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Outcomes of Patients with Metastatic Renal Cell Carcinoma Treated with Targeted Therapy After Immuno-oncology Checkpoint Inhibitors

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Abstract

Background: Immuno-oncology (IO) therapies have changed the treatment standards of metastatic renal cell carcinoma (mRCC). However, the effectiveness of targeted therapy following discontinuation of IO therapy in real-world settings has not been well studied.

Objective: To describe treatment sequence and assess clinical effectiveness of targeted therapy for mRCC patients who received prior IO therapy.

Design, setting, and participants: A retrospective, longitudinal cohort study using data from eight international cancer centers was conducted. Patients with mRCC were ≥18 yr old, received IO therapy in any line, and initiated targeted therapy following IO therapy discontinuation.

Intervention: Patients were treated with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) or mammalian target of rapamycin inhibitors (mTORIs).

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Outcome measurements and statistical analysis: Outcomes were time to treatment discontinuation (TTD), overall survival (OS), and objective response rate (ORR). Crude and adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazard models. Models were adjusted for age, sex, therapy line, and International Metastatic RCC Database Consortium risk group.
Results and limitations: Among 314 patients, 276 (87.9%) and 38 (12.1%) were treated with VEGFR-TKI and mTORI therapy, respectively. The most common tyrosine kinase inhibitor treatments were axitinib, cabozantinib, and sunitinib following IO therapy. In adjusted models, patients treated with VEGFR-TKI versus mTORI therapy had lower hazard of TTD after IO treatment (aHR = 0.46; 95% CI: 0.30–0.71; $p < 0.01$). One-year OS probability (65% vs 47%, $p < 0.01$) and proportion of ORR (29.8% vs 3.6%, $p < 0.01$) were significantly greater for patients treated with VEGFR-TKIs versus those treated with mTORIs.
Conclusions: Targeted therapy has clinical activity following IO treatment. Patients who received VEGFR-TKIs versus mTORIs following IO therapy had improved clinical outcomes. These findings may help inform treatment guidelines and clinical practice for patients post-IO therapy.
Patient summary: Patients may continue to experience clinical benefits from targeted therapies after progression on immuno-oncology treatment.

1. Introduction

An estimated 400 000 cases of kidney cancer, of which renal cell carcinoma (RCC) accounts for approximately 90%, are diagnosed annually worldwide [1]. Owing to a lack of early symptoms or clinical indications of disease, approximately 20% of patients present with metastatic RCC (mRCC) at diagnosis [2]. During the last decade, targeted therapies including vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) and mammalian target of rapamycin inhibitors (mTORIs) became the standard of care for mRCC patients. Targeted therapy has been associated with improved clinical efficacy, including progression-free survival (PFS) and overall survival (OS), favorable safety profiles, and improved health-related quality of life [3–9].

Recently, immuno-oncology (IO) therapeutic agents changed the treatment paradigm for mRCC by blocking immune checkpoints (eg, programmed death-1 [PD-1]/PD-ligand 1 [PD-L1]) and restoring tumor-specific T-cell–mediated immune responses [10]. IO agents demonstrated antitumor activity and durable responses in pretreated and treatment-naïve mRCC [11–13]. The IO combination therapy nivolumab with ipilimumab demonstrated improvement in OS and response rate versus sunitinib, and subsequently became a category 1, preferred first-line therapy for mRCC patients with International Metastatic RCC Database Consortium (IMDC) intermediate or poor risk [13,14]. Additional first-line IO therapies in combination with vascular endothelial growth factor (VEGF) inhibition [15–17] showed that patients treated with IO plus VEGFR-TKIs have improved outcomes versus patients treated with first-line sunitinib. However, despite promising early results of IO therapy, only a subset of patients experienced durable response, and the majority of patients developed progressive disease requiring subsequent systemic therapy [18].

Selecting optimal treatment sequences for mRCC patients who discontinue IO therapy is challenging because treatment guidelines and regulatory policies are not yet available. Real-world evidence on treatment sequences for mRCC patients who discontinue IO therapy is limited, and no prospective studies evaluating antitumor activity of targeted therapy following IO therapy have been reported. Several studies suggested antitumor activity of targeted therapy after PD-1/PD-L1 inhibition [18–21]. One retrospective study examined targeted therapies following IO therapy, and found that both VEGFR-TKIs and mTORIs demonstrated antitumor activity following PD-1/PD-L1 blockade [18]. However, these results lack generalizability to real-world settings as only mRCC patients enrolled in clinical trials were included.

To address these questions, this study aimed to evaluate the clinical effectiveness of targeted therapies immediately after IO treatment among mRCC patients.

2. Patients and methods

2.1. Study design

This was a retrospective, longitudinal cohort study among mRCC patients treated with targeted therapy following the discontinuation of IO therapy between 2010 and 2018. Data were collected from medical charts at MD Anderson Cancer Center and seven participating IMDC cancer centers representing Belgium, Canada, Denmark, and the USA, using standardized definitions to ensure consistent data collection.

