Check for updates

Real-World Treatment Patterns and Effectiveness of Patients With Advanced Renal Cell Carcinoma: A Nationwide Observational Study

Laurence Albigès,[1] Carine Bellera,[2] Sébastien Branchoux,[3] Mickael Arnaud,[4] Amandine Gouverneur,[4] Sonia Néré,[5] Anne-Françoise Gaudin,[3] Isabelle Durand-Zaleski,[6] Sylvie Négrier[7]

Abstract

Given the treatment landscape evolution for aRCC, real-world data are needed. All French patients newly treated for aRCC initiated in 2016 were included. In first-line, patients were mainly treated with sunitinib, and in second-line half were treated with nivolumab. The highest OS was observed for patients treated with sunitinib in first-line and for patients treated with nivolumab in second-line.

Background: Treatment landscape for advanced renal cell carcinoma (aRCC) has evolved quickly and few data about the real-world treatment patterns are available. This study aimed at describing the real-world treatment patterns and effectiveness of all systemic treatments available for aRCC in first and second-line treatment. **Materials and Methods:** A cohort of patients initiating a first-line systemic treatment for aRCC in 2016 was extracted from the French nationwide healthcare insurance system database (SNDS). The first-line treatment initiation date constituted the index date and patients were followed until death, loss to follow-up, or December 31, 2019, whichever occurred first. aRCC was identified using hospital diagnosis, long-term disease, or renal biopsy before index date. All analyses were performed for first and second-line treatment. Overall survival (OS) and time-to-next treatment or death (TNT-D) were estimated using Kaplan-Meier approach. **Results:** In 2016, 1629 patients initiated a first-line treatment for aRCC. Most of them were male (75.9%) and the median age was 67 years. Most of patients (91.7%) had received a tyrosine kinase inhibitor as first-line treatment, mainly sunitinib (64.4%), and 53.5% received a second-line, among which 43.7% nivolumab. Median OS (95% confidence interval [CI]) was 20.7 (95% CI:18.2-22.4) months from first-line treatment initiation and 15.4 (13.9-17.5) months from second-line treatment initiation. Median TNT-D were respectively 9.3 (9.7-12.1) months and 6.9 (5.9-7.7) months. **Conclusion:** This study highlights the limited survival of aRCC patients These results provide a valuable baseline and highlight the need for innovation, such as immune checkpoint inhibitor-based combinations that have recently became first-line standard of care.

Clinical Genitourinary Cancer, Vol. 22, No. 2, 295–304 © 2023 The Author(s). Published by Elsevier Inc.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)
Keywords: Carcinoma, Renal cell, Treatment patterns, Real-world outcomes

Key Take Home Messages

1. Given the rapid evolution of available cancer treatments, large real-world studies are needed to define the landscape of treatment patterns. We performed a nationwide real-world study to highlight the landscape of the treatment of patients with advanced renal cell cancer (aRCC) when second-line immunotherapy became available (2016-2019).
2. In first-line, the tyrosine kinase inhibitors remained the most administered class of drug, mainly sunitinib; yet in second-line, nivolumab was administered to almost half of patients with aRCC.

[1]Institut Gustave Roussy, Paris, France
[2]Department of Clinical Epidemiology and Clinical Research, Institut Bergonié, Bordeaux, France
[3]Department of Health Economics & Outcomes Research, Bristol Myers Squibb, Rueil-Malmaison, France
[4]IQVIA, Real World Solutions, Bordeaux, France
[5]Department of Medical Affairs, Bristol Myers Squibb, Rueil-Malmaison, France
[6]AP-HP Hôtel Dieu, Clinical Research Unit Eco Ile de France, Paris, France
[7]Université Lyon I, Centre Léon Bérard, Lyon, France

Submitted: Jul 21, 2023; Revised: Nov 16, 2023; Accepted: Nov 19, 2023; Epub: 24 November 2023

Address for correspondence: Laurence Albigès, MD, PhD, Gustave Roussy Cancer Campus, Paris Saclay University, 114 Rue Edouard Vaillant, Villejuif, 94880 France
E-mail contact: laurence.albiges@gustaveroussy.fr

1558-7673/$ - see front matter © 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)
https://doi.org/10.1016/j.clgc.2023.11.012

3. The median overall survival (OS) from first-line treatment initiation was 20.7 months (95% CI: 18.2; 22.5), the median OS from second-line treatment initiation was 15.4 (95% CI: 13.9; 17.5). This study highlights the limited survival of aRCC patients and the need for treatments increasing it.

Introduction

Renal cancer is the 7th most frequent cancer worldwide, with more than 400,000 cases diagnosed every year.[1] Most common type of renal cancer is renal cell carcinoma (RCC), which has several histologic types: clear cell (ccRCC, the most common and aggressive) or nonclear cell RCC.[2] A third of patients present with distant metastases at diagnosis, and around 20% to 50% will eventually have advanced or metastatic RCC (aRCC).[2] The 5-year overall survival (OS) ranges from 93% at local stage I to 12% at metastatic stage.[2] In France, 15,323 incident cancers were reported in 2018, among which 86.9% were RCC.[3] More than two-third were diagnosed in men and the median age at diagnosis was around 68 years.[3]

Systemic treatments indicated for aRCC evolved quickly. During the last 10 years, the standard of care was tyrosine kinase inhibitors (TKIs) monotherapies, (eg, sunitinib and pazopanib) targeting the vascular endothelial growth factor (VEGF) pathway.[4] Recently, the therapeutic arsenal has been strengthened with the launch of newer TKI agents (eg, cabozantinib) and immune checkpoint inhibitors (ICIs), especially agents targeting programmed cell death-1 (PD-1) receptor (eg, nivolumab).[4,5] Recently, ICI-based combinations became the standard first-line treatment for advanced or metastatic ccRCC.[5,6]

Despite being the gold standard to evaluate the efficacy and safety of treatments, RCTs have limited external validity due to specific selection criteria and subsequent underrepresentation of key patient populations (eg, elderly, frail patients).[7-9] Real-world evidence can complement the findings from RCTs by reflecting clinical practice across a broader and more diverse population of patients and healthcare facilities.[10] However, real-world studies in aRCC have remained limited and mostly based on specific healthcare settings (eg, specialized cancer centers).[11-18] In order to evaluate the real-life benefit of systemic treatments, the description of care pathways and related effectiveness are necessary, notably when a new therapeutic class becomes available. To assess the treatment benefit in real-world studies, the time to next treatment or death (TNT-D) has a significant association with OS that may reflect a sustained survival benefit, even for patients who discontinue treatment prematurely due to toxicity or other non–progression-related reasons.[19,20] The aim of this study was to describe the real-world treatment patterns, the TNT-D, and OS in aRCC according to treatment line in France.

Material and Methods

Data Source

This cohort study used the French nationwide healthcare insurance system claims database ("*Système National des Données de Santé*" [SNDS]), which includes anonymized individual data for all persons affiliated, covering at least 99% of French residents (around 66 million persons).[21] The SNDS contains information on (i) sociodemographic characteristics; (ii) outpatient healthcare claims and reimbursement; (iii) hospital discharge summaries; and (iv) registration status for 30 long-term diseases (LTDs). Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification, hospitalization diagnoses, and LTD are coded according to the International Classification of Diseases, 10th revision (ICD-10), and medical and surgical procedures are coded according to the *Classification Commune des Actes Médicaux* (CCAM). The study protocol was approved by the "*Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé"* (CESREES; file number 1622015) and the "*Commission Nationale de l'Informatique et des Libertés*" (CNIL; file number 920314).

