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Reduced efficacy of nivolumab following prior immunotherapy in metastatic renal cell carcinoma: Implications for sequential immune checkpoint inhibition

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ABSTRACT

Aim: To evaluate the effect of first-line interferon therapy on survival outcomes in patients treated with nivolumab for renal cell carcinoma (RCC).

Methods: This retrospective study included 67 patients with mRCC who received nivolumab between March 2016 and September 2024 at our institution. Patients were stratified according to whether they had received interferon as first-line therapy. Survival outcomes following nivolumab were compared between the interferon and non-interferon groups.

Results: Among the 67 patients, 47 (70.1%) were male and 20 (29.9%) were female. At diagnosis, 36 patients (53.8%) had metastatic disease. Patients previously treated with interferon had a median progression-free survival (mPFS) of 6.7 months with nivolumab, compared with 13.7 months among those without prior interferon (p = 0.049). Similarly, the median overall survival (mOS) was 7.2 months in the interferon group versus 23.0 months in the non-interferon group (p = 0.003).

Conclusion: Prior interferon therapy appears to diminish the efficacy of subsequent nivolumab treatment in mRCC, suggesting potential limitations to sequential ICI strategies. These findings highlight the need for prospective studies to optimize the sequencing of immunotherapeutic agents in mRCC.

Keywords: Metastatic renal cell carcinoma, interferon-alpha, nivolumab.

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1. Introduction

Tumors of the kidney and renal pelvis account for 3-5% of newly diagnosed cancers. Renal cell carcinoma (RCC) accounts for 90% of all malignant neoplasms of the kidney [1]. RCC is approximately twice as common in men. The prevalence of RCC is highest in the sixth to eighth decade of life, with an average age at diagnosis of approximately 64 years. The incidence of RCC is extremely low in patients under the age of 40 [2].

The presentation of symptoms is diverse, with the classic triad of RCC (flank pain, hematuria and palpable abdominal renal mass) occurring in up to 9% of patients. This is suggests locally advanced disease when present. At the time of diagnosis, approximately 25 per cent of individuals have either distant metastases or advanced local regional disease [3]. RCC demonstrates resistance to

chemotherapy. Historically, interferon-alpha and interleukin-2 were widely employed as first-line treatments for metastatic disease over an extended period. Interferon alpha, a treatment used in the management of mRCC, has been demonstrated to enhance the immune response by stimulating T lymphocyte and natural killer (NK) cell activation and proliferation, and inducing apoptosis of tumour cells. The immunomodulatory and antiproliferative properties of interferon alpha contribute to its antitumour activity [4].

In accordance with novel therapeutic modalities, vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) and ICI agents have been employed in the management of mRCC [5]. TKIs and ICI agents are currently preferred more frequently because they show better response rates compared to interferon. Despite their success, concerns remain regarding the diminished efficacy of ICIs when administered after previous immune-based therapies. This has been particularly evident in the context of ICI rechallenge or sequential ICI strategies. Emerging evidence suggests that early immune modulation—whether via cytokines such as interferon or other ICIs—may reprogramme the tumour microenvironment in a way that impairs subsequent ICI responses. [6]. However, the underlying mechanisms and clinical impact of this phenomenon remain poorly defined.

In this study, we hypothesised that prior immune modulation with interferon, as an early immunotherapeutic intervention, might compromise the efficacy of subsequent immune checkpoint inhibition. Therefore, we aimed to evaluate the impact of first-line interferon therapy on survival outcomes in mRCC patients treated with nivolumab and to explore the broader implications for sequential ICI treatment strategies.

2. Materials and methods

This retrospective study included patients diagnosed with mRCC who received nivolumab therapy at the Department of Medical Oncology, Necmettin Erbakan University, between March 2016 and September 2024. The study protocol was approved by the institutional ethics committee (approval number: 2024/5160). Clinical and demographic data were collected from electronic medical records, including age, sex, histology, Fuhrman grade, presence of sarcomatoid differentiation, sites of metastasis, nephrectomy status, and prior systemic therapies. Patients were categorized according to their first-line treatment: IFNor TKI. Nivolumab was administered at a dose of 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. PFS was defined as the interval between the initiation of nivolumab and radiologically confirmed disease progression or death from any cause, whichever occurred first. OS was defined as the time from nivolumab initiation to death from any cause or last follow-up. Radiologic evaluations were performed every 10–12 weeks based on RECIST v1.1 criteria.

The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk score was calculated based on six baseline clinical and laboratory parameters:

1- Time from diagnosis to systemic therapy < 1 year;
2- Karnofsky performance status < 80%;
3- Hemoglobin level below the lower limit of normal;
4- Corrected serum calcium > 10 mg/dl;
5- Neutrophil count above the upper limit of normal; and
6- Platelet count above the upper limit of normal.