Patients who received IO therapy after mRCC diagnosis, initiated targeted therapy as the subsequent line of therapy following IO therapy, and were at least 18 yr old at targeted therapy initiation were eligible. The observation period spanned from targeted therapy initiation (index date) to the

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date of last contact or death. The baseline period was defined from mRCC diagnosis to the index date.

Demographic and clinical characteristics were collected prior to and on the index date. The IMDC prognostic risk group was computed at the index date based on the presence of six individual risk factors (ie, <1 yr from RCC diagnosis to treatment initiation, Karnofsky performance status <80%, serum hemoglobin < lower limit of normal, corrected calcium > upper limit of normal [ULN], neutrophil count > ULN, and platelet count > ULN). Those with no risk factors were of favorable risk, those with one to two risk factors were of intermediate risk, and those with more than three risk factors were of poor risk [22].

Data on treatment sequences and clinical outcomes during follow-up were collected. Time to treatment discontinuation (TTD) for targeted therapy was defined as the time from initiation to discontinuation for any reason. OS was defined as the time from targeted therapy initiation to death due to any reason. Real-world physician-assessed best response was based on clinical criteria or radiographic criteria using Response Evaluation Criteria in Solid Tumors guidelines, with imaging assessments occurring at clinically variable time points. The best response is reported as an objective response rate (ORR), defined as the proportion of patients with a partial or complete response [23].

All data were deidentified and complied with patient confidentiality requirements of the Health Insurance Portability and Accountability Act. All study materials were approved by local institutional review boards at each center.

2.2. Statistical analyses

Treatment groups were identified based on targeted therapy received following IO therapy. Patients treated with antiangiogenic therapies, referred to as VEGFR-TKIs (axitinib, bevacizumab, cabozantinib, pazopanib, sorafenib, and sunitinib) versus mTORIs (everolimus and temsirolimus) were compared. Baseline demographic and clinical characteristics are presented by treatment group using frequencies and percentages for categorical variables and means, standard deviations (SDs), and medians for continuous variables. Pearson chi-square or Fisher's exact tests for categorical variables, and *t* tests or Wilcoxon rank-sum tests for continuous variables were conducted as appropriate.

Real-world treatment sequences for IO therapy and subsequent targeted therapy were described by line of therapy in a Sankey flow chart. Reasons for treatment discontinuation were described using relative frequencies and compared using Pearson chi-square or Fisher's exact test, where appropriate.

For TTD, median time and 95% confidence intervals (CIs) were estimated using Kaplan-Meier analysis, where those who did not have the event were censored at the date of the last follow-up. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% CIs between groups, adjusting for potential baseline confounders selected a priori. These confounders included age, sex, IMDC risk, and line of targeted therapy. One-year OS probability was reported. Physician-assessed best tumor response (ie, ORR) was presented. All clinical outcomes were reported for the three most common VEGFR-TKI agents by line of therapy among patients treated with targeted therapy after nivolumab (alone or with ipilimumab) to minimize heterogeneity between agent specific cohorts.

All *p* values were two sided, and a threshold of <0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient characteristics

Among 314 mRCC patients who initiated targeted therapy following IO therapy, the median age was 63 yr (range 24–90 yr) at the index date (Table 1). Most patients were male (75.2%), were white (81.9%), had IMDC intermediate risk (62.0%), and had clear-cell tumor pathology (89.9%). Following IO therapy, 276 (87.9%) and 38 (12.1%) patients were treated with VEGFR-TKIs and mTORIs, respectively. Compared with patients who received mTORIs after IO therapy, those who received VEGFR-TKIs more frequently had only one line of prior therapy (37.0% vs 5.3%; $p < 0.01$).

3.2. Treatment sequences

The most common IO therapy received was nivolumab alone (67.2%) or with ipilimumab (14.0%). Most patients received IO therapy in first or second line (71.9%). Fig. 1 illustrates treatment sequence for all 314 eligible patients. Sunitinib was the most common first-line therapy, while nivolumab was the most common second-line therapy. A total of 210 patients (66.9%) received a third-line, 88 (28.0%) received a fourth-line, and 17 (0.5%) received a fifth-line therapy. Comparing line of treatment in patients receiving VEGFR-TKIs ($n = 276$) versus mTORIs ($n = 38$), 174 (63.0%) versus 36 (94.7%) received third-line, 75 (27.2%) versus 13 (34.2%) received fourth-line, and 17 (6.2%) versus 0 (0.0%) received fifth-line therapy.