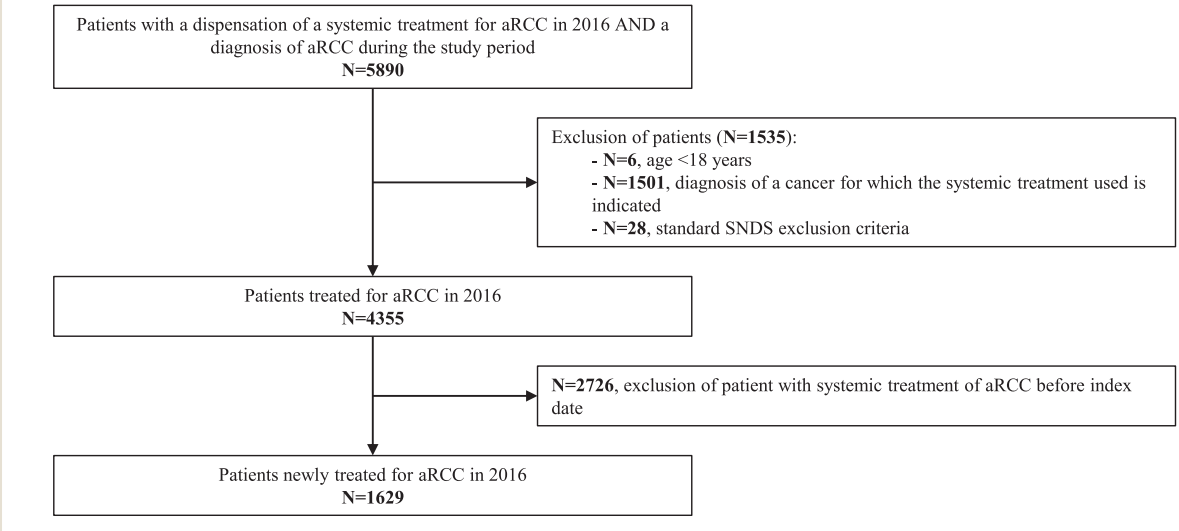
Study Population

Patients with aRCC newly treated with anticancer medications between 1st January 2016 and 31st December 2016 were identified within the SNDS and followed up until the 31st December 2019. A maximum follow-up of 48 months was deemed suitable given median OS in aRCC.[3] Inclusion criteria were: (i) a first systemic treatment for aRCC dispensed in 2016, and (ii) a diagnosis of aRCC during the study period (historical and follow-up). The date of first systemic treatment for aRCC dispensed in 2016 constituted the index date, and aRCC was identified by applying an algorithm based on ICD-10 code C64 for hospital diagnoses and LTDs, and on CCAM codes for renal biopsy in the 6 months before index date (Supplemental Table 1 and 2). Exclusion criteria were: (i) aged <18 years at index date, (ii) another cancer diagnosis prior to index date for which the first systemic treatment is reimbursed (Supplemental Table 3), (iii) another systemic treatment for aRCC dispensed prior to index date (Supplemental Table 1), (iv) less than 1 year of history prior to index date, and (v) standard SNDS exclusion criteria (ie, same-sex twins, affiliation to Mayotte, missing or aberrant values). The look-back period was from 1st January 2006 or date of entry in the SNDS (whichever occurred first) to the index date. All patients were followed until death from any cause, loss to follow-up (ie, absence of care consumption for at least 6 months) or end of the study period on 31st December 2019, whichever occurred first.

Patients' Characteristics and Outcomes

Patient's and clinical characteristics were assessed at index date (corresponding to the initiation of the first-line treatment) and at the initiation of second-line. Treatment patterns were defined based on drug and therapeutic class, based on numbers of patients. The first treatments identified were considered as first-line treatment and the initiation of a new systemic treatment as second-line. The third-line treatment was identified in order to describe the end of the second-line treatment, and thus, the third-line treatment is not described further here. For each line, the first dispensing date was the initiation date (considered as index date for the first-line), and the duration of treatment was the time between the first dispensing date and the discontinuation date (last dispensing supplemented by the number of days of exposure) or the date of death. OS was defined as the time from the initiation date (of first- or second-line treatment) and the date of death from any cause, whichever occurred first. Additionally, TNT-D was estimated from the initiation date (of first- or second-

Figure 1 Selection of the study population. Systemic treatment for aRCC includes: aldesleukin, sunitinib, pazopanib, sorafenib, bevacizumab + interferon α, axitinib, temsirolimus, everolimus, cabozantinib and nivolumab.



line treatment) until the date of initiation of the next treatment or death from any cause, whichever came first.[22] Censoring for both endpoints was performed at loss to follow up or study end (31st December 2019).

Statistical Analysis

From the first-line population, which included all patients initiating first-line treatment as described above, a second-line population was also identified, which consisted solely of patients initiating a second-line treatment.

Descriptive analyses were performed for first- and second-line populations. Qualitative variables were described using counts and proportions of patients and quantitative variables were described using median and interquartile range (IQR). According to the General Data Protection Regulation (GDPR) requirement in France, all results under 10 patients were not displayed. The median follow-up was estimated using the reverse Kaplan-Meier (KM) approach. The OS, duration of treatment line and TNT-D rates and medians were estimated using the KM method. All survival analyses were performed for first- and second-line populations, and were stratified according to main drugs or therapeutic classes for each line. The statistical analysis was performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Results

Selection of the Study Population

In 2016, 5890 patients with a dispensation of systemic treatment for aRCC and a diagnosis of RCC during the study period were identified. Among these, 1501 (25.5%) patients were excluded for another cancer diagnosis for which the systemic treatment is reimbursed prior to index date, and 2726 (46.3%) were excluded for a dispensation of a systemic treatment for aRCC prior to index date. Finally, 1629 (27.7%) newly treated aRCC patients in 2016 were included in the study (Figure 1).

Baseline Characteristics

Among the 1629 included patients (first-line population), most of them were male (75.9%) and the median age was 66.6 years. Two-thirds (68.6%) of the patients had at least 1 metastatic site, mainly synchronous diagnosis (present at RCC diagnosis, 62.6%%), and localized in lung (47.6%) and bones (32.9%). At the initiation of first-line systemic treatment, 60.1% of patients had benefited from a radical nephrectomy. One-fifth of patients had diabetes and 13.6% a chronic pulmonary disease (Table 1).

Treatment Patterns

Most patients (91.7%) had a first-line treatment with TKI therapy, mainly sunitinib (64.4%), and pazopanib (25.2%). mTOR inhibitors were dispensed to 8.2% of patients. Median duration (95% CI) of the first-line treatment was 5.6 (5.3-6.3) months; it was 6.9 (6.1-7.5) months for sunitinib, 5.0 (4.2-5.8) months for pazopanib, and 3.0 (2.1-3.6) months for other TKI and anticancer drugs. Half of patients (53.5%) received a second-line treatment: 55.5% of these patients previously received a TKI and 31.6% of patients mTOR inhibitors. Among the 872 patients with a second-line treatment (second-line population), 43.7% received nivolumab and 42.2% a TKI, mainly axitinib (16.9%) and cabozantinib (10.1%, Figure 2). Median duration (95% CI) of the second-line was 4.5 (4.1-5.1) months; it was 5.1 (4.2-6.1) months for nivolumab, 4.9 (4.2-5.6) months for TKI and 3.0 (2.7-3.5) months for other anticancer drugs.

