Clinical Outcomes of First-line Sunitinib Followed by Immuno-oncology Checkpoint Inhibitors in Patients With Metastatic Renal Cell Carcinoma

J. Connor Wells,[1] Jeffrey Graham,[2] Benoit Beuselinck,[3] Georg A. Bjarnason,[4] Frede Donskov,[5] Aaron R. Hansen,[6] Rana R. McKay,[7] Ulka Vaishampayan,[8] Guillermo De Velasco,[9] Mei S. Duh,[10] Lynn Huynh,[10] Catherine Nguyen,[10] Giovanni Zanotti,[11] Krishnan Ramaswamy,[11] Toni K. Choueiri,[12] Daniel Y.C. Heng[1]

Abstract

Limited data are available on how the first-line duration can affect clinical outcomes observed after subsequent immuno-oncology treatment among patients with metastatic renal cell carcinoma. The present retrospective cohort study of 161 patients found that the first-line sunitinib duration might have a minimal effect on subsequent immuno-oncology therapy effectiveness. These findings could aid healthcare practitioners in the treatment decision process for sequencing therapies.

Background: The present retrospective, longitudinal cohort study assessed the association between the first-line sunitinib treatment duration and clinical outcomes with second-line immuno-oncology (IO) therapy among patients with metastatic renal cell carcinoma (mRCC). **Patients and Methods:** A total of 161 patients with mRCC who had been treated with first-line sunitinib and subsequent IO therapy from select International mRCC Database Consortium centers were included. The overall survival, time to next therapy, time to treatment discontinuation, and real-world physician-assessed best response measured from IO therapy initiation were analyzed and compared between patients treated with first-line sunitinib for $\geq$ 6 months and those treated for $<$ 6 months. **Results:** The 116 patients treated with sunitinib for $\geq$ 6 months tended to be older and to have a better International mRCC Database Consortium risk than the 45 patients treated for $<$ 6 months (favorable, 36% vs. 8%, $P =$ .001; intermediate, 59% vs. 70%, $P =$ .21; poor, 5% vs. 22%, $P =$ .007). The receipt of sunitinib for $\geq$ 6 months versus $<$ 6 months was associated with longer survival (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.21-0.87; $P =$ .02). No significant association was observed between the first-line sunitinib duration and second-line IO outcomes, including the time to next therapy (HR, 0.89; 95% CI, 0.52-1.51; $P =$ .66), time to treatment discontinuation (HR, 0.85; 95% CI, 0.54-1.34; $P =$ .49), and tumor response (odds ratio, 0.73; 95% CI, 0.22-2.49; $P =$ .62). **Conclusions:** We found no statistically significant association between the first-line sunitinib duration and clinical outcomes with second-line IO therapy. Patients receiving first-line sunitinib for $\geq$ 6 months compared with $<$ 6 months was associated with better overall survival, although potential unadjusted confounders could have been

[1]Department of Oncology, University of Calgary, Calgary, AB, Canada
[2]Department of Oncology, CancerCare Manitoba, University of Manitoba, Winnipeg, MB, Canada
[3]Department of Oncology, University Hospital Leuven, Kathoieke Universiteit Leuven, Leuven, Belgium
[4]Department of Oncology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada
[5]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark
[6]Department of Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada
[7]Department of Oncology, University of California, San Diego, San Diego, CA
[8]Department of Oncology, Karmanos Cancer Institute, Detroit, MI

[9]Department of Oncology, University Hospital 12 de Octubre, Madrid, Spain
[10]Analysis Group, Inc, Boston, MA
[11]Pfizer, Inc, New York, NY
[12]Department of Oncology, Dana-Farber Cancer Institute, Boston, MA

present. These findings support the paradigm that previous therapy will not dictate the effectiveness of subsequent immunotherapy.