3.3. Clinical outcomes

Median TTD for targeted therapy following IO therapy was longer for patients who received VEGFR-TKIs versus those who received mTORIs (6.1 mo [95% CI: 5.4, 7.8] vs 2.8 mo [95% CI: 2.0, 3.4]; $p < 0.01$; Fig. 2). After adjusting for baseline characteristics including therapy line, patients who received VEGFR-TKIs versus mTORIs following IO therapy had a 54% reduction in the hazard of TTD (adjusted HR = 0.46 [95% CI: 0.30, 0.71], $p < 0.01$).

Reasons for discontinuing IO therapy did not differ by subsequent targeted therapy type (VEGFR-TKIs vs mTORIs; Supplementary Table 1). Disease progression was the most common reason for discontinuing prior IO therapy (82.9% and 84.6% among VEGFR-TKI and mTORI patients, respectively). Similarly, the most frequent reason for discontinuing targeted therapy was disease progression (61.7% and 47.8% among VEGFR-TKI and mTORI patients, respectively).

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Table 1 – Baseline demographic and clinical characteristics among patients treated with any targeted therapy, and by targeted therapy group (ie, VEGFR-TKI vs mTORI) after IO treatment.[a].

Characteristics	All targeted therapies *N* = 314	VEGFR-TKI *N* = 276	mTORI *N* = 38	*p* value[b]
Demographic characteristics				
Age (yr), mean ± SD (median)[c]	62.3 ± 10.6 (62.8)	62.3 ± 10.7 (62.8)	62.4 ± 10.3 (62.8)	0.99
Race, *n* (%)	215	188	27	0.79
White	176 (81.9)	153 (81.4)	23 (85.2)	
Non–white	39 (18.1)	35 (18.6)	4 (14.8)	
Sex, *n* (%)	314	276	38	0.33
Male	236 (75.2)	205 (74.3)	31 (81.6)	
Female	78 (24.8)	71 (25.7)	7 (18.4)	
Clinical characteristics				
IMDC prognostic risk group, *n* (%)[d,e]	258	224	34	
Favorable	28 (10.9)	24 (10.7)	4 (11.8)	0.77
Intermediate	160 (62.0)	142 (63.4)	18 (52.9)	0.24
Poor	70 (27.1)	58 (25.9)	12 (35.3)	0.25
Tumor characteristics				
Pathology, *n* (%)	298	261	37	0.08
Clear cell	268 (89.9)	238 (91.2)	30 (81.1)	
Non–clear cell	30 (10.1)	23 (8.8)	7 (18.9)	
Subtypes	19	15	4	
Papillary	14 (73.7)	13 (86.7)	1 (25.0)	0.08
Chromophobe	5 (26.3)	2 (13.3)	3 (75.0)	0.07
Prior treatment				
Nephrectomy, *n* (%)	314	276	38	0.60
Yes	275 (87.6)	240 (87.0)	35 (92.1)	
No	39 (12.4)	36 (13.0)	3 (7.9)	
Prior IL-2 or IFN therapy, *n* (%)	270	232	38	0.48
Yes	18 (6.7)	17 (7.3)	1 (2.6)	
No	252 (93.3)	215 (92.7)	37 (97.4)	
Number of prior lines (including IO treatment)	314	276	38	
1	104 (33.1)	102 (37.0)	2 (5.3)	<0.01 *
2	122 (38.9)	99 (35.9)	23 (60.5)	<0.01 *
≥3	88 (28.0)	75 (27.2)	13 (34.2)	0.37

IFN = interferon; IL-2 = interleukin 2; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IO = immuno-oncology; mTORI = mammalian target of rapamycin inhibitor; RCC = renal cell carcinoma; SD = standard deviation; VEGFR-TKI = vascular endothelial growth factor receptor tyrosine kinase inhibitor.

[a] The baseline period was defined as the time from advanced RCC diagnosis to the date of initiation of targeted therapy following IO (the index date).

[b] *p* values were computed using a global chi-square test (or Fisher's exact test as appropriate) for categorical variables and Wilcoxon rank sum test for continuous variables.

[c] Age was calculated at the time of initiation of targeted therapy after IO.

[d] IMDC prognostic risk groups were calculated by adding prognostic risk factors, which included the following: (1) <1 yr from time of RCC diagnosis to first-line therapy initiation, (2) Karnofsky performance status <80%, (3) hemoglobin < lower limit of normal, (4) corrected calcium > upper limit of normal (ULN), (5) neutrophil > ULN, and (6) platelets > ULN. Patients with zero risk factors were categorized as favorable-risk, one to two risk factors as intermediate-risk, and three or more risk factors as poor-risk patients.

[e] Measurements were taken at the time of the first subsequent targeted therapy following IO therapy.

Discontinuation due to toxicity was observed in 26.3% and 30.4% of VEGFR-TKI and mTORI patients, respectively.

