multiple kinase inhibitors and immune checkpoint inhibitors are commonly used for treating metastatic RCC because they are characterized by hypervascularization and an increased immune response. The current 1st-line treatment comprises dual immunotherapy (IO+IO) or immunotherapy and multikinase inhibitor (IO+TKI) combinations.[7] However,

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Received: 30.12.2024 **Accepted:** 21.02.2025 **Publication Date:** 29.04.2025

Cite this article as: Doğan E, Fırat ST, Dişli AK, et al. Second line therapies after tyrosine kinase inhibitory in metastatic renal cell carcinoma. J Oncol Sci. 2025;11(1):30-35

***This study was presented as a summary poster in Current Developments in Cancer 2024; Urological and Gynecological Cancers Symposium in September 21-22, 2024, İstanbul, Türkiye.**

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several patients have not yet received 1st-line immunotherapy. Currently, several choices are available after the progression of first-line VEGF/VEGFR axis inhibitors. One option is continuing the inhibition of the VEGF/VEGFR axis with or without an immune checkpoint inhibitor.[8] Another option is to use dual- or monotherapy immune checkpoint inhibitors in patients in whom immunotherapy has not been used. No consensus exists on the best strategy for 2nd-line treatment. A few patients benefit more from tyrosine kinase inhibitors (TKIs), whereas other patients benefit more from immunotherapies. Patients with longer progression-free survival (PFS) rates to 1st-line TKI treatment may respond better to TKIs than to immunotherapy after progression on 1st-line TKIs. Conflicting data exist concerning this hypothesis.[9,10]

We compared the efficacy of 2nd-line treatments after the progression of 1st-line TKI treatments and determined the predictive factors for the efficacy of 2nd-line treatments in patients with metastatic RCC. In addition, we determined whether 2nd-line TKI treatments are more efficacious for longer PFS rates than 1st-line TKI (PFS1) treatments are compared with immunotherapy and mammalian target of rapamycin inhibitors.

MATERIAL AND METHODS

Study Design and Patient Characteristics

The medical records of patients diagnosed with metastatic RCC who had received 2nd-line treatment at the Kayseri City Hospital and Erciyes University Department of Medical Oncology were retrospectively reviewed between January 2007 and July 2024. Patients under the age of 18 years and those with non-metastatic diseases were excluded from the study.

Patients were divided into 3 groups, namely, the axitinib arm, the everolimus arm, and the nivolumab arm, according to 2nd-line treatments. The following patient characteristics were recorded for each study group: age at diagnosis, gender, histological subtype of the tumor, nephrectomy status, time from diagnosis to metastasis, metastatic site, number of metastatic organs, Memorial Sloan-Kettering Cancer Center (MSKCC) risk score, and the PFS rate of 1st-line TKI treatment. The study was approved by Kayseri City Hospital Non-Interventional Clinical Research Ethics Committee (date: March 14, 2024; no: 20).

Statistical Analysis

Frequencies and percentages (descriptive statistics) were used for categorical variables, and medians (minimum-maximum) were used for continuous variables. The PFS rates for 2nd-line treatments and OS rates were calculated using Kaplan-Meier analysis. Cox regression analyses were conducted to determine the associations between the PFS rates of 2nd-line treatments and other explanatory variables. In addition, Cox regression analyses were performed to determine the associations between OS rates and other explanatory variables. The PFS rates of patients who received 2nd-line treatments were compared with those of patients with PFS ≥6 mn to 1st-line TKI with PFS <6 mn, and Kaplan-Meier analyses were performed for each of the 3 groups. PFS was defined as the beginning time of treatment to death or progression of the disease. OS was defined as the time from the diagnosis of metastatic disease to death or the last control time. $p<0.05$ was considered to indicate statistical significance.

The study protocol adhered to the principles of the Declaration of Helsinki at all stages.

RESULTS

Patients and Patient Characteristics

The study included 82 patients who were diagnosed with metastatic RCC and had received 2nd-line treatment after 1st-line TKI treatment. Forty-one (50%) patients received axitinib as a 2nd-line treatment, 30 (37%) patients received everolimus as a 2nd-line treatment, and 11 (13%) patients received nivolumab as a 2nd-line treatment.

All the patient characteristics are summarized in Table 1.