Introduction

Immuno-oncology (IO) therapies have revolutionized the treatment paradigm for metastatic renal cell carcinoma (mRCC), adding to standard therapies, including tyrosine kinase inhibitors (TKIs), anti-vascular endothelial growth factor (VEGF) antibodies, and mammalian target of rapamycin inhibitors.[1,2] IO therapy includes immune checkpoint inhibitors such as nivolumab, which was approved in 2015 for treatment of advanced RCC after previous antiangiogenic therapy.[3,4] In 2018, combination nivolumab plus ipilimumab was approved for patients with treatment-naive International Metastatic Renal Cell Carcinoma (mRCC) Database Consortium (IMDC) intermediate- or poor-risk advanced RCC.[5,6] Additional first-line IO therapies combined with VEGF inhibitor therapies, including avelumab plus axitinib and pembrolizumab plus axitinib, were evaluated in clinical trials and approved in 2019.[7,8]

Limited data are available on how the first-line duration and clinical response might affect the clinical outcomes observed immediately after subsequent IO treatment. Previous studies have shown that sunitinib inhibits angiogenesis, has direct antitumor effects, and exacerbates intratumoral heterogeneity. Also, IO therapies might be more effective for tumors with a high mutational burden.[9-11] A subgroup analysis of the phase III CheckMate 025 trial demonstrated that patients with ≥ 6 months of first-line therapy with sunitinib, pazopanib, or interleukin-2 versus those with < 6 months had better median overall survival (OS) when subsequently treated with nivolumab (27.4 vs. 18.2 months) or everolimus (22.8 vs. 14.0 months).[12] Further study of the effect of first-line treatment duration on the second-line clinical outcomes is warranted, given the changing treatment landscape.

The objective of the present study was to evaluate the effect of the first-line sunitinib treatment duration (≥ 6 months vs. < 6 months) before IO therapy on the clinical outcomes in a real-world setting using data from the IMDC.

Patients and Methods

Study Design and Study Population

The present retrospective, longitudinal cohort study used data from the patient medical records at select IMDC cancer centers in Belgium, Canada, Denmark, and the United States. Uniform database templates and standardized definitions were used to ensure the data were collected consistently.[13] The eligible patients were adults with mRCC who had initiated first-line sunitinib therapy from 2006 to 2018 and had received subsequent IO therapy, either alone or combined with another therapy.

The observation period spanned the date from IO therapy initiation (index date) to the date of last contact or death. The baseline period was defined as the interval from the mRCC diagnosis to the index date. Data on the demographic and clinical characteristics during the baseline period to the index date were collected. The sunitinib treatment duration was defined as the interval from treatment initiation to discontinuation for any reason. The IMDC prognostic risk group was computed at sunitinib initiation and the index date according to the individual risk factors (ie, < 1 year from RCC diagnosis to sunitinib initiation, Karnofsky performance status < 80%, serum hemoglobin less than the lower limit of normal, corrected calcium greater than the upper limit of normal [ULN], neutrophil count greater than the ULN, platelet count greater than the ULN). Those with no risk factors were deemed to have favorable risk, those with 1 to 2 risk factors were deemed to have intermediate risk, and those with ≥ 3 factors were deemed to have poor risk.[13]

Data on the clinical characteristics, treatment patterns, and clinical endpoints in the follow-up period were collected. OS for IO therapy was defined as the interval from IO therapy initiation to death. The time to next therapy (TTNT) was defined as the interval from IO therapy initiation to initiation of the next line of therapy or death. The TTNT was used as an objective proxy for progression-free survival (PFS) owing to the difficulty in determining the true timing of progression during IO therapy, with many patients deriving clinical benefit from IO therapy even after discontinuing because of adverse events. The time to treatment discontinuation (TTD) for IO therapy was defined as the interval from IO therapy initiation to IO therapy discontinuation for any reason. The reasons for treatment discontinuation were collected. The real-world physician-assessed best response was determined from clinical and/or radiographic criteria using the Response Evaluation Criteria in Solid Tumors guidelines, with the imaging assessments occurring at clinically variable intervals. The objective response rate (ORR) was reported as the proportion of patients with a partial or complete response.[14]

All data were de-identified and complied with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act. The local institutional review board at each of the institutions approved all the study materials.