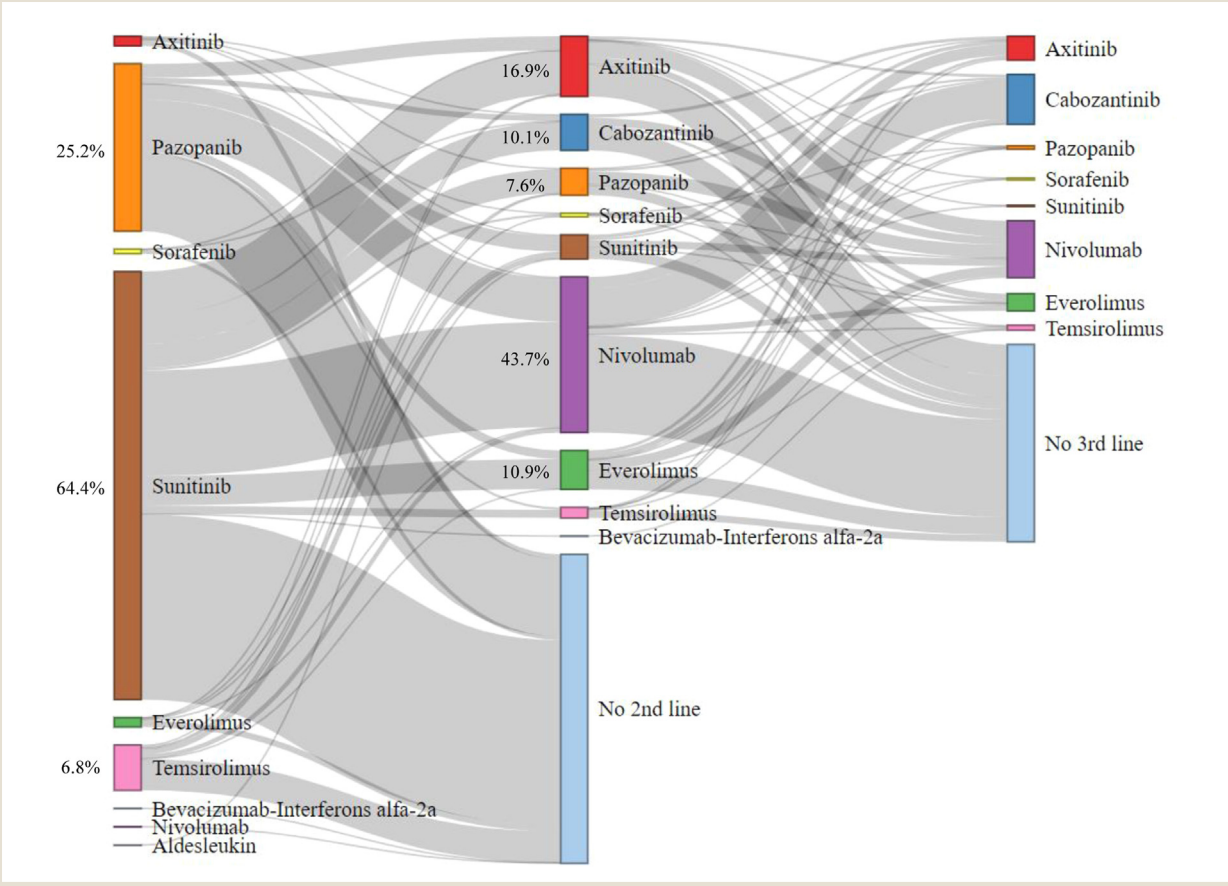
In first-line setting, the patients' characteristics were slightly different between treatments. Patients treated by sunitinib were younger than patients treated by pazopanib (64.4 and 70.8 years,

Table 1 Baseline Characteristics of aRCC Patients According to Line (First or Second-Line) and Type of Systemic Treatment

Characteristics, n (%)	Patients With First-Line				Patients With Second-Line			
	All (N = 1629)	Sunitinib (N = 1049)	Pazopanib (N = 410)	Other (N = 170)	All (N = 872)	Nivolumab (N = 381)	TKI (N = 368)	Other (N = 123)
Male	1236 (75.9)	805 (76.7)	295 (72.0)	136 (80.0)	669 (76.7)	299 (78.5)	277 (75.3)	93 (75.6)
Age (years), median (IQR)	66.6 (58.8-74.6)	64.7 (57.4- 72.3)	70.8 (62.6- 78.3)	69.5 (60.9- 78.4)	66.5 (58.5-74.3)	67.4 (59.5-74.3)	65.5 (57.3- 74.4)	66.3 (56.1- 74.0)
CMU-c	81 (5.0)	58 (5.5)	12 (2.9)	11 (6.5)	39 (4.5)	18 (4.7)	12 (3.3)	9 (7.3)
Time from RCC diagnosis to treatment (months), median (IQR)	6.9 (2.4-32.0)	6.7 (2.4-32.0)	9.7 (2.8-37.9)	3.9 (1.6-19.8)	7.9 (2.7-30.9)	8.4 (3.3-32.4)	8.7 (2.7-29.4)	5.2 (1.9-22.4)
At least 1 metastatic site	1117 (68.6)	712 (67.9)	268 (65.4)	137 (80.6)	578 (66.3)	250 (65.6)	256 (69.6)	72 (58.5)
Type of metastases[a]								
Synchronous	699 (62.6)	452 (63.5)	152 (56.7)	95 (69.3)	349 (60.4)	142 (56.8)	156 (60.9)	51 (70.8)
Short-term metachronous	64 (5.7)	37 (5.2)	17 (6.3)	10 (7.3)	35 (6.1)	18 (7.2)	14 (5.5)	<10
Long-term metachronous	354 (31.7)	223 (31.3)	99 (36.9)	32 (23.4)	194 (33.6)	90 (36.0)	86 (33.6)	18 (25.0)
Localisation of metastases[a]								
Lung metastases	532 (47.6)	333 (46.8)	122 (45.5)	77 (56.2)	436 (75.4)	215 (86.0)	162 (63.3)	59 (81.9)
Bone metastases	367 (32.9)	219 (30.8)	101 (37.7)	47 (34.3)	290 (50.2)	132 (52.8)	122 (47.7)	36 (50.0)
Liver metastases	171 (15.3)	95 (13.3)	40 (14.9)	36 (26.3)	140 (24.2)	69 (27.6)	48 (18.8)	23 (31.9)
Lymph node metastases	253 (22.6)	167 (23.5)	52 (19.4)	34 (24.8)	211 (36.5)	101 (40.4)	84 (32.8)	26 (36.1)
Brain metastases	134 (12.0)	75 (10.5)	40 (14.9)	19 (13.9)	111 (19.2)	48 (19.2)	45 (12.2)	18 (25.0)
History of local treatment								
Radiotherapy	241 (14.8)	130 (12.4)	85 (20.7)	26 (15.3)	213 (24.4)	106 (27.8)	92 (25.0)	15 (12.2)
Partial nephrectomy	143 (8.8)	93 (8.9)	40 (9.8)	10 (5.9)	71 (8.1)	33 (8.7)	33 (9.0)	<10
Radical nephrectomy	979 (60.1)	667 (63.6)	244 (59.5)	68 (40.0)	603 (69.2)	270 (70.9)	257 (69.8)	76 (61.8)
Metastasectomy	84 (5.2)	57 (5.4)	22 (5.4)	<10	68 (7.8)	30 (7.9)	26 (7.1)	12 (9.8)
Comorbidities								
Diabetes	314 (19.3)	174 (16.6)	93 (22.7)	47 (27.6)	149 (17.1)	74 (19.4)	50 (13.6)	25 (20.3)
Myocardial infarction	70 (4.3)	34 (3.2)	20 (4.9)	16 (9.4)	34 (3.9)	21 (5.5)	<10	<10
Heart failure	47 (2.9)	22 (2.1)	17 (4.1)	<10	40 (4.6)	21 (5.5)	14 (3.8)	<10
Cerebrovascular disease	57 (3.5)	26 (2.5)	16 (3.9)	15 (8.8)	29 (3.3)	10 (2.6)	<10	10 (8.1)
Moderate to severe renal disease	157 (9.6)	101 (9.6)	40 (9.8)	16 (9.4)	82 (9.4)	35 (9.2)	35 (9.5)	12 (9.8)
Chronic pulmonary disease	222 (13.6)	142 (13.5)	56 (13.7)	24 (14.1)	108 (12.4)	42 (11.0)	45 (12.2)	21 (17.1)

Abbreviations: aRCC = advanced renal cell carcinoma; IQR = interquartile range; mTOR = mammalian target of rapamycin; TKI = tyrosine kinase inhibitors.
[a] Among patients with metastases. Synchronous metastases: diagnosis <6 months from aRCC diagnosis; short-term metachronous: (6-12) months from aRCC; long-term metachronous metastasis: > 12 months from aRCC.