Patients were stratified into three prognostic categories: good (0 factors), intermediate (1–2 factors), and poor (≥ 3 factors).

2.1. Statistical Analysis:

The analysis was conducted using IBM SPSS V 20 software. The descriptive statistics comprised numerical data, percentages, and ratios. The chi-square test was employed to compare categorical variables between groups. The distribution of the continuous variables was assessed using the Kolmogorov–Smirnov test. The comparison of normally distributed variables was conducted through the utilization of the independent samples t-test, while non-normally distributed variables were comparatively analyzed through the employment of the Mann–Whitney U test. Survival analyses were performed using the Kaplan–Meier method, and survival distributions between groups were compared with the log-rank test. A p-value of less than 0.05 was considered to be statistically significant.

3. Results

In the study population, a total of 67 patients with metastatic RCC were evaluated. Patients were divided into two groups based on first-line treatments: 21 patients (31.3%) received interferon (IFN) and 46 patients (68.7%) received tyrosine kinase inhibitors (TKI). Table 1 presents the demographic and clinical characteristics of the study population.

Among the patients who received IFN, 18 out of 21 (85.7%) received nivolumab in the third-line setting. In contrast, among those who received TKI in the first-line setting, 36 patients (78.3%) received nivolumab in the second-line, while 5 patients (10.9%) received it in the third-line. Thus, the majority of patients in both groups received nivolumab as second- or third-line therapy.

The median age distribution between groups was similar, with no statistically significant difference. In the IFN group, 26.1% of patients were under 65 years, while 42.9% were aged 65 and above. In the TKI group, 73.9% were under 65 years, and 57.1% were 65 and older (p=0.170). Gender distribution did not differ significantly between the groups (p=0.319). In the IFN group, 40% of patients were female, while 60% were male. In the TKI group, 27.7% were female, and 72.3% were male.

Regarding histological type, clear cell carcinoma was observed in 37% of patients in the IFN group and 63% in the TKI group, whereas non-clear cell histology was found in 19% and 81% of patients, respectively (p=0.143). Furhman grade distribution was similar between the groups (p=0.722). Among IFN-treated patients, 38.9% had Grade 1 or 2 tumors, 28.6% had Grade 3 or 4, and 28.6% had an unknown grade. In the TKI group, 61.1% had Grade 1 or 2 tumors, 71.4% had Grade 3 or 4, and 71.4% were unknown. The presence of metastasis at diagnosis did not differ significantly between groups (p=0.705). Sarcomatoid features were present in 20% of patients in the IFN group and 80% in the TKI group (p=0.105). The proportion of cases with unknown sarcomatoid features was 42.3% in the IFN group and 57.7% in the TKI group.

Metastatic disease was observed in 33.3% of patients in the IFN group and 66.7% in the TKI group. Nephrectomy history was comparable between the groups (p=0.802). In the IFN group, 32.1% of patients had undergone nephrectomy, whereas 67.9% had not. Similarly, in the TKI group, 28.6% had a history of nephrectomy, while 71.4% had not.

IMDC risk classification showed no significant difference between the groups (p=0.261). In the IFN group, 47.1% of patients

Table 1. Clinical and pathological characteristics of the patients.

First Line Treatment	**IFN (n:21, %)**	**TKI (n:46,%)**	***p***
Age, median			
<65 years	12(26,1)	34 (73,9)	*0,170*
≥ 65 years	9 (42,9)	12 (57,1)	
Gender			
Female	8 (40)	12 (60)	*0,319*
Male	13 (27,7)	34 (72,3)	
Histological type			
Clear cell	17 (37)	29 (63)	*0,143*
Other	4 (19)	17 (81)	
Furhman Grade			
Grade 1 and 2	7 (38,9)	11 (61,1)	*0,722*
Grade 3 and 4	8 (28,6)	20 (71,4)	
Bilinmiyor	6 (28,6)	15 (71,4)	
Metastasis at diagnosis			
Yes	12 (33,3)	24 (66,7)	*0,705*
No	9(29)	22 (71)	
Nephrectomy history			
Yes	17 (32,1)	36 (67,9)	*0,802*
No	4 (28,6)	10 (71,4)	
Sarcomatoid features			
Present	7 (20)	28 (80)	*0,105*
Absent	3(50)	3 (50)	
Unknown	11 (42.3)	15 (57.7)	
IMDC risk group			
Good risk	8 (47,1)	9 (52,9)	*0,261*
Intermediate risk	11 (26,8)	30 (73,2)	
Poor risk	2 (22.2)	7 (77,8)	
MSKCC risk group			
Good risk	11 (50)	11 (50)	***0,05***
Intermediate risk	9 (25)	27(75)	
Poor risk	1 (11,1)	8(88,9)	

were classified as good risk, 26.8% as intermediate risk, and 22.2% as poor risk. In the TKI group, 52.9% were good risk, 73.2% were intermediate risk, and 77.8% were poor risk.