Statistical Analysis

The patients were categorized into treatment groups according to the duration of first-line sunitinib therapy. A 6-month threshold was chosen to reflect previous studies, which had investigated ≥ 6 months and < 6 months.[12,15] Descriptive statistics were calculated using frequencies and proportions for categorical variables and the mean ± standard deviation, and median for continuous variables. Differences between patients were compared using the Pearson χ^2 test or the Fisher exact test, as appropriate, for categorical variables, and continuous variables were compared using t tests or Wilcoxon rank-sum tests.

The real-world treatment patterns were described using a flow chart of the time between treatments using the median and
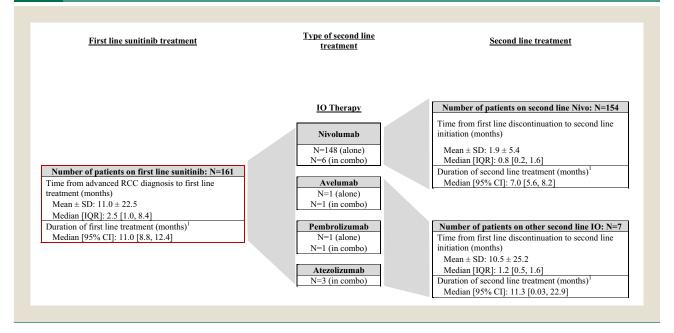
Table 1 Baseline Demographic and Clinical Characteristics[a]

Characteristic	First-line Sunitinib Duration		P Value
	<6 mo (n = 45)	≥6 mo (n = 116)	
Demographic			
Age at index date, y			.004[b]
Mean ± SD	57.8 ± 10.7	63.4 ± 11.1	
Median	58.9	65.0	
Race, n (%)			.85
White	25 (75.8)	60 (74.1)	
Nonwhite	8 (24.2)	21 (25.9)	
Sex, n (%)			.98
Male	35 (77.8)	90 (77.6)	
Female	10 (22.2)	26 (22.4)	
Tumor characteristic			
Pathologic findings, n (%)			.08
Clear cell	32 (76.2)	98 (87.5)	
Nonclear cell	10 (23.8)	14 (12.5)	
Sarcomatoid features, n (%)			.54
Yes	3 (9.7)	12 (16.2)	
No	28 (90.3)	62 (83.8)	
No. of metastases, n (%)			.88
1	8 (19.5)	21 (20.6)	
>1	33 (80.5)	81 (79.4)	
Brain metastases, n (%)			.67
Yes	1 (3.3)	5 (7.0)	
No	29 (96.7)	66 (93.0)	
Previous treatment			
Previous nephrectomy, n (%)			.0005[b]
Yes	32 (71.1)	107 (92.2)	
No	13 (28.9)	9 (7.8)	
Previous IL-2 or IFN therapy, n (%)			.67
Yes	1 (2.2)	6 (5.2)	
No	44 (97.8)	110 (94.8)	
Year of sunitinib initiation, n (%)			
2006-2009	1 (2.2)	4 (3.4)	>.99
2010-2013	7 (15.6)	34 (29.3)	.07
2014-2017	37 (82.2)	78 (67.2)	.06
IMDC prognosis risk group at first-line, n (%)	37	99	
Favorable	3 (8.1)	36 (36.4)	.001[b]
Intermediate	26 (70.3)	58 (58.6)	.21
Poor	8 (21.6)	5 (5.1)	.007[b]
IMDC prognosis risk group at second-line, n (%)	41	98	
Favorable	2 (4.9)	12 (12.2)	.23
Intermediate	29 (70.7)	69 (70.4)	.97
Poor	10 (24.4)	17 (17.4)	.34

Abbreviations: IFN = interferon; IL-2 = interleukin-2; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IO = immuno-oncology; SD = standard deviation.
[a]For categorical variables, proportions were calculated after excluding those patients with missing data.
[b]*P* < .05.