After IO, VEGFR-TKI patients also experienced longer OS and a higher ORR than mTORI patients (Table 2). The 1-yr OS probability was significantly higher for VEGFR-TKI patients than for mTORI patients (65% vs 47%, $p < 0.01$). Patients who received post-IO VEGFR-TKIs had higher ORRs than those who received post-IO mTORIs (29.8% vs 3.6%, $p < 0.01$).

Among 255 patients treated with targeted therapy after nivolumab (alone or with ipilimumab), 83 (32.6%) had axitinib, 64 (25.1%) had cabozantinib, 31 (12.2%) had sunitinib, 30 (11.8%) had everolimus, 29 (11.4%) had pazopanib, 11 (4.3%) had sorafenib, five (2.0%) had temsirolimus, and two (0.8%) had bevacizumab. The three most common VEGFR-TKIs (axitinib, cabozantinib, and sunitinib) were included in agent-specific analysis. Overall, clinical outcomes (ie, median TTD, 1-yr OS, and ORR) for specific therapeutic agents differed by line of therapy (Table 3).

4. Discussion

The current analysis represents the largest clinical effectiveness study of targeted therapy following IO therapy to date. Our results demonstrate that patients may experience clinical benefit from targeted therapies after IO progression. Patients treated with VEGFR-TKIs versus mTORIs after IO therapy had longer TTD, higher 1-yr OS, and greater ORR. The study findings imply that mRCC appears to remain sensitive to VEGF inhibition following IO therapy. We also found tyrosine kinase inhibitor (TKI) following IO therapy to be safe, with frequencies of treatment discontinuation reasons to be in line with previous drug experiences

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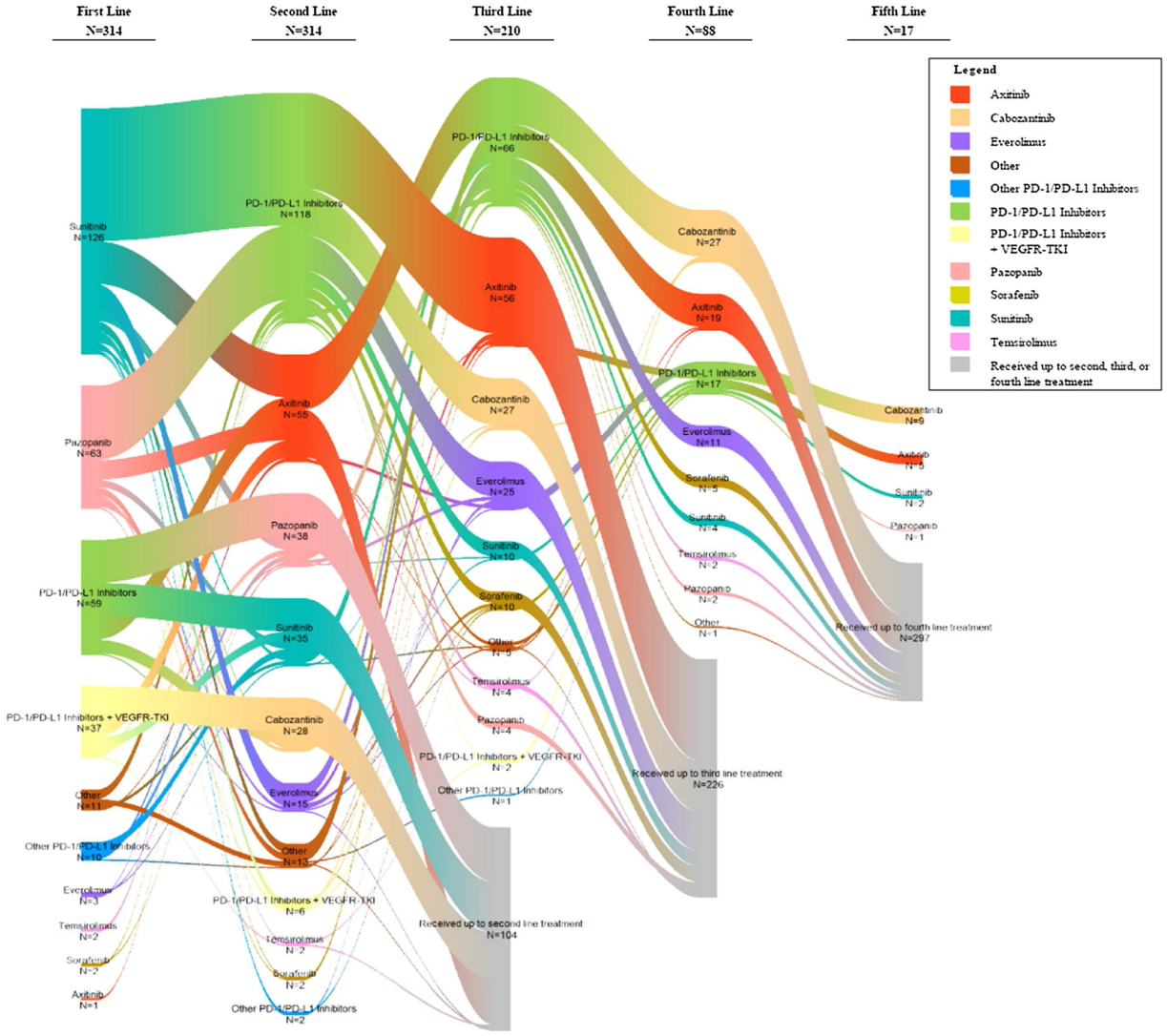