Progression-Free Survival and Overall Survival

The PFS rate after 2nd-line treatment (PFS2) was 7 months (2.82-11.17) for the axitinib arm, 7 months (5.53-8.46) for the everolimus arm, and 8 months (6.73-9.26) for the nivolumab arm. No significant differences were present between these 3 arms (p=0.50). The OS rate was 21 months (10.98-31.01) for the axitinib arm, 35 months (23.96-46.03) for the everolimus arm, and 59 months (not reached) for the nivolumab arm, with no significant differences between these OS rates (p=0.205) (Figure 1).

The PFS2 rate was 2 months (0.974-3.026) in patients with PFS1<6 months and 9 months (0.339-17.661) in those with PFS1 ≥6 months on axitinib treatment (p<0.001). The PFS2 rates were 3 months (0.00-8.544) in patients with PFS1 <6 and 7 months (5.912-8.088) in those with PFS1 ≥6 on everolimus treatment (p=0.108). The PFS rates were 8 months (not reached) in patients with PFS1 <6 months and 19 months (7.560-30.440) in those with PFS1 ≥6 months on nivolumab treatment (p=0.659) (Figure 1).

Univariate analysis revealed that PFS1 <6 months was associated with poor PFS2 rates, with a hazard ratio of 0.373 (0.198-0.702, p=0.002) (Table 2).

TABLE 1: General characteristics.

	Axitinib, n=41 (50%)	Everolimus, n=30 (37%)	Nivolumab, n=11 (13%)
Age	58 (30-77)	59 (24-77)	67 (36-75)
Age <65 Age ≥65	33 (81) 8 (19)	19 (63) 11 (37)	5 (46) 6 (54)
Gender			
Female	13 (32)	5 (17)	2 (18)
Male	28 (68)	25 (83)	9 (82)
Histology			
Clear cell	36 (88)	26 (87)	11
Other	5 (12)	4 (13)	0
Nephrectomy			
No	6 (15)	9 (30)	4 (36)
Yes	35 (85)	21 (70)	7 (64)
Intervention			
No intervention	4 (10)	8 (27)	3 (27)
Nephrectomy	35 (85)	21 (70)	7 (64)
Embolisation	2 (5)	1 (3)	1 (9)
First line treatment			
Sunitinib	30 (73)	19 (63)	9 (82)
Pazopanib	8 (20)	3 (10)	2 (18)
Sorafenib	3 (7)	8 (7)	0
De novo metastatic disease			
No	17 (42)	12 (40)	3 (27)
Yes	24 (58)	18 (60)	8 (73)
MSKCC risk score			
Favorable	7 (17)	4 (13)	2 (18)
Intermediate	21 (51)	22 (74)	7 (64)
Poor	13 (32)	4 (13)	2 (18)
Liver metastasis			
No	29 (71)	24 (80)	9 (82)
Yes	12 (29)	6 (20)	2 (18)
Lung metastasis			
No	6 (15)	7 (23)	2 (18)
Yes	35 (85)	23 (77)	9 (82)
Bone metastasis			
No	28 (68)	24 (80)	7 (64)
Yes	13 (32)	6 (20)	4 (36)
Brain metastasis			
No	39 (95)	24 (80)	9 (82)
Yes	2 (5)	6 (20)	2 (18)
≥6 months 1st-line PFS			
No	7 (17)	8 (27)	3 (27)
Yes	34 (83)	22 (73)	8 (73)

MSKCC: Memorial Sloan-Kettering Cancer Center.

Furthermore, the univariate analysis revealed that a poor MSKCC score was significantly correlated with a poor OS rate, with a hazard ratio of 2.539 (1.180-5.463, p=0.017), and PFS1 <6 months was correlated with a poor OS rate, with a hazard ratio of 0.252 (0.149-0.426, p<0.001). The multivariate analyses revealed that PFS1 <6 months was correlated with a poor OS rate, with a hazard ratio of 0.229 (0.125-0.420, p<0.001) (Table 2).