Figure 1 Flow Diagram for First-line Sunitinib Patients With Second-line Immuno-Oncology (IO) Therapy. [1]Duration of First- or Second-line Treatment Was Calculated Using Kaplan-Meier Analysis, With Treatment Discontinuation as the Event of Interest. Patients Were Censored at the Earlier Date of Death or Lost to Follow-up Prior to Treatment Discontinuation

Abbreviations: CI = confidence interval; IQR = interquartile range; Nivo = nivolumab; RCC = renal cell carcinoma; SD = standard deviation.

interquartile range and mean ± standard deviation. The durations of first-line sunitinib and second-line IO therapy were calculated for each patient and plotted and compared using a scatter plot and the Pearson correlation coefficient. For the time-to-event analyses (ie, OS, TTNT, TTD), Kaplan-Meier analyses and Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). For the TTNT and TTD analyses, the models were adjusted for age, sex, and baseline IMDC risk group. For the OS analysis, inverse probability weighting (IPW)-adjusted estimates were calculated.[16] The model included time-varying weights to predict the probability of censoring, discontinuing IO therapy, and initiating a third-line therapy because these could influence the OS and could have varied according to the duration of first-line sunitinib. The weights were estimated using data on the sunitinib duration, baseline IMDC risk group, age, sex, and IMDC risk group at the initiation of IO.

The real-world first-line sunitinib and second-line IO physician-assessed best tumor responses were compared between groups using the χ^2 test for trend. In addition, the ORR for second-line IO therapy was assessed using multivariable logistic regression models. The odds ratios, with 95% CIs, and P values are reported.

All analyses were performed using SAS, version 9.4 (SAS Institute, Inc, Cary, NC).
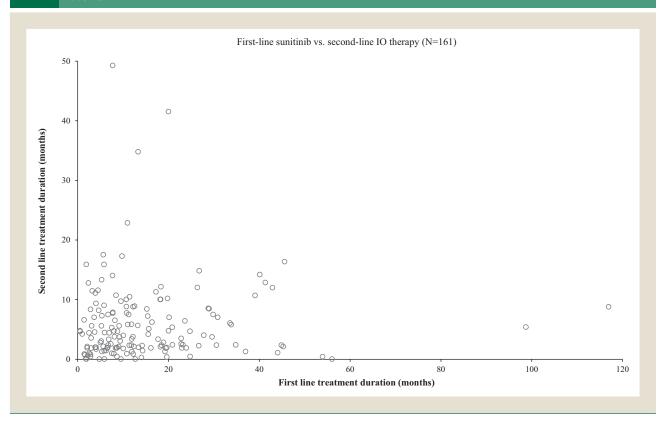
Results

Demographic and Clinical Characteristics

Of the 161 patients with mRCC, 116 had received ≥ 6 months and 45 patients had received < 6 months of first-line sunitinib treatment (Table 1). Overall, the median duration of first-line

sunitinib was 11.0 months (Figure 1). A greater proportion of patients treated ≥ 6 months versus < 6 months with first-line sunitinib were older and had previously undergone nephrectomy (mean age at index date, 63 vs. 58 years, $P = .004$; previous nephrectomy, 92% vs. 71%, $P < .001$). Patients with ≥ 6 months of first-line sunitinib treatment also tended to have a better IMDC risk at the initiation of sunitinib compared with patients with < 6 months of treatment. At the initiation of second-line IO, patients with ≥ 6 months of first-line sunitinib had had an IMDC risk similar to that for those treated for < 6 months. From the start of first-line sunitinib to the start of second-line IO, 74 patients (53%) had remained within the same IMDC risk group, 7 patients (5%) had moved to an improved IMDC group, and 41 patients (30%) had moved to a worse IMDC risk group.

Treatment Patterns

Most patients (n = 154; 96%) had received nivolumab as their second-line IO therapy, although others had received avelumab, atezolizumab, or pembrolizumab as second-line IO therapy. A slightly greater proportion of patients with ≥ 6 months versus < 6 months of first-line sunitinib treatment had received third-line treatment (39% vs. 33%; $P = .52$; Supplemental Table 1; available in the online version). No significant association was observed between the first-line sunitinib duration and second-line IO duration on a scatterplot analysis among all patients (Pearson correlation coefficient, 0.040; $P = .62$; Figure 2). For the patients who discontinued second-line IO therapy, we also found no significant association between the first-line sunitinib treatment duration and second-line IO therapy duration using a scatterplot analysis (Pearson correlation coefficient, 0.034; $P = .73$).