MSKCC risk classification revealed a statistical significance between the groups (p=0.05). In the IFN group, 50% of patients were classified as good risk, 25% as intermediate risk, and 11.1% as poor risk. In the TKI group, 50% were good risk, 75% were intermediate risk, and 88.9% were poor risk.

The median follow-up duration was similar between the groups, with 29.5 months in the IFN group and 29.2 months in the non-IFN group (p=0.799). Among patients who received interferon as first-line therapy, the median progression-free survival (mPFS) with nivolumab was 6.7 months, whereas in those

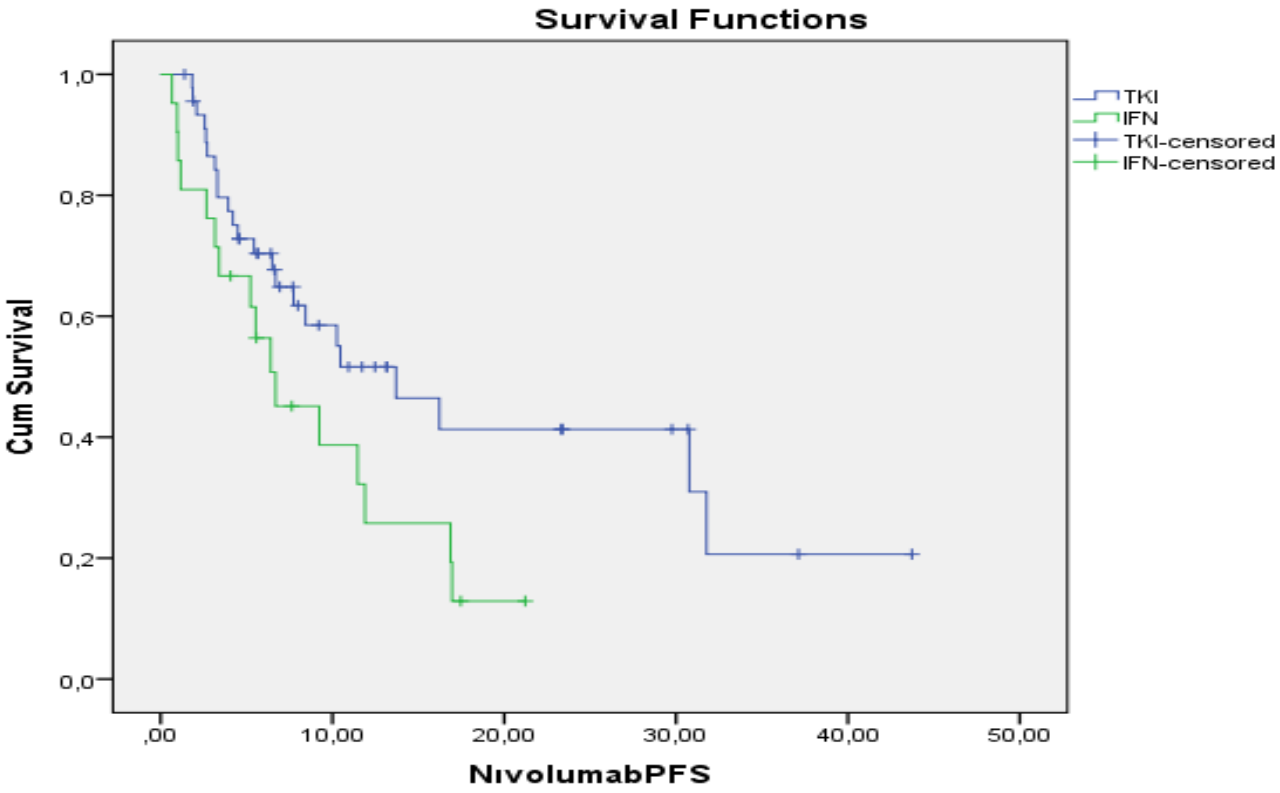

Figure 1. Nivolumab PFS after TKI/IFN.