Figure 2 Distribution of systemic treatments used in aRCC patients in 2016 in France. Number of patients: first-line: 1629 patients, second-line: 872 patients and third-line: 389 patients.



respectively). Patients treated with pazopanib were more frequently women (72.0% vs. 76.7%), more often beneficiaries of individual complementary universal insurance (*couverture maladie universelle complémentaire,* CMUc, 2.9% vs. 5.5%) which is a precariousness indicator, and more likely to have diabetes (22.7% vs. 16.6%) than patients treated by sunitinib. Patients treated by sunitinib and pazopanib had similar main metastatic sites, but patients treated by pazopanib had more frequently synchronous metastases (ie, metastases present at RCC diagnosis, 56.7% vs. 63.5%) and they initiated their first-line treatment later after the diagnosis (9.7 [IQR 2.8-37.9] months vs. 6.7 [2.4-32.0] months). Patients treated by sunitinib had less radiotherapy (12.4%) in comparison to those treated by pazopanib (20.7%) but similar nephrectomy rates. Overall, patients treated by other treatments were older, with more comorbidities, and with less frequent nephrectomy prior to treatment initiation (Table 1).

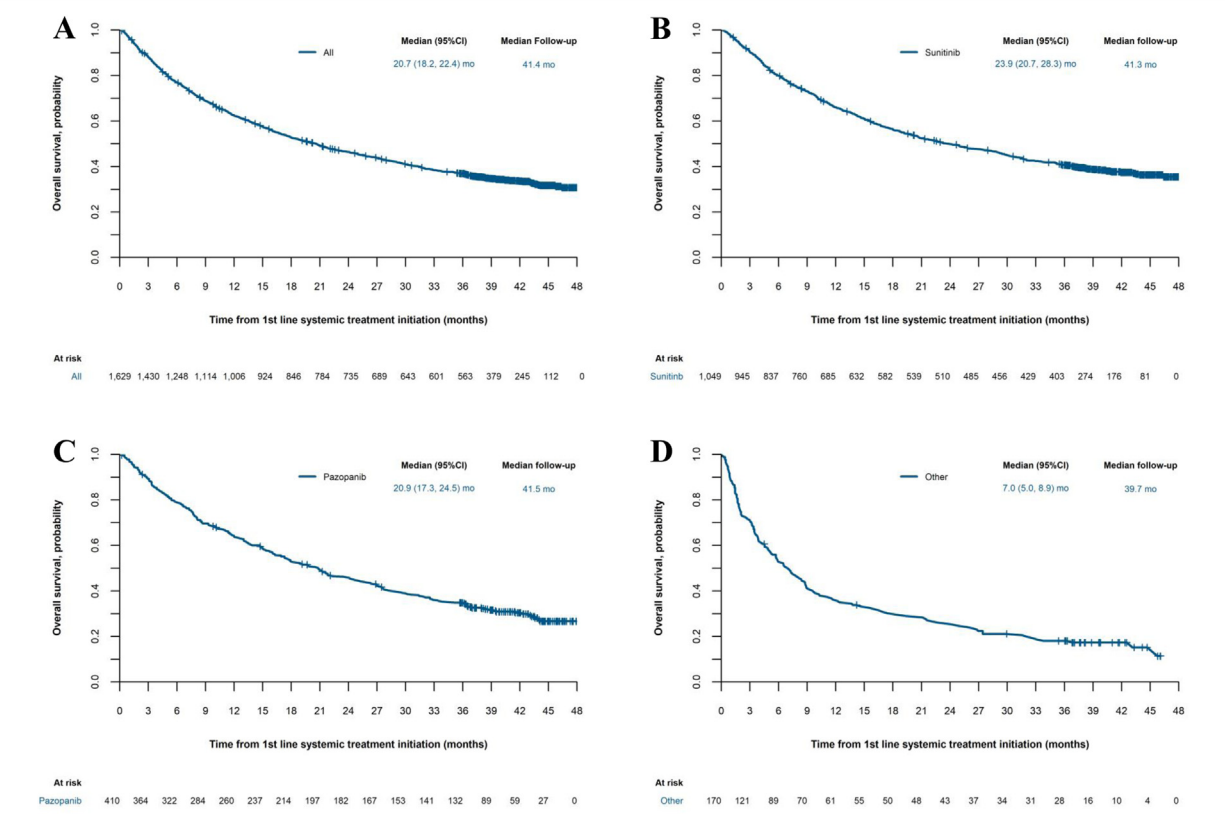
The distribution of specific metastases localization (eg, lung and bone), radiotherapy and radical nephrectomy were more frequent at the initiation of the second-line in comparison to first-line, highlighting the evolution of the cancer between these two lines of treatment. Among patients initiating a second-line treatment, there were no differences between patients initiating second-line treatment with TKI or nivolumab, in age, sex, history of local treatment, or time from aRCC diagnosis to initiation. Patients treated by nivolumab had more lung metastases (86.0% vs. 63.3%), and diabetes (19.4% vs. 13.6%, Table 1) than patients treated by TKIs as second-line treatment.

Survival Outcomes

OS. After a maximum of 48 months of follow-up, 1068 patients (65.6%) had died, and the median follow-up was 41.4 (95% CI: 40.8-41.9) months. The OS rate at 36 months was 36.9% (95% CI: 34.5-9.2). The median OS was 20.7 months (95% CI: 18.2-22.4), treatment with sunitinib was associated with a longer median OS (23.9 months, 95% CI: 10.7-28.3, Table 2a and Figure 3).

Among patients receiving a second-line treatment, 525 patients (60.2%) had died, and the median follow-up was 28.3 months (95% CI: 26.9-30.3). The OS rate at 24 months was 40.3% (95% CI: 37.0-43.5), and the median OS was 15.4 months (95% CI: 13.9-17.5) calculated from the second-line treatment initiation. Overall, median OS since initiation of second-line was 19.6 (95% CI: 15.7-24.4) months for patients treated with nivolumab and 15.2

Figure 3 Overall survival in patients from first-line treatment initiation, overall and by type of first-line treatment. (A) all patients; (B) patients treated by sunitinib; (C) patients treated by pazopanib; (D) patients treated by other systemic treatments.



(95% CI: 11.8-18.9) months for those treated with TKIs (Table 2B and Supplemental Figure 1).

TNT-D. After a maximum of 48 months of follow-up, 872 patients (53.5%) had a second-line treatment, and 543 patients (33.3%) had died without receiving a second-line treatment. The TNT-D rate at 36 months was 8.7% (95% CI: 7.4-10.1), and the median TNT-D was 9.3 months (95% CI: 9.7-10.1). Treatment with sunitinib treatment with sunitinib was associated with a longer median TNT-D (10.7 months, 95% CI: 9.7-12.1, Table 2A and Supplemental Figure 2).