Figure 2 Scatterplot Analysis of Treatment Duration for First-line Sunitinib Versus Second-line Immune-oncology (IO) Therapy for All Patients

First-line sunitinib vs. second-line IO therapy (N=161)

Clinical Outcomes

The unadjusted median OS was numerically longer for the patients treated with ≥ 6 months of first-line sunitinib than for those treated with < 6 months (median, 24.9 months; 95% CI, 16.4-47.8 months; vs. median, 17.5 months; 95% CI, 10.3-30.9 months). In the adjusted OS analyses using IPW, the patients treated with ≥ 6 months of first-line sunitinib had a significantly lower hazard of death compared with the patients treated for < 6 months (adjusted HR, 0.42; 95% CI, 0.21-0.87; $P = .02$; Table 2). In the unadjusted analyses, the median TTNT was numerically greater for patients treated with ≥ 6 months of first-line sunitinib compared with those treated for < 6 months (median TTNT, 9.2 months; 95% CI, 6.8-11.3 months; vs. median TTNT, 8.0; 95% CI, 5.6-10.8 months). However, no significant association was observed in the adjusted analyses for TTNT (Table 2). The unadjusted median TTD was numerically greater for the patients receiving ≥ 6 months of first-line sunitinib treatment group than for the patients receiving < 6 months (median TTD, 7.0 months; 95% CI, 4.7-8.4 months; vs. median TTD, 4.8 months; 95% CI, 3.0-8.2 months). However, no significant association was observed in the adjusted analysis (Table 2).

The reasons for treatment discontinuation are presented in Table 3. Numerically fewer patients with ≥ 6 months of sunitinib treatment compared with those receiving < 6 months had

Table 2 Analysis of Treatment Outcomes For Patients Who Had Received First-line Sunitinib Before Second-line IO Therapy

	HR (95% CI)			ORR
Variable	**OS**	**TTNT of IO Therapy**	**TTD for IO Therapy**	**OR (95% CI)**
Sunitinib duration ≥ 6 mo (ref, < 6 mo)	0.42 (0.21-0.87)	0.89 (0.52-1.51)	0.85 (0.54-1.34)	0.73 (0.22-2.49)
Favorable/intermediate IMDC prognosis risk group (ref, poor risk group)	0.58 (0.19-1.79)	0.52 (0.29-0.96)	0.58 (0.34-0.98)	0.46 (0.13-1.64)
Age ≥ 60 y at index date (ref, age < 60 y)	1.99 (0.95-4.19)	0.76 (0.46-1.26)	0.89 (0.57-1.38)	0.33 (0.11-1.05)
Sex (ref, female)	1.64 (0.66-4.12)	0.88 (0.48-1.61)	0.78 (0.47-1.28)	2.23 (0.44-11.28)

Abbreviations: CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IO = immuno-oncology; OR = odds ratio; ORR = overall response rate; ref = reference; TTD = time to treatment discontinuation; TTNT = time to next therapy.

Table 3	Reasons for Treatment Discontinuation Stratified by First-line Sunitinib Duration		

	First-line Sunitinib Duration		
Characteristic	**<6 mo (n = 45)**	**≥6 mo (n = 116)**	**P Value**
First-line treatment			
Patients who discontinued, n	45	116	
Reason for treatment discontinuation, n (%)			
Disease progression	28 (84.8)	73 (76.0)	.29
Toxicity	3 (9.1)	15 (15.6)	.56
Disease progression and toxicity	0 (0.0)	5 (5.2)	.33
Other	2 (6.1)	3 (3.1)	.60
Second-line treatment[a]			
Patients who discontinued	31	75	
Reason for treatment discontinuation, n (%)			
Disease progression	17 (73.9)	41 (64.1)	.39
Toxicity	2 (8.7)	12 (18.8)	.34
Disease progression and toxicity	0 (0.0)	2 (3.1)	NA
Death	4 (17.4)	7 (10.9)	.47
Other	0 (0.0)	2 (3.1)	NA

Abbreviations: IO = immuno-oncology; NA = not applicable.
[a]$P < .05$.

discontinued sunitinib because of disease progression (76% vs. 85%; $P = .29$) or had discontinued IO therapy because of disease progression (64% vs. 74%; $P = .39$).