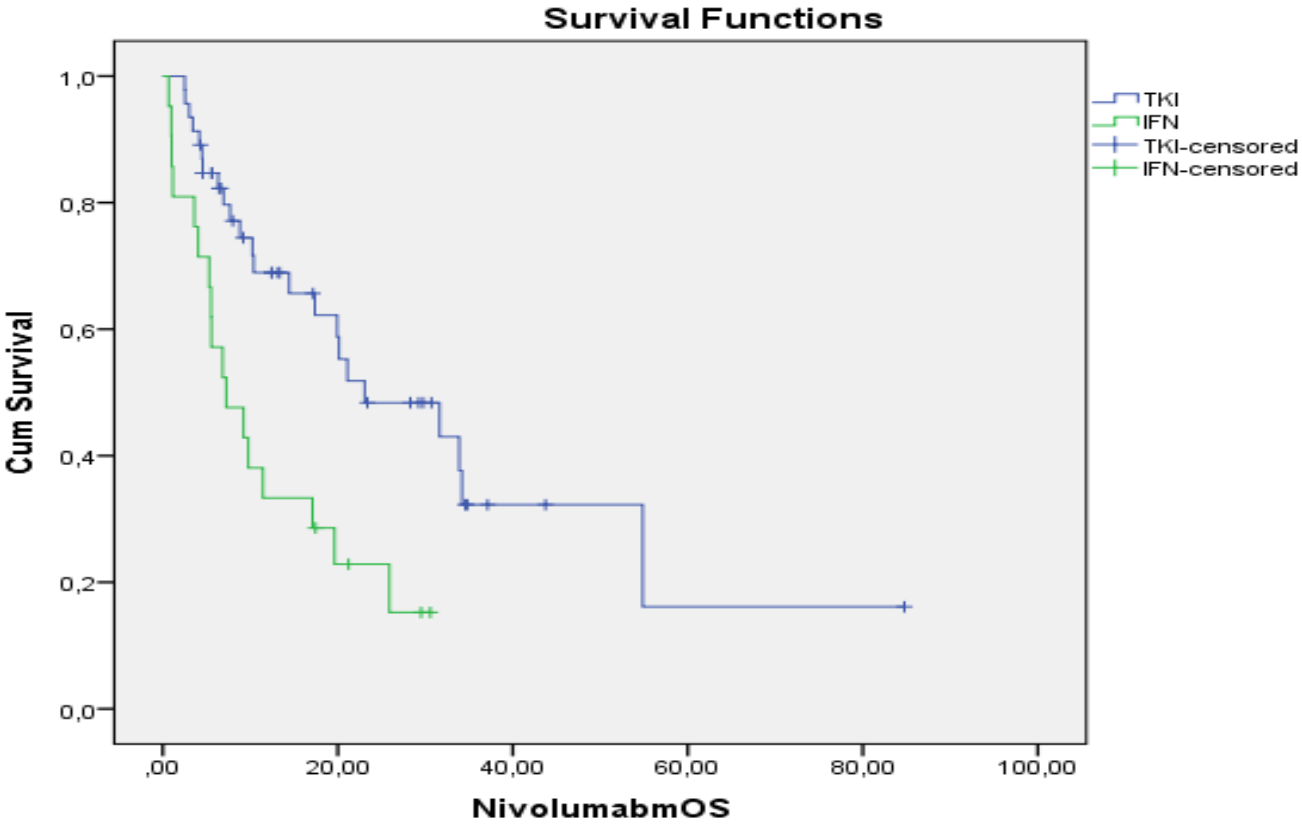

Figure 2. Nivolumab OS after TKI/IFN.

who did not receive interferon, the mPFS was 13.7 months (p=0.049) (Figure 1). Similarly, the median overall survival (mOS) with nivolumab was 7.2 months in the interferon-treated group, compared to 23 months in the non-interferon group (p=0.003) (Figure 2) (Table 2).

Table 2. Comparison of mPFS and mOS between IFN and TKI as first-line treatment.

First Line Treatment	**IFN (n:21)**	**TKI (n:46)**	***p***
mPFS (months)	6,7	13,7	***0,049***
mOS (months)	7,2	23	***0,003***

4. Discussion

This study demonstrated that first-line IFN therapy in mRCC patients significantly reduced the efficacy of subsequent nivolumab treatment, as evidenced by shorter mPFS and mOS compared to patients who did not receive prior IFN therapy. Although a higher proportion of patients were categorized in the poor-risk group according to the MSKCC criteria, the response to nivolumab was better in those who did not receive IFN. These results suggest that early immune modulation, even with a short course of interferon, may alter the tumor microenvironment in ways that impair subsequent ICI efficacy.