Fig. 1 – Treatment sequence for all lines of therapy among patients treated with any targeted therapy (ie, VEGFR-TKI and mTORI) after IO treatment.[a,b,c,d,e] IO = immuno-oncology; mTORI = mammalian target of rapamycin inhibitor; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1; VEGFR-TKI = vascular endothelial growth factor receptor tyrosine kinase inhibitor. [a] The study population was made up of 314 patients who received IO treatment (in any line of therapy) and subsequently received targeted therapy. For these 314 patients, the treatment sequence from these patients' first line of therapy to their fifth line of therapy is presented from left to right. The width of the arrows for each specific therapy agent is proportional to the number of patients who received that therapy. [b] PD-1/PD-L1 inhibitors included nivolumab (alone or in combination with Ipilimumab). [c] PD-1/PD-L1 inhibitors + VEGFR-TKI included nivolumab + bevacizumab, atezolizumab + bevacizumab, avelumab + axitinib, pembrolizumab + bevacizumab, pembrolizumab + axitinib, avelumab + bevacizumab, pembrolizumab + afatinib, and nivolumab + sunitinib. [d] Other PD-1/PD-L1 inhibitors included avelumab, atezolizumab, and pembrolizumab. [e] Therapies with small numbers (four or fewer patients) not grouped into previously created categories were classified as "other." Other included investigational drug, interleukin-2, nivolumab + interleukin-2, nivolumab + varlilumab, nivolumab + X4P, savolitinib, bevacizumab, and cediranib.

[20,24,25]. These findings may assure clinicians and patients in the treatment decision process following failure of IO therapy.

In this study, most patients received IO therapy, usually nivolumab alone or with ipilimumab, in first or second-line followed by targeted therapy. This is reflective of the current treatment landscape, where nivolumab was approved in mRCC patients who received prior antiangiogenic therapy and nivolumab plus ipilimumab was approved as front-line treatment for advanced RCC patients with IMDC intermediate or poor risk. IO therapy including nivolumab plus ipilimumab has an antitumor effect through activation of the endogenous immune system to target cancer at the cellular level by enabling checkpoint inhibition [26]. A hypothesis-generating prospective trial of IO therapy via PD-1/PD-L1 blockade demonstrated an increase in lymphocytic presence and reversal of T-cell exhaustion [27]. Thus, IO therapy, and particularly nivolumab, may produce enduring changes to the tumor microenvironment, which in turn may activate and enhance the impact of subsequent

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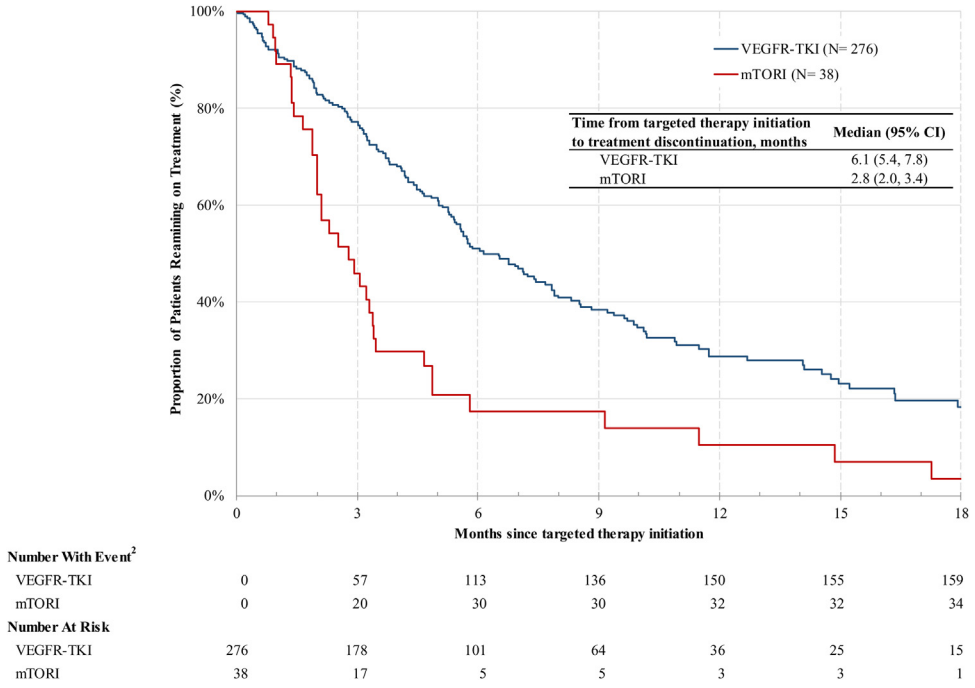