Patients with ≥ 6 months of first-line sunitinib versus < 6 months had a significantly greater ORR (30% vs. 6%; $P = .01$) during sunitinib therapy. During second-line IO therapy, the ORR was similar for patients with ≥ 6 months of first-line sunitinib versus < 6 months (18% vs. 23%, $P = .61$; Supplemental Table 2; available in the online version). No significant association was observed between the first-line sunitinib tumor response and the second-line IO tumor response ($P = .48$; Figure 3).

Discussion

In the present real-world analysis of patients with mRCC, the TTNT, TTD, and tumor response to second-line IO therapy were not significantly different between patients who had received ≥ 6 months and those who had received < 6 months of first-line sunitinib. These results suggest that first-line sunitinib therapy resistance does not preclude a second-line IO therapy response and that the mechanisms of resistance are likely independent. The present study also found that patients treated with first-line sunitinib for ≥ 6 months versus < 6 months had significantly better OS. Thus, the first-line sunitinib duration might serve as a disease prognosis marker. The results from the present study and others have provided information on how the initial targeted therapy decisions could affect the clinical outcomes of subsequent IO therapies, although selection of the optimal second-line therapy will require further research.
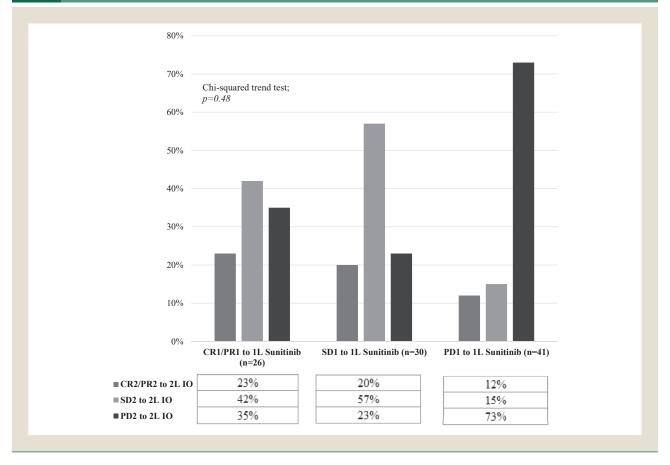
Other studies have examined whether the second-line treatment outcomes will vary according to the duration of the previous therapy.[12,15,17] A stratified analysis of the phase III trial INTORSECT (investigating Torisel as second-line therapy) data showed no

significant PFS advantage for second-line sorafenib versus temsirolimus, regardless of the previous sunitinib therapy duration.[15] The median survival was significantly longer for patients treated with second-line sorafenib versus temsirolimus for patients who had received first-line sunitinib treatment for > 180 days but not for those with a treatment duration of ≤ 180 days.[15] The investigators proposed that this discrepancy between PFS and OS could relate to the unaccounted for use of poststudy anticancer therapy.[15] Another study that showed a differential effect of second-line therapy according to the duration of first-line therapy was a phase III trial comparing sorafenib and axitinib.[17] In the axitinib arm, patients with longer previous cytokine therapy had significant PFS and OS advantages.[17] The same was true in the sorafenib arm, with patients with longer previous cytokine or sunitinib treatment experiencing better OS. Similarly, an analysis of the data from CheckMate 025, the phase III trial comparing second-line nivolumab to everolimus, found that for patients treated with second-line nivolumab, the OS for those with ≥ 6 months versus < 6 months of first-line therapy was 27.4 months (95% CI, 23.2 months to not reached) versus 18.2 months (95% CI, 13.9-25.0 months).[12] The present study, which focused on real-world patients and has improved on previous analyses by adjusting for confounding, also observed numeric favorability in the TTD and TTNT for second-line IO therapy among patients with ≥ 6 months of first-line sunitinib therapy versus < 6 months and, thus, a significant OS benefit for those with ≥ 6 months of first-line sunitinib therapy versus < 6 months.