Interferons, specifically IFN-α used in cancer therapy, have profound immunomodulatory effects. It has been demonstrated that IFN-α enhances the activation and proliferation of T lymphocytes and natural killer (NK) cells, thereby promoting cytotoxic activity against tumor cells. IFN-α has been observed to upregulate MHC class I molecule expression, thereby enhancing antigen presentation and facilitating CD8+ T cell-mediated immune responses. IFN-α modulates the Th1/Th2 balance by favouring Th1 differentiation, thereby strengthening cellular immunity. Furthermore, IFN-α exerts a direct influence on B cells, regulating their proliferation and antibody production. Beyond immune activation, it has been demonstrated that IFN-α can induce tumor cell apoptosis and inhibit angiogenesis, thus contributing to its antitumor efficacy [7,8]. However, prolonged or intense immune stimulation may paradoxically induce immune exhaustion, regulatory T-cell expansion, and tolerogenic antigen-presenting cell phenotypes—mechanisms that are increasingly recognized as contributing to resistance to checkpoint blockade [9-11].

This asks the crucial question: Could long-lasting changes in the immune landscape caused by any previous immune-based therapy—not just IFN—compromised the efficacy of later ICIs? Despite being based on IFN, our results might be indicative of a larger issue with the clinical sequencing of immune treatments. Studies showing that patients with stable or progressive disease receiving initial ICI treatment respond less well to ICI rechallenge than those who receive full or partial responses [6] lend support to this. These findings imply that the efficacy of subsequent immune checkpoint blockade may be influenced by the nature and circumstances of the initial immune activation.

The findings of Albiges et al., which demonstrated that clear cell histology—a favorable prognostic factor—was associated with a superior ICI response in mRCC, provide further substantiation for this theory [12]. The efficacy of nivolumab was found to be lower in this study, despite the higher numerical frequency of clear cell histology observed in the IFN group. This finding implies that previous immune modulation may override histological predictors. Gore et al.'s findings, which showed a median progression-free survival (mPFS) of 5.5 months and a median overall survival (mOS) of 18.7 months for IFN in mRCC, further support the historical use of IFN as a first-line treatment [13]. Despite the enhanced efficacy of TKIs and ICIs in comparison to IFN, the immunological consequences of IFN therapy may still exert an influence on the tumor microenvironment. This is of particular significance in the context of nivolumab, which has been demonstrated to reinvigorate exhausted T cells and modify immune dynamics, thereby restoring anti-tumour immunity [14]. According to the study's findings, the benefits might be lessened in situations where the immune system has already been exposed to therapeutic interventions.

There is currently little research on ICI therapy after previous ICI treatment, and the results of the available studies are not always consistent. The diminished efficacy of sequential ICI strategies is hypothesized to be attributable to alterations in the immune microenvironment, encompassing diminished antigen presentation, T-cell dysfunction, and the emergence of immune tolerance. The results of this study underscore the imperative for further exploration into the alterations of the tumor-immune interface triggered by prior immune interventions. In the context of subsequent ICI use, further research is warranted into the well-established capacity of interferon to alter T-cell responses and, in particular, NK cell activity. The notable decreases in mPFS and mOS after IFN treatment observed in this study underscore the potential for such interactions and provide novel clinical data in this area. However, it is important to acknowledge the limitations of this study. The retrospective, single-center design of the study may be regarded as a limitation concerning the generalizability of the results. Furthermore, the mechanistic insight into how IFN exposure might affect nivolumab efficacy was limited due to the absence of comprehensive immune profiling.

Two principal objectives should be identified for future research purposes. It is imperative to initiate this study by elucidating the direct and enduring immunological consequences of IFN on the tumor microenvironment. Secondly, further research is necessary to ascertain whether sequential ICI resistance is a more prevalent occurrence. In order to ascertain the most effective sequencing techniques and thereby enhance the efficacy of immune checkpoint inhibitors in mRCC, it is essential to undertake comprehensive, multicenter studies incorporating detailed immune biomarker analyses.

4.1. Conclusion

This study provides valuable insights into the reduced efficacy of nivolumab, an ICI, following prior IFN therapy—a drug that activates the immune system within the tumor microenvironment. These findings raise crucial questions regarding the diminished efficacy of sequential ICI therapies and underscore the need for a more nuanced approach to the sequencing of such treatments. Future research is essential to unravel the underlying mechanisms driving this resistance and to refine

therapeutic strategies to optimize patient outcomes in the context of prior ICI treatment.

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Ethical Statement: *This study was conducted in accordance with the principles of the Declaration of Helsinki. The present study, application ID: 20828, received ethical approval from Necmettin Erbakan University Ethics Committee with the decision numbered 2024/5160. Written informed consent were obtained from the patients.*

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