Among patients receiving a second-line treatment, 394 patients (45.2%) had a third-line treatment and 300 patients (34.4%) had died without receiving a third-line treatment. The TNT-D rate at 24 months was 16.7% (95% CI: 14.2-19.2), and the median TNT-D was 6.9 months (95% CI: 5.9-7.7). Half of patients treated with TKI or other treatment received a third-line, yet only 38.3% of patients treated with nivolumab. Overall, median TNT-D since initiation of second-line was 6.9 (95% CI: 5.9-7.7) months. It was 8.5 (95% CI: 7.0-10.1) months for patients treated with nivolumab and 6.8 (95% CI: 5.8-7.8) months for those treated with TKIs (Table 2B and Supplemental Figure 3).

Discussion

To our knowledge, this is the first nationwide population-based study of aRCC patients describing treatment patterns, OS, and TNT-D according to all systemic treatments available in France. Based on the representativeness of our cohort and the large description of the treatment patterns at the beginning of the ICI era, our study provides useful insight into real-world treatment practices. It is planned to use the methodology and results presented here to benchmark the effectiveness of ICI-based combinations in first-line.

The consistency between demographic and clinical characteristics of our cohort and the scientific literature allows us to consider that our algorithm is robust in identifying all cases of aRCC with a first-line treatment.[3,12,14,16,23,24] As in other observational studies based in medico-administrative claims database, the lack of clinical data (such as Eastern Cooperative Group Performance Status, cancer histology, or exhaustiveness of metastasis localization) does not allow one to adjust for all individual confounding factors. Moreover, it is not possible to identify the risk category (scores Memorial Sloan-Kettering Cancer Center or International Metastatic RCC Database Consortium) of the aRCC, whereas the risk has an impact on the systemic treatment choice and the OS.[25] However, by considering the time from aRCC diagnosis to first-line treatment and the type of first-line treatment (eg, use of temsirolimus mostly in poor-

Table 2A Overall Survival and Time to Next Treatment or Death in Patients From First-Line Treatment Initiation

	Overall Survival			Time to Next Treatment or Death			
	Event, n (%)	Rate at 36 Months (95% CI)	Median (95% CI), Months	Event Subsequent Line, n (%)	Event Death, n (%)	Rate at 36 Months (95% CI)	Median (95% CI), Months
First-line treatment							
All patients (N = 1629)	1068 (65.6)	36.9 (34.5-39.2)	20.7 (18.2-22.4)	872 (53.5)	543 (33.3)	14.6 (12.8-16.3)	9.3 (8.7-10.1)
Sunitinib (N = 1049)	644 (61.4)	40.7 (37.7-43.7)	23.9 (20.7-28.3)	595 (56.7)	298 (28.4)	16.9 (14.6-19.1)	10.7 (9.7-12.1)
Pazopanib (N = 410)	283 (69.0)	34.8 (30.2-39.4)	20.9 (17.3-24.5)	221 (53.9)	142 (34.6)	12.4 (9.2-15.6)	8.6 (7.4-10.2)
Other (N = 170)	141 (82.9)	18.0 (12.3-23.8)	7.0 (5.0-8.9)	56 (32.9)	103 (60.6)	5.4 (2.0-8.8)	4.9 (3.6-6.0)

Other: aldesleukin, axitinib, bevacizumab + interferon alfa-2a, everolimus, nivolumab, sorafenib, temsirolimus.

Table 2B Overall Survival and Time to Next Treatment or Death in Patients From Second-Line Treatment Initiation

	Overall Survival			Time to Next Treatment or Death			
	Event, n (%)	Rate at 24 Months (95% CI)	Median (95% CI), Months	Event Subsequent Line, n (%)	Event Death, n (%)	Rate at 24 Months (95% CI)	Median (95% CI), Months
Second-line treatment							
All patients (N = 872)	525 (60.2)	40.3 (37.0-43.5)	15.4 (13.9-17.5)	394 (45.2)	300 (34.4)	16.7 (14.2-19.2)	6.9 (5.9-7.7)
TKI (N = 368)	226 (61.4)	40.8 (35.7-45.8)	15.2 (11.8-18.9)	186 (50.5)	119 (32.3)	12.4 (9.0-15.7)	6.8 (5.8-7.8)
Nivolumab (N = 381)	197 (51.7)	46.0 (41.0-51.0)	19.6 (15.7-24.4)	146 (38.3)	124 (32.5)	25.5 (21.1-29.9)	8.5 (7.0-10.1)
Other (N = 123)	102 (82.9)	23.2 (15.8-30.7)	8.0 (5.9-10.8)	62 (50.4)	57 (46.3)	4.9 (1.1-8.7)	4.4 (3.5-5.2)

TKI: axitinib, cabozantinib, pazopanib, sorafenib, sunitinib.
Other: aldesleukin, bevacizumab + interferon alfa-2a, everolimus, temsirolimus.

risk aRCC), it is possible to approach this risk. Data of metastatic disease could be underestimated in the SNDS. Metastases codes are available only in hospital data, yet it has been shown that the presence or absence of metastases was well documented, as well as the main locations.[26] However, patient treated with TKI may not have hospitalization and therefore information on metastases. The underestimation of metastatic disease could be significant, in particular for synchronous metastases. For patients with several metastatic locations, only the main locations involving organs are coded in the SNDS. Another underestimation lies in the number of aRCC treated patients in France due to the feature of SNDS. This database includes only reimbursed treatment and care. Patients who received first-line treatment in the frame of a RCT are consequently not included in this study. This limitation may have affected the inclusion of patients in our study, particularly as several RCTs on ICI-based combinations were actively recruiting in France during the study period.

The treatment patterns were consistent with previous observational studies and with the European Society for Medical Oncology (ESMO) and the *Association Française d'Urologie* (AFU) guidelines.[4,12,27,28] In first-line setting, sunitinib (administered to 64.4% of patients) had the higher level of evidence. In second-line, nivolumab (administered to 43.7% of patients) and axitinib (administered to 16.9% of patients) had the higher level of evidence.[4] Consistent results were found among the 53.5% of patients receiving a second-line treatment, mostly based on nivolumab and TKI, in particular axitinib. Few patients received cabozantinib in second-line, the treatment being reimbursed in 2018 in France. The limitation for using mTOR inhibitors may be due to the results of the randomized trials of cabozantinib or nivolumab that demonstrated the superiority of both treatments over everolimus the most used mTOR inhibitor.[29,30] However, half (55.5%) of patients with TKI in first-line have a second-line treatment but only one-third (31.6%) of patients with mTOR.

The OS for all patient population was 20.7 months and treatment with sunitinib was associated with longer OS (23.9 months) than treatment with pazopanib (20.9 months) or other anticancer drugs (7.0 months). Although no causal relation can be established in the present descriptive study, the survival difference between sunitinib and pazopanib may be attributed to clinical characteristics such as age (about 6 years older for patients initiated pazopanib) which drove physicians' choice. This is consistent with other French real-world cohort studies of aRCC patients with a first-line treatment with any targeted therapy. They estimated an overall median OS of 19.4 months and of 23.6 months for patients treated with sunitinib.[16,25] A meta-analysis using real-world studies with patients treated with pazopanib in first-line found a median OS of 22.7 months.[31] As anticipated in a real-world setting, our results are slightly lower than the results of pivotal RCTs which reported a median OS for sunitinib between 26.4 and 29.1 months and for pazopanib of 28.3 months.[32,33] This is expected as patients in clinical trials might be younger, with less comorbidities and better performance status.