Biologic reasons exist for why a longer duration of first-line treatment might be associated with better OS after second-line treatment.[18-21] The association might partly reflect the underlying tumor biology. Thus, patients with slower growing tumors might continue with the initial treatment longer and survive longer with

Figure 3 Physician-assessed Best Response to Second-line Immuno-oncology (IO) Therapy Stratified by Initial Best Response to First-line Sunitinib Therapy.[1,2] [1]Based on Patients' Best Response to First-line Sunitinib Therapy, Patients Were Grouped Into 3 Categories: CR1/PR1, SD1, and PD1. Among Those 3 Groups, the Patient's Best Response to Second-line IO Therapy was Assessed and Presented Numerically and in bar Graph Form. [2]Patients With Information Available on First- and Second-line Physician-assessed Best Response Were Included in the Analysis

	CR1/PR1 to 1L Sunitinib (n=26)	SD1 to 1L Sunitinib (n=30)	PD1 to 1L Sunitinib (n=41)
■CR2/PR2 to 2L IO	23%	20%	12%
■SD2 to 2L IO	42%	57%	15%
■PD2 to 2L IO	35%	23%	73%

Chi-squared trend test; *p=0.48*

Abbreviations: 1L = first line; 2L = second line; CR1 = complete response to first line; CR2 = complete response to second line; PD1 = progressive disease with first line; PD2 = progressive disease with second line; PR1 = partial response to first line; PR2 = partial response to second line; SD1 = stable disease to first line; SD2 = stable disease to second line.

subsequent therapy. In contrast, patients with rapidly progressive disease and deterioration in IMDC risk factors will have shorter survival. This association could also vary according to the type of first-line treatment used and tumor heterogeneity. The results from previous studies have suggested that a patient's response to nivolumab might be influenced by earlier TKI treatment that affected the tumor microenvironment.[11,12,22] Sunitinib has been shown to have direct antitumor effects and to exacerbate intratumoral heterogeneity, and checkpoint immunotherapies work best with high mutational burden tumors, although this is still being studied in mRCC.[9,23,24]

The treatment landscape for mRCC has changed from the treatment paradigm in which advanced RCC was treated with a VEGF inhibitor, followed by mammalian target of rapamycin-targeted therapy.[3] The approval of the combination of nivolumab plus ipilimumab for front-line treatment of patients with advanced RCC with an intermediate or a poor IMDC risk and avelumab plus axitinib or pembrolizumab plus axitinib for first-line treatment for all patients with mRCC have led to a changed treatment landscape.[5,7,8] Thus, most of the patients in the present study might have been treated differently today. However, some patients will still

initiate first-line sunitinib or TKI therapy for favorable-risk disease or various reasons, including the inability to use IO therapy because of autoimmune disease, steroid requirements, IO therapy costs, or access because many areas worldwide might not have IO therapy or combination therapies available. Therefore, the findings in the present study will be important for patient counseling.

The present study had some limitations. First, with any analysis of nonrandomized treatment groups, unmeasured confounding and potential biases (eg, selection bias) could account for the observed associations. For the TTNT, TTD, and physician-assessed best response, we attempted to reduce the bias by adjusting for confounders, including age, sex, and IMDC risk group. For OS, an IPW analysis was used such that exposure was not associated with time-varying covariates; thus, confounding by measured potential confounders was eliminated. Second, because the present study was from 2006 to 2018, the sunitinib treatment practices could have changed over time and affected the results. However, this effect was likely minimal because the sunitinib initiation year was not significantly different between those receiving ≥ 6 months and those receiving < 6 months of treatment (Table 1). Third, we had missing data, which could have biased the study results if the missing data

were not completely random. Further analysis showed that only a small proportion of patients (25 of 161; 15%) had missing data for the IMDC risk group. Thus, bias from missing data might have been minimal. Furthermore, in contrast to clinical trials with protocol-specified definitions of clinical events, the progression and clinical response assessments in retrospective studies of real-world clinical practice might not be performed consistently for all patients and across physician practices. Finally, the sample size of patients with < 6 months of sunitinib treatment was limited.