DISCUSSION

Metastatic RCCs are vascular and immunogenic tumors for which new therapeutic strategies are being continuously developed. Although 1st-line IO+IO or IO+TKI combinations are recommended therapies for metastatic RCC, certain patients are unable to receive 1st-line immunotherapy, making TKIs an appropriate 1st-line treatment option. Which drug should be used as a 2nd-line treatment after the progression of 1st-line TKIs remains unclear. We demonstrated that the PFS rates associated with 3 drugs, namely, nivolumab, everolimus, and axitinib, were statistically similar to those associated with 2nd-line treatments. The OS rate was not significantly different among these 3 groups. In addition, we demonstrated that PFS1 ≥6 months is an independent prognostic factor for PFS2 and OS. Patients who received 2nd-line axitinib and whose PFS1 was ≥6 months had significantly greater PFS2 rates than patients whose PFS1 was <6 months. No significant differences in PFS2 were noted between patients with PFS1

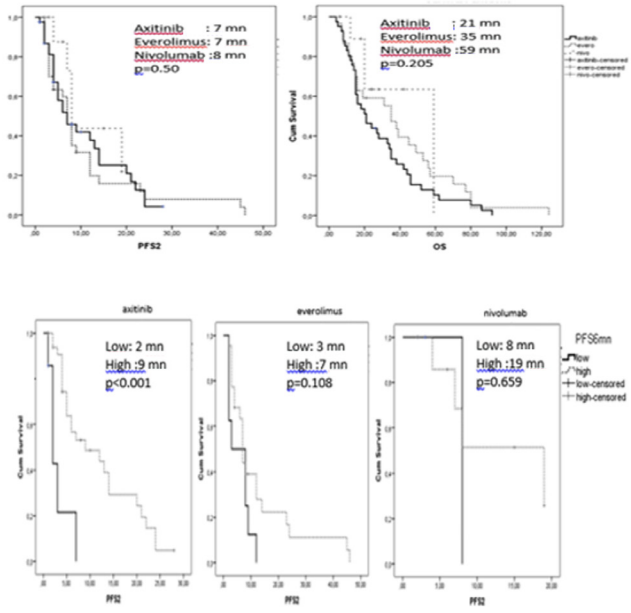

FIGURE 1: PFS2 and OS for axitinib, everolimus and nivolumab arm and progression free survival of second line treatments according to PFS1.

PFS2: Progression free survival-2; OS: Overall Survival

TABLE 2: Univariate and multivariate analyses for PFS2 and overal survival.

Characteristics	PFS2		OS			
	Univariate		Univariate		Multivariate	
	HR, 95% CI	p value	HR, 95% CI	p value	HR, 95% CI	p value
Age	0.995 (0.976-1.015)	0.631	1.004 (0.985-1.024)	0.682		
Gender Female or male	1.017 (0.561-1.845)	0.955	0.791 (0.452-1.384)	0.411		
Nephrectomy No or yes	0.666 (0.382-1.160)	0.151	0.792 (0.456-1.377)	0.408		
De novo metastatic Yes or no	0.839 (0.505-1.394)	0.499	1.381 (0.851-2.241)	0.191		
MSKCC risk score Favorable or intermediate Intermediate or poor	1.017 (0.532-1.942) 0.966 (0.393-2.374)	0.960 0.939	1.20 (0.614-2.343) 2.539 (1.180-5.463)	0.594 **0.017**	1.047 (0.532-2.060) 1.999 (0.913-4.378)	0.894 0.083
Liver metastasis No or yes	1.148 (0.660-1.997)	0.626	0.742 (0.427-1.288)	0.289		
Lung metastasis No or yes	1.330 (0.689-2.565)	0.395	1.711 (0.838-3.493)	0.141		
Bone metastasis No or yes	1.147 (0.638-2.062)	0.646	0.690 (0.405-1.176)	0.173		
Brain metastasis No or yes	1.171 (0.521-2.631)	0.703	1.040 (0.471-2.294)	0.923		
≥6 months 1st-line PFS No or yes	0.373 (0.198-0.702)	**0.002**	0.210 (0.116-0.379)	**<0.001**	0.229 (0.125-0.420)	**<0.001**

PFS2: Progression free survival-2; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; MSKCC: Memorial Sloan-Kettering Cancer Center.

≥6 months and those with PFS1 <6 months who received 2nd-line everolimus or nivolumab treatments.