Half of patients received a second-line treatment. This could appear low, in particular in comparison to observational studies in other countries,[12,34] but it is consistent with another French observational study.[16] Patients treated with nivolumab had the highest median OS (19.6 months) and the median OS for patients treated with TKI was 15.2 months. These results are consistent with European observational studies, in terms of patient's characteristics and OS.[17,24,27] The rapid market spread of nivolumab, available in France since 2016, shows the interest for this new therapeutic class and the importance of rapidly assessing the ICI-based combinations for first-line treatment. However, ICI could be contraindicated or discussed for some patients (eg, altered general state, concomitant treatment that may affect the efficacy of ICI) and may lead to adverse events, notably immune-related.[35–37] Other patients discontinue these systemic treatments, requiring a change of therapeutic class. In such cases, TKI monotherapy may remain an effective alternative in first and subsequent lines of treatment.

In first-line, the TNT-D highlighted the important differences of patients treated with other drugs in comparison to those treated with sunitinib and pazopanib. The differences between OS and TNT-D were about 12 months for sunitinib and pazopanib but only 2 months for other drugs, mainly temsirolimus, which is reimbursed in poor-risk patients only. In second-line setting, the TNT-D was 8.5 (95% CI: 7.0-10.1) months for patients treated with nivolumab and 6.8 (5.8-7.8) with TKI, and patients receiving nivolumab had less frequent third-line treatment (38.3% vs. 50.5%). The TNT-D assess the time to the initiation of subsequent line or death. In real-world setting, the TNT-D highlights a substantial survival benefit, especially since the SNDS does not include detailed clinical information, the progression of the disease cannot be assessed. Consequently, it constitutes a valuable intermediate endpoint and could be useful to clinicians and patients because it reflects treatment patterns and its impact in real-world setting.[19,20]

Conclusion

This nationwide study provides robust information about treatment patterns, OS, and the TNT-D of aRCC patients at the beginning of the ICI era, with first second-line indication in 2016. The recent evolution of the treatment guidelines, with the recommendation of ICI-based combinations in first-line, required new evaluations.

Clinical Practice Points

- Systemic treatments for advanced renal cell carcinoma (aRCC) evolved quickly over the last decade.
- Recommendations are based on results of randomized controlled trials (RCT), but these may have limited external validity due in part to the selection of patients and access to tertiary care facilities. Real-world evidence is needed to estimate outcomes in routine clinical practice and confirm RCT data.
- This nationwide study, exhaustive of all French patients with an initiation of first-line treatment for aRCC in 2016, highlights treatment patterns including first-line treatment choice, overall survival (OS), and time to next treatment or death (TNT-D). Most patients (91.7%) were treated with tyrosine kinase inhibitor (TKI) as first-line treatment, mainly sunitinib, and among those initiating a second-line, nearly half (43.7%) of patients were treated with nivolumab, as recommended by European guidelines.

The median OS of patients treated with sunitinib in first-line was 23.9 months and the TNT-D was 10.7 months. In second-line, the median OS of patients treated with nivolumab was 19.6 months and the median TNT-D was 8.5 months.

- These data on the use of an immune checkpoint inhibitor (ICI) in real-world practice confirmed the effectiveness of nivolumab in aRCC. The present study provides a benchmark for future studies to assess the real-life effectiveness of ICI-based combinations in first-line for aRCC. As such, the next steps are to longitudinally evaluate treatment patterns when ICI-based combinations have become the main first-line treatment for aRCC.

Disclosure

Laurence Albigès (LA) has received advisory or consulting or honoraria (all paid to Institution) from Astellas, BMS, Ipsen, Janssen, Merck, MSD, Novartis, Pfizer, EISAI, and Roche; and has received travel, accommodations, and expenses from BMS, MSD and Ipsen. Carine Bellera (CB) has received consulting fees from BMS. Isabelle Durand-Zaleski (IDZ) has received advisory board or educational sessions with personal fees from Amgen, BMS, Boston scientific, MSD, Pfizer, Roche, and Takeda. Sylvie Négrier (SyN) has honoraria from Pfizer, Ipsen, BMS, MSD Oncology, and EISAI.; and has received consulting or advisory role from Ipsen, MSD Oncology, and EISAI; and has received research funding from Pfizer, Ipsen, and MSD; and has received travel, accommodations, expenses from Pfizer, BMS, Ipsen, and MSD. Sébastien Branchoux (SB), Sonia Néré (SoN), Anne-Françoise Gaudin (AFG) are employees of BMS France. Mickael Arnaud (MA) and Amandine Gouverneur (AG) are employees of IQVIA, with which BMS France contracted to support data acquisition and analysis for this study.

Author Contributions

All authors conceptualized the study design, MA and AG contributed to data analysis, all authors contributed to interpretation, MA, AG and SB drafted the manuscript, and LA, CB, SoN, AFG, IDZ and SyN critically reviewed the manuscript. All authors approved the final manuscript.

Acknowledgments

The authors would like to thank Pascaline Rabiega (IQVIA) and Carole Quentric (Bristol Myers Squibb) for their contributions to the study design and interpretation of the results. This work was supported by Bristol-Myers Squibb France.