Fig. 2 – Kaplan-Meier analysis of time to treatment discontinuation for patients treated with VEGFR-TKI and those treated with mTORI after IO treatment.[a] CI = confidence interval; IO = immuno-oncology; mTORI = mammalian target of rapamycin inhibitor; VEGFR-TKI -= vascular endothelial growth factor receptor tyrosine kinase inhibitor. [a] Time to treatment discontinuation was defined as the time from the initiation to discontinuation of the first subsequent targeted therapy following IO therapy for any reason including progression, death, or toxicity. Patients who were still on their first subsequent targeted therapy following IO therapy or lost to follow-up were censored at their date of the last follow-up. [b] Over the entire follow-up period, 165 (59.8.0%) patients receiving VEGFR-TKI compared with 35 (92.1%) receiving mTORI had the event.

Table 2 – Treatment outcomes among patients treated with VEGFR-TKI and those treated with mTORI after IO treatment.

	Total *N*	Time to treatment discontinuation[a]		Overall survival		Physician-assessed best response[b]
		No. of discontinuation	Median (95% CI), mo	No. of deaths[c]	1-yr probability, % (95% CI)	Objective response rate, *n* (%)[d]
VEGFR-TKI						
All lines	276	165	6.1 (5.4, 7.8)	67	65 (58, 72)	57 (29.8)
2nd line	102	62	7.5 (5.4, 10.0)	18	78 (68, 86)	30 (35.7)
3rd line	99	63	5.6 (4.2, 7.8)	26	61 (48, 72)	13 (21.0)
≥4th line	75	40	6.1 (4.7, 9.2)	23	47 (30, 62)	14 (31.1)
mTORI						
All lines	38	35	2.8 (2.0, 3.4)	18	47 (30, 63)	1 (3.6)
2nd line	2	2	4.1 (3.3, 4.9)	1	50 (1, 91)	0 (0.0)
3rd line	23	23	2.3 (1.9, 3.1)	12	47 (26, 65)	1 (5.6)
≥4th line	13	10	3.3 (1.4, 4.7)	5	50 (17, 76)	0 (0.0)

CI = confidence interval; IO = immuno-oncology; mTORI = mammalian target of rapamycin inhibitor; *N* = sample size; VEGFR-TKI = vascular endothelial growth factor receptor tyrosine kinase inhibitor.

[a] Time to treatment discontinuation was calculated using Kaplan-Meier analysis and was defined as the time from the initiation to discontinuation of the first subsequent targeted therapy following IO therapy for any reason including progression, death, or toxicity. Patients who were still on their first subsequent targeted therapy following IO therapy or lost to follow-up were censored at their date of last follow-up.

[b] Physician-assessed best response was based on clinical criteria or radiographic criteria using the Response Evaluation Criteria in Solid Tumors guidelines, and assessed during the first targeted therapy subsequent to IO treatment. The best response was assessed in 219 out of 314 patients.

[c] The number of deaths was assessed in the 12-mo period following the index date (date of the first subsequent targeted therapy initiation after IO therapy).

[d] The objective response rate is defined as the sum of partial plus complete responses and is a direct measure of drug antitumor activity.

targeted agents. Additional clinical trials examining IO plus VEGFR-TKI therapies for first-line treatment also show promising results, suggesting that there may be potential additive effects between the two therapies [15–17]. An observational study comparing efficacy between nivolumab plus ipilimumab with IO therapy plus VEGFR-TKIs in the first-line setting found greater second-line response rates to targeted therapy in patients who received the IO-IO combination of nivolumab plus ipilimumab [28]. Our study further expands on those results by examining patients who received IO therapy beyond first-line, another clinically relevant patient population. In addition, while first-line IO combinations are becoming more common, some health care systems may not have access to these therapies;

Table 3 – Treatment outcomes among patients treated with the three most common VEGFR-TKI targeted therapy agents after nivolumab (alone or in combination with ipilimumab) IO therapy (total *N* = 255).