Motzer et al.[9] conducted a phase 3 study that included 821 patients with advanced RCC and compared nivolumab and everolimus treatments after the progression of 1st- or 2nd-line antiangiogenic therapy. They reported that the median PFS rates were 4.6 months and 4.4 months, respectively, with nivolumab and everolimus treatments (p=0.11). This finding is consistent with that of our study. Our PFS rates were higher than those reported by Motzer et al.[9] for both nivolumab and everolimus treatments. The median OS rates were 25.0 months and 19.6 months in the nivolumab and everolimus groups, respectively, and these values were significantly different. In our study, the OS rates were 59 months and 35 months for the nivolumab and everolimus treatments, respectively. Although a 24-month OS rate difference existed between the everolimus and nivolumab treatment groups, this difference was not significant. The 1st reason for this result could be the small size of our study. Second, crossover was present in our study. Another difference from the other study was that certain patients had received 2 lines of antiangiogenic agents before their treatment. In our study, all patients received only 1 line of antiangiogenic agent. Another study revealed prolonged survival with nivolumab treatment compared with everolimus treatment, irrespective of the MSKCC score. Our univariate analysis revealed that the MSKCC score was an independent prognostic marker. However, this result was significant in multivariate analyses. Both uni- and multivariate analyses revealed longer PFS1 as the only independent prognostic factor for PFS and OS. The CheckMate 025 trial demonstrated improved PFS rates in patients who received nivolumab treatment compared with those who received everolimus treatment.[11] Pehlivan et al.[12] compared second-line axitinib and nivolumab treatments. They reported higher PFS and OS rates with second-line nivolumab treatment than with axitinib treatment. In our study, more patients had poor MSKCC scores in the nivolumab arm group than in both the axitinib and everolimus arm groups. Instudy from Pehlivan et al.[12] poor MSKCC scores were similarly found. Although a high rate of poor MSKCC scores in the nivolumab arm group was noted in our study, the OS rate was higher in the nivolumab arm group. However, the results were not significantly different. The nivolumab arm group did not report sufficient progression or death; therefore, the PFS and OS results were immature.

Busch et al.[13] conducted a study comparing 2nd-line everolimus and TKI treatments and reported no statistically significant difference in PFS between the 2 groups. However, sunitinib or sorafenib was used as a 2nd-line TKI in their study. In contrast, the present study exclusively utilized axitinib as a 2nd-line TKI following prior TKI failure.

These findings indicate that PFS1 serves as an independent prognostic marker for both PFS2 and OS. Additionally, patients with PFS1 ≥6 months demonstrated a statistically significant response to 2nd-line axitinib treatment compared with those with PFS1 <6 months. However, this statistical significance was not observed in the everolimus and nivolumab treatment arms. A subanalysis of the phase III Axis trial revealed that patients with prolonged responses to 1st-line cytokine therapy exhibited improved survival outcomes with 2nd-line axitinib treatment.[10,14] However, a prolonged response to 1st-line sunitinib did not influence the response to 2nd-line axitinib. In that study, responders were defined as those who achieved a complete or partial response. In the present study, patient groups were categorized on the basis of PFS1 ≥6 months or PFS1 <6 months following 1st-line treatment. Among patients receiving prior sunitinib, the median duration of 1st-line therapy in the axitinib group was 9.7 months, which was used as the cut-off for a prolonged response. Similarly, Seidel et al.[15] identified 1st-line PFS duration as an independent prognostic marker, with a cut-off of 6 months, which aligns with the findings of the present study.

To the best of our knowledge, this study is the only 1 comparing 3 distinct second-line agents with different mechanisms of action-nivolumab, axitinib, and everolimus. However, several limitations must be acknowledged, including the retrospective design and the relatively small study population.

CONCLUSION

No statistically significant differences were observed in PFS or OS among 2nd-line treatments with axitinib, everolimus, or nivolumab. Axitinib treatment significantly improved PFS2 in patients with PFS1 ≥6 months compared with those with PFS1 <6 months. However, in the nivolumab and everolimus groups, PFS2 rates did not significantly differ on the basis of PFS1 duration. This finding should be interpreted with caution due to the limited sample size.

Ethics

Ethics Committee Approval: The study was approved by Kayseri City Hospital Non-Interventional Clinical Research Ethics Committee (date: March 14, 2024; no: 20).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.D., A.K.D., Ş.Y.D., O.B., M.İ., M.Ö., Concept: E.D., M.Ö., Design: E.D., S.T.F., A.K.D., Ş.Y.D., O.B., M.İ., M.Ö., Data Collection or Processing: E.D., Ş.Y.D., A.K.D., S.T.F., Analysis or Interpretation: E.D., Literature Search: E.D., S.T.F., A.K.D., Ş.Y.D., Writing: E.D., Ş.Y.D.

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

Financial Disclosure: The authors declared that this study received no financial support.

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