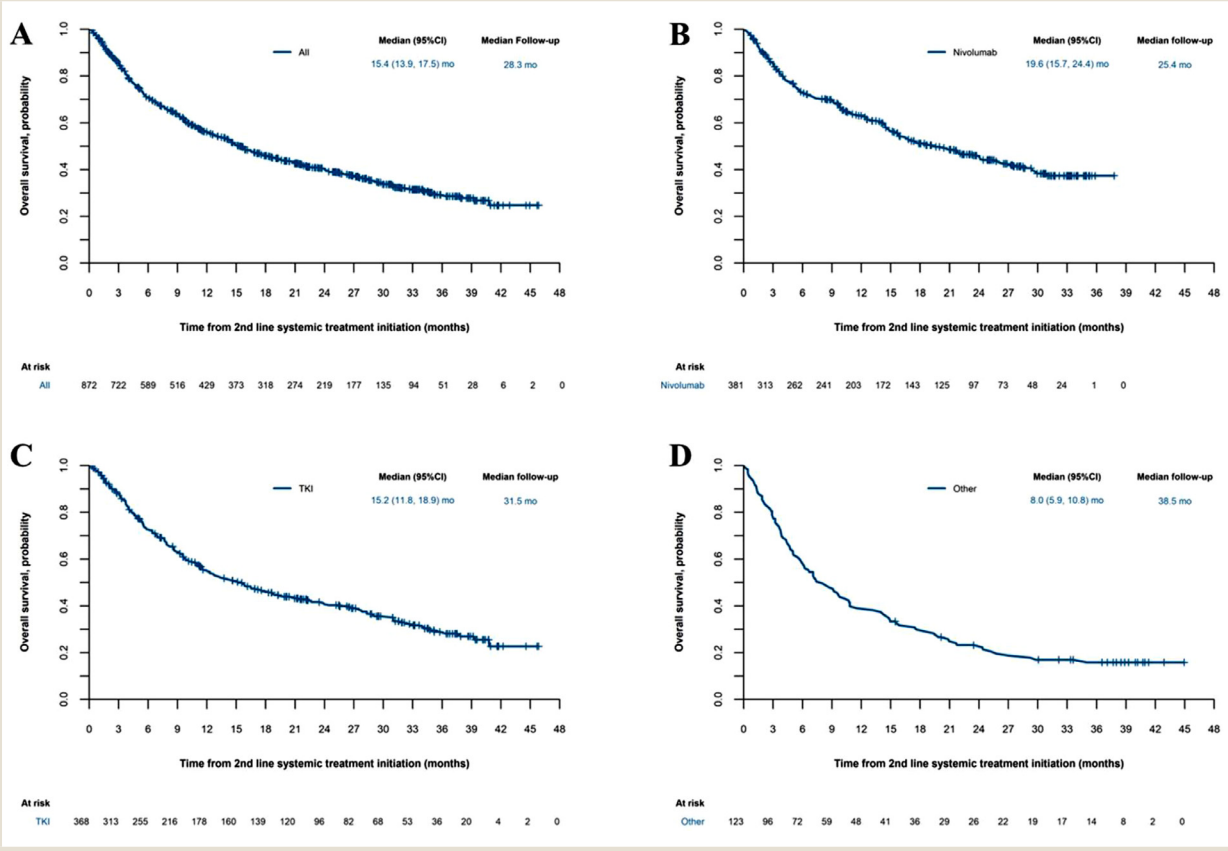
References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660.
2. Padala SA, Barsouk A, Thandra KC, et al. Epidemiology of renal cell carcinoma. *World J Oncol*. 2020;11(3):79–87. doi:10.14740/wjon1279.
3. Defossez G, Uhry Z, Delafosse P, et al. Cancer incidence and mortality trends in France over 1990-2018 for solid tumors: the sex gap is narrowing. *BMC Cancer*. 2021;21(1):726. doi:10.1186/s12885-021-08261-1.
4. Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27(suppl 5):v58–v68. doi:10.1093/annonc/mdw328.
5. Powles T, Albiges L, Bex A, et al. ESMO Clinical Practice Guideline update on the use of immunotherapy in early stage and advanced renal cell carcinoma. *Ann Oncol*. 2021;32(12):1511–1519. doi:10.1016/j.annonc.2021.09.014.
6. Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2019;30(5):706–720. doi:10.1093/annonc/mdz056.
7. Gouverneur A, Salvo F, Berdaï D, Moore N, Fourrier-Réglat A, Noize P. Inclusion of elderly or frail patients in randomized controlled trials of targeted therapies for the treatment of metastatic colorectal cancer: a systematic review. *J Geriatr Oncol*. 2018;9(1):15–23. doi:10.1016/j.jgo.2017.08.001.
8. Graham J, Heng DY. Real-world evidence in metastatic renal cell carcinoma. *Tumori J*. 2018;104(2):76–82. doi:10.1177/0300891618761004.
9. Mitchell AP, Harrison MR, Walker MS, George DJ, Abernethy AP, Hirsch BR. Clinical trial participants with metastatic renal cell carcinoma differ from patients treated in real-world practice. *J Oncol Pract*. 2015;11(6):491–497. doi:10.1200/JOP.2015.004929.
10. Nazha B, Yang JCH, Owonikoko TK. Benefits and limitations of real-world evidence: lessons from EGFR mutation-positive non-small-cell lung cancer. *Future Oncol*. 2021;17(8):965–977. doi:10.2217/fon-2020-0951.
11. van Laar SA, Gombert-Handoko KB, Groenwold RHH, et al. Real-world metastatic renal cell carcinoma treatment patterns and clinical outcomes in The Netherlands. *Front Pharmacol*. 2022;13:803935. doi:10.3389/fphar.2022.803935.
12. Schmidinger M, Pichler R, Loidl W, et al. Real-world evidence data on metastatic renal-cell carcinoma treatment in Austria: the RELACS study. *Clin Genitourin Cancer*. 2019;17(5):e957–e967. doi:10.1016/j.clgc.2019.05.017.
13. Waddell T, Fife K, Griffiths R, et al. Real-world treatment sequencing and survival in previously treated advanced renal cell carcinoma patients receiving nivolumab monotherapy: a UK retrospective cohort study. *BMC Cancer*. 2022;22(1):617. doi:10.1186/s12885-022-09694-y.
14. Maroun R, Fleury L, Nachbaur G, Maunoury F, Vanhille JL, Durand-Zaleski I. Real-world costs and outcomes in metastatic renal cell carcinoma patients treated with targeted therapies: a cohort study from the French health insurance database. *Curr Med Res Opin*. 2017;33(10):1755–1762. doi:10.1080/03007995.2017.1360850.
15. Maroun R, Mitrofan L, Benjamin L, et al. Real life patterns of care and progression free survival in metastatic renal cell carcinoma patients: retrospective analysis of cross-sectional data. *BMC Cancer*. 2018;18(1):214. doi:10.1186/s12885-018-4117-z.
16. Noize P, Grelaud A, Bay JO, et al. Real-life patterns of use, safety and effectiveness of sunitinib in first-line therapy of metastatic renal cell carcinoma: the SANTORIN cohort study. *Pharmacoepidemiol Drug Saf*. 2017;26(12):1561–1569. doi:10.1002/pds.4228.
17. Vrdoljak E, Magri C, Gamulin M, et al. Real-world safety and efficacy of nivolumab for ≥ 2nd line treatment of metastatic renal cell carcinoma: a retrospective cohort study in Croatia, Hungary, and Malta. *Neoplasma*. 2021;68(1):208–215. doi:10.4149/neo_2020_200512N519.
18. Costello BA, Bhavsar NA, Zakharia Y, et al. A prospective multicenter evaluation of initial treatment choice in metastatic renal cell carcinoma prior to the immunotherapy era: the MaRCC registry experience. *Clin Genitourin Cancer*. 2022;20(1):1–10. doi:10.1016/j.clgc.2021.07.002.
19. Khozin S, Miksad RA, Adami J, et al. Real-world progression, treatment, and survival outcomes during rapid adoption of immunotherapy for advanced non-small cell lung cancer. *Cancer*. 2019;125(22):4019–4032. doi:10.1002/cncr.32383.
20. Dudani S, Graham J, Wells JC, et al. First-line immuno-oncology combination therapies in metastatic renal-cell carcinoma: results from the international metastatic renal-cell carcinoma database consortium. *Eur Urol*. 2019;76(6):861–867. doi:10.1016/j.eururo.2019.07.048.
21. Bezin J, Duong M, Lassalle R, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: powerful tools for pharmacoepidemiology. *Pharmacoepidemiol Drug Saf*. 2017;26(8):954–962. doi:10.1002/pds.4233.
22. Branchoux S, Sofeu CL, Gaudin AF, et al. Time to next treatment or death as a candidate surrogate endpoint for overall survival in advanced melanoma patients treated with immune checkpoint inhibitors: an insight from the phase III CheckMate 067 trial. *ESMO Open*. 2021;7(1):100340. doi:10.1016/j.esmoop.2021.100340.
23. Albiges L, Negrier S, Dalban C, et al. Safety and efficacy of nivolumab in metastatic renal cell carcinoma (mRCC): final analysis from the NIVOREN GETUG AFU 26 study. *J Clin Oncol*. 2019;37(suppl 7):542. doi:10.1200/JCO.2019.37.7_suppl.542.
24. Thiery-Vuillemin A, Albiges L, Escudier B, et al. 674P WITNESS: real-world outcomes of patients (pts) with advanced renal cell carcinoma (aRCC) treated with nivolumab in France and subgroup analysis of patients receiving concomitant medications at baseline. *Ann Oncol*. 2021;32:S697. doi:10.1016/j.annonc.2021.08.070.
25. Thiery-Vuillemin A, Cholley T, Calcagno F, et al. Factors influencing overall survival for patients with metastatic clear-cell renal-cell carcinoma in daily practice. *Clin Genitourin Cancer*. 2018;16(2):e297–e305. doi:10.1016/j.clgc.2017.09.006.
26. Gouverneur A, Dolatkhani D, Rouyer M, et al. Agreement between hospital discharge diagnosis codes and medical records to identify metastatic colorectal cancer and associated comorbidities in elderly patients. *Rev Epidemiol Sante Publique*. 2017;65(4):321–325. doi:10.1016/j.respe.2017.03.132.
27. Verzoni E, Cartenì G, Cortesi E, et al. Real-world efficacy and safety of nivolumab in previously-treated metastatic renal cell carcinoma, and association between immune-related adverse events and survival: the Italian expanded access program. *J Immunother Cancer*. 2019;7(1):99. doi:10.1186/s40425-019-0579-z.