	Total *N*	Time to treatment discontinuation[a]		Overall survival		Physician-assessed best response[b]
		No. of discontinuation	Median (95% CI), mo	No. of deaths[c]	1-yr probability, % (95% CI)	Objective response rate, *n* (%)[d]
Axitinib						
Received in 2nd line	12	7	10.2 (6.5, NR)	1	89 (45, 98)	7 (58.3)
Received in 3rd line	49	30	5.7 (3.6, 10.2)	12	61 (41, 76)	5 (17.9)
Received in ≥4th line	22	16	4.7 (2.4, 12.7)	8	49 (22, 71)	2 (16.7)
Cabozantinib						
Received in 2nd line	7	4	11.4 (6.8, 15.0)	1	83 (27, 97)	3 (50.0)
Received in 3rd line	24	10	7.0 (3.0, 16.4)	6	47 (16, 73)	4 (26.7)
Received in ≥4th line	33	10	9.2 (5.3, NR)	6	59 (26, 82)	10 (41.7)
Sunitinib						
Received in 2nd line	17	12	5.5 (3.2, 14.8)	3	78 (46, 92)	7 (53.8)
Received in 3rd line	8	6	11.6 (2.8, NR)	2	75 (31, 93)	2 (25.0)
Received in ≥4th line	6	4	7.2 (0.7, NR)	3	40 (5, 75)	1 (33.3)

CI = confidence interval; IO = immuno-oncology; *N* = sample size; NR = not reached; VEGFR-TKI = vascular endothelial growth factor receptor tyrosine kinase inhibitor.

[a] Time to treatment discontinuation was calculated using Kaplan-Meier analysis and was defined as the time from the initiation to discontinuation of the first subsequent targeted therapy following IO therapy for any reason including progression, death, or toxicity. Patients who were still on their first subsequent targeted therapy following IO therapy or lost to follow-up were censored at their date of last follow-up.

[b] Physician-assessed best response was based on clinical criteria or radiographic criteria using the Response Evaluation Criteria in Solid Tumors guidelines, and assessed during the first targeted therapy subsequent to IO treatment. The best response was available in 146 out of 213 patients.

[c] The number of deaths was assessed in the 12-mo period following the index date (date of the first subsequent targeted therapy initiation after IO therapy).

[d] The objective response rate is the sum of the proportion of patients with partial and complete responses.

therefore, understanding different treatment outcomes following first-line IO therapy will be important for clinicians selecting subsequent therapy.

Results from this study are similar to those of previous studies [18–21]. A targeted literature review presented in Table 4 examines the impact of specific VEGFR-TKI and mTORI after IO therapy on median PFS/TTF, 1-yr OS probability, and ORR across six studies and a total of 278 patients (253 [91.0%] VEGFR-TKI patients and 25 [9.0%] mTORI patients). Overall, patients treated with VEGFR-TKIs following IO therapy achieved median PFS ranging from 4.8 to 10 mo, an ORR ranging from 16% to 42%, and a 1-yr OS probability ranging from 61% to 88%. The Auvray et al [20] study among patients treated with VEGFR-TKIs after first-line nivolumab plus ipilimumab demonstrated an ORR to subsequent TKI of 36% and median PFS of 8 mo (95% CI: 5, 13). In addition, among 56 patients enrolled in clinical trials of IO therapy who received subsequent targeted therapy, Albiges et al [18] reported longer median time to treatment failure (6.9 mo [95% CI: 0.2, 19.3] vs 5.7 mo [95% CI: 0.5, 23.0]) and higher ORR (16% vs 0%) for patients treated with VEGFR-TKIs versus mTORIs. Although statistical comparison of these differences were not reported, these results support the findings that patients treated with VEGFR-TKIs may have improved clinical outcomes than those treated with mTORIs following IO therapy. Further research into the effectiveness of VEGFR-TKIs for subgroups of patients who are TKI naïve and patients with prior TKI therapy may be warranted.

Following IO therapy, our study found VEGFR-TKIs in particular have activity, with patients staying on treatment longer, increased survival, and improvement in response rate. The clinical benefits were observed in subsequent lines of therapy following VEGFR-TKI and IO failure. The clinical activity observed might be explained by "pseudoprogression" due to inflammation of the tumor caused by IO therapy. Administration of VEGFR-TKIs may thus lead to "pseudotumor shrinkage" due to anti-inflammatory effect of VEGF inhibition, which is not observed with mTORIs. However, interestingly, there may be a role for mTORI plus VEGFR-TKI therapy in this post-IO setting. Recent data found that patients who had progressed on previous VEGFR-TKI therapy who then recieved everolimus plus lenvatinib had a PFS benefit [29,30]. While no patients in this study received this combination, further research to determine whether patients treated with everolimus plus lenvatinib subsequent to IO therapy would have better clinical outcomes is warranted. It should also be noted that 37% of patients in our study received VEGF-TKI in second-line versus only 5.3% of everolimus-treated patients. The differences in outcomes may be related to the line of therapy in which the agent was used. This may also reflect that mTORI is an available option in later lines, after patients have failed both IO and VEGFR-TKI therapies.