Conclusions

The present study showed that the first-line sunitinib treatment duration might not be associated with TTNT, TTD, and tumor response with second-line IO therapy. This suggests that first-line sunitinib resistance will not preclude a second-line IO therapy response, and the mechanisms of resistance might not overlap. The present study also found that patients receiving IO therapy with first-line sunitinib treatment for ≥ 6 months versus < 6 months might have a survival advantage, although other unmeasured confounders might have been present. The findings from the present study might aid healthcare practitioners in deciding how to sequence therapies, which involves both the choice of therapy and its duration. The findings from the present study support the paradigm that previous therapy will not dictate the efficacy of subsequent IO therapy.

Clinical Practice Points

- Previous sunitinib therapy will not dictate the effectiveness of subsequent immunotherapy.
- We found no significant association between the first-line sunitinib duration and the clinical outcomes with second-line IO therapy.
- The findings from the present study have provided information on how the initial targeted therapy treatment decisions might affect the clinical outcomes of subsequent IO therapies, although the selection of the optimal second-line therapy is still warranted.

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2019.12.007.

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Supplemental Data

Supplemental Table 1	Treatment Sequence of Patients Stratified by First-line Sunitinib Before Second-line IO Therapy		
	First-line Sunitinib Duration, n (%)		
Characteristic	**<6 mo (n = 45)**	**≥6 mo (n = 116)**	**P Value**
Second-line treatment	45	116	
IO therapy			
Nivolumab[a]	44 (97.8)	110 (94.8)	.67
Atezolizumab[b]	1 (2.2)	2 (1.7)	>.99
Avelumab[c]	0 (0.0)	2 (1.7)	>.99
Pembrolizumab[d]	0 (0.0)	2 (1.7)	>.99
Third-line treatment	15 (33.3)	45 (38.8)	.52
IO therapy			
Nivolumab[e]	1 (6.7)	2 (4.4)	>.99
Atezolizumab[b]	1 (6.7)	0 (0.0)	.25
Targeted therapy			
Axitinib	5 (33.3)	18 (40.0)	.65
Everolimus	0 (0.0)	9 (20.0)	.10
Cabozantinib	2 (13.3)	6 (13.3)	>.99
Investigational drug	1 (6.7)	4 (8.9)	>.99
Sorafenib	1 (6.7)	3 (6.7)	>.99
Pazopanib	2 (13.3)	2 (4.4)	.26
Sunitinib	1 (6.7)	1 (2.2)	.44
Temsirolimus	1 (6.7)	0 (0.0)	.25

Abbreviation: IO = immuno-oncology.
[a]Nivolumab in second-line therapy included nivolumab treatment alone (n = 148) and combined with other therapy (n = 6).
[b]Atezolizumab was combined with other treatment.
[c]Avelumab in second-line therapy included avelumab treatment alone (n = 1) and combined with other therapy (n = 1).
[d]Pembrolizumab in second-line therapy included pembrolizumab treatment alone (n = 1) and combined with other therapy (n = 1).
[e]Nivolumab in third-line therapy included nivolumab treatment alone (n = 1) and combined with other therapy (n = 2).

Supplemental Table 2	Physician-assessed Best Response Stratified by First-line Sunitinib Duration Before Second-line IO Therapy		
Physician-assessed Best Response	**First-line Sunitinib Duration, n (%)**		
	<6 mo (n = 45)	**≥6 mo (n = 116)**	**P Value**
First-line treatment (sunitinib)			
Complete/partial response (ORR)	2 (6.3)	31 (30.1)	.01[a]
Complete response	0 (0.0)	3 (2.9)	NA
Partial response	2 (6.3)	28 (27.2)	.01[a]
Stable disease	7 (21.9)	38 (36.9)	.12
Progressive disease	23 (71.9)	34 (33.0)	.0001[a]
Second-line treatment (IO)			
Complete/partial response (ORR)	6 (23.1)	15 (18.5)	.61
Complete response	0 (0.0)	3 (3.7)	NA
Partial response	6 (23.1)	12 (14.8)	.37
Stable disease	8 (30.8)	27 (33.3)	.81
Progressive disease	12 (46.2)	39 (48.1)	.86

Abbreviation: IO = immuno-oncology; NA = not applicable; ORR = overall response rate.
[a]$P < .05$.