These results should be interpreted with caution in light of several limitations. First, this is a retrospective analysis of nonrandomized treatment groups whereby unmeasured confounding and potential biases (eg, selection bias) could account for some heterogeneity and observed associations. The heterogeneity observed reflects the treatment landscape of real-world patients, as opposed to a more narrow clinical trial study population, which is one of the key strengths of our study. For TTD, we attempted to reduce bias by adjusting for potential confounders including age, sex, IMDC prognostic risk group, and line of targeted therapy.

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Table 4 – Select clinical outcomes among patients treated with VEGFR-TKI or mTORI therapies after IO therapy.

Targeted therapy	Treatment agent(s)	Prior IO therapy	*N*	Median PFS/TTF[a] (95% CI), mo	1-yr OS probability (95% CI), %	ORR[b] (%)	Source
VEGFR-TKI	Axitinib	PD-1/PD-L1 inhibitors	20	10.0 (range: 0.2+, 19.3)	69 (34, 88)	15.8	Albiges et al (2015) [18] [c]
		Nivolumab-ipilimumab	8	7 (5, NR)	–	–	Auvray et al (2019) [20]
	Cabozantinib	PD-1/PD-L1 inhibitors	18	NR (3.8, NR)	–	22.2	Powles et al (2018) [34]
		ICIs	55	8.1 (6.4–14.9)	64 (45–78)	41.9	McGregor et al (2018) [35]
	Sunitinib	Nivolumab-ipilimumab	17	8 (3, NR)	–	–	Auvray et al (2019) [20]
	Pazopanib	PD-1/PD-L1 inhibitors	14	4.8 (range: 0.6, 11.1)	61 (27, 84)	–	Albiges et al (2015) [18]
	Axitinib, sunitinib, pazopanib, sorafenib	PD-1/PD-L1 inhibitors alone or in combination with VEGFR-TKI	70	6.4 (4.3, 9.5)	–	27.9	Nadal et al (2016) [21] [d]
	Axitinib, cabozantinib, pazopanib	ICIs	43	10 (7.4, NR)	87.5 (74.6–100)	41	Shah et al (2018) [19]
	Pazopanib, cabozantinib	Nivolumab-ipilimumab	8	5 (1, NR)	–	–	Auvray et al (2019) [20]
mTORI	Everolimus	PD-1/PD-L1 inhibitors	14	4.1 (1.9, 6.6)	–	0	Powles et al (2018) [34]
		PD-1/PD-L1 inhibitors	11	4.8 (range: 0.5, 23.0)	27 (4, 58)	–	Albiges et al (2015) [18]

CI = confidence interval; ICI = immune checkpoint inhibitor; IO = immuno-oncology; mTORI = mammalian target of rapamycin inhibitor; *N* = sample size; NR = not reached; ORR = objective response rate; OS = overall survival; PD-1 = programmed death-1; PD-L1 = programmed death ligand 1; PFS = progression-free survival; TTF = time to treatment failure; VEGFR-TKI = vascular endothelial growth factor receptor tyrosine kinase inhibitor.

[a] For McGregor et al [35] and Albiges et al [18], time to treatment failure was defined as the time period from treatment initiation to discontinuation due to disease progression, treatment toxicity, patient preference, death, or loss to follow-up. PFS was defined as treatment discontinuation due to disease progression, treatment toxicity, death, or loss to follow-up for Auvray et al [20] and Nadal et al [21]. PFS was assessed as per an independent radiology committee for Powles et al [34].

[b] The objective response rate is defined as the sum of partial plus complete responses and is a direct measure of drug antitumor activity.

[c] ORR was evaluated in 19 out of 20 patients.

[d] ORR was evaluated in 68 out of 70 patients.

While IMDC risk groups have been validated in first-, second-, and third-line settings, further studies may be warranted to validate fourth or later lines of therapy, as more patients with mRCC are being observed with longer follow-up time [31–33]. Second, in contrast to clinical trials, assessments of progression and clinical response in retrospective studies of real-world clinical practice may not be consistent across patients and physician practices. Third, missing data also exist, which may bias study results if the data are not missing completely at random. Further analysis showed that only a small proportion of patients (52/276 [18.8%] of VEGFR-TKI and 4/38 [10.5%] of mTORI patients) had missing data for IMDC risk. Thus, the bias due to missing data may be minimal. Furthermore, for the agent-specific analysis, comparisons between therapeutic agents were not possible due to limited sample size.

5. Conclusions

In conclusion, patients who received VEGFR-TKI treatment following IO therapy discontinuation had improved clinical outcomes, including TTD, OS, and ORR, versus patients who received mTORI treatment. These results demonstrate that VEGFR-TKI–based therapies continue to have activity following IO therapy and continue to translate into clinical benefits. For clinicians and researchers, these findings may provide benchmarks for future clinical trials and mRCC patient counseling.

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Appendix A. Supplementary data

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