28. Bensalah K, Bigot P, Albiges L, et al. [French ccAFU guidelines - update 2020-2022: management of kidney cancer]. *Prog Urol*. 2020;30(suppl 12):S2–S51. doi:10.1016/S1166-7087(20)30749-1.
29. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373(19):1814–1823. doi:10.1056/NEJMoa1510016.
30. Motzer RJ, Escudier B, George S, et al. Nivolumab versus everolimus in patients with advanced renal cell carcinoma: updated results with long-term follow-up of the randomized, open-label, phase 3 CheckMate 025 trial. *Cancer*. 2020;126(18):4156–4167. doi:10.1002/cncr.33033.
31. Climent MA, Muñoz-Langa J, Basterretxea-Badiola L, Santander-Lobera C. Systematic review and survival meta-analysis of real world evidence on first-line pazopanib for metastatic renal cell carcinoma. *Crit Rev Oncol Hematol*. 2018;121:45–50. doi:10.1016/j.critrevonc.2017.11.009.
32. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2009;27(22):3584–3590.
33. Motzer RJ, Hutson TE, McCann L, Deen K, Choueiri TK. Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. *N Engl J Med*. 2014;370(18):1769–1770. doi:10.1056/NEJMc1400731.
34. Savard MF, Wells JC, Graham J, et al. Real-world assessment of clinical outcomes among first-line sunitinib patients with clear cell metastatic renal cell carcinoma (mRCC) by the International mRCC Database Consortium Risk Group. *Oncologist*. 2020;25(5):422–430. doi:10.1634/theoncologist.2019-0605.
35. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol*. 2018;71(16):1755–1764. doi:10.1016/j.jacc.2018.02.037.
36. Parikh M, Bajwa P. Immune checkpoint inhibitors in the treatment of renal cell carcinoma. *Semin Nephrol*. 2020;40(1):76–85. doi:10.1016/j.semnephrol.2019.12.009.
37. Kostine M, Mauric E, Tison A, et al. Baseline co-medications may alter the anti-tumoural effect of checkpoint inhibitors as well as the risk of immune-related adverse events. *Eur J Cancer*. 2021;157:474–484. doi:10.1016/j.ejca.2021.08.036.

Supplementary materials

Supplemental Figure 1 Overall survival in patients from second-line treatment initiation, overall and by type of second-line treatment. (A) all patients; (B) patients treated by nivolumab; (C) patients treated by tyrosine kinase inhibitors (TKI); (D) patients treated by other systemic treatments.



Supplemental Table 1 Identification Procedure for Systemic Treatment Approved for Advanced Renal Cell Cancer

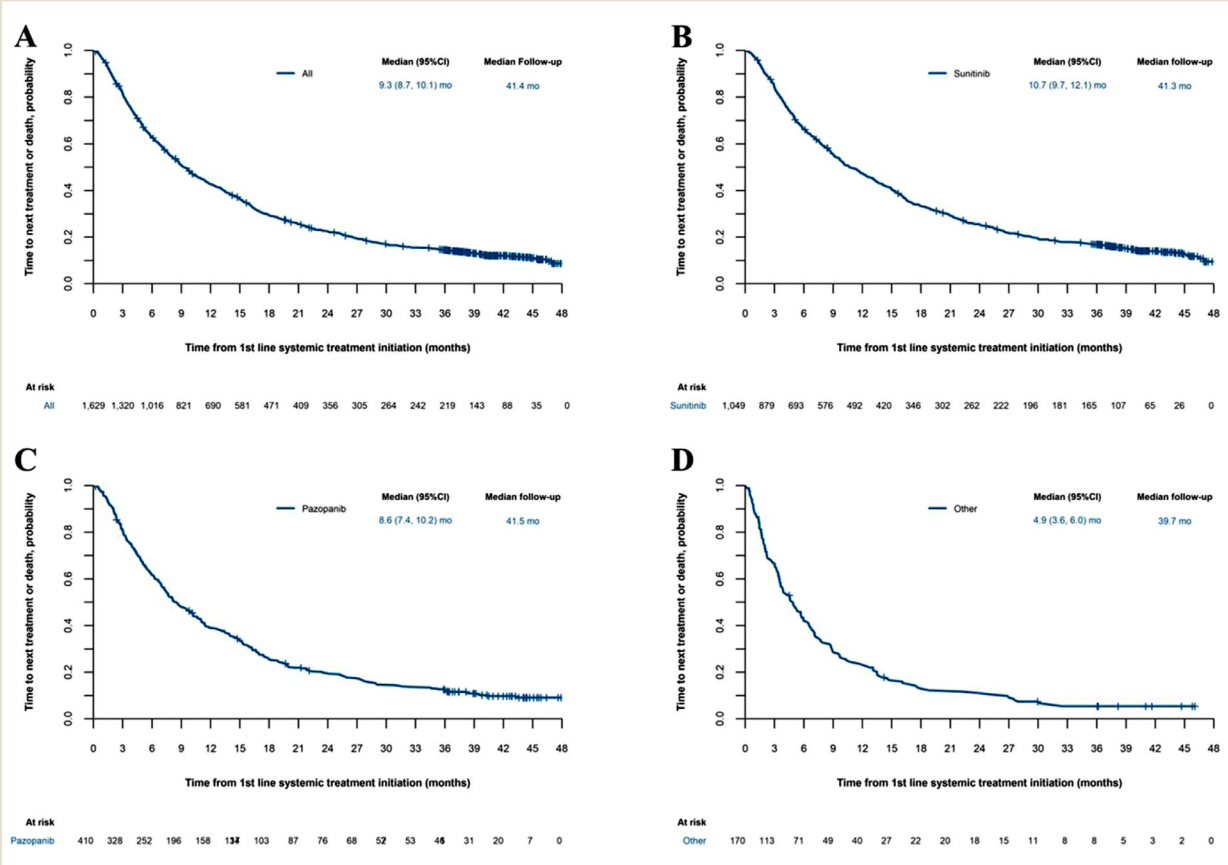
ATC Code	Term	UCD Codes	CIP Codes
L03AC01	Aldesleukin	9233214	
		9233220	
L01XE04	Sunitinib		3400938210224
			3400938210392
			3400938210453
L01XE11	Pazopanib		3400949131341
			3400949131570
			3400949131631
L01XE05	Sorafenib		3400937613729
L01FG01	Bevacizumab	9261104	
		9261110	
L03AB04	Interferon alfa-2a		3400934902697
			3400934902758
			3400935255716
			3400935256027
			3400935256256
			3400935256546
			3400935256775
			3400935257147
			3400935257376
			3400935257727
			3400935258557
			3400935258847
			3400936077027
			3400936077317
L01XE17	Axitinib		3400926648046
			3400927547379
			3400926648275
			3400927547669
L01EG01	Temsirolimus	9304776	
L01XE10	Everolimus		3400926788414
			3400939628288
			3400930152621
			3400930152645
			3400930152669
			3400930152676
			3400930152690
			3400930148402
			3400930148419
			3400930148464
			3400930156643
			3400930156582
			3400930156544
			3400930152409
			3400930152423
			3400930152447
			3400930117613
			3400930117637
			3400930117675
			3400930159132

(*continued on next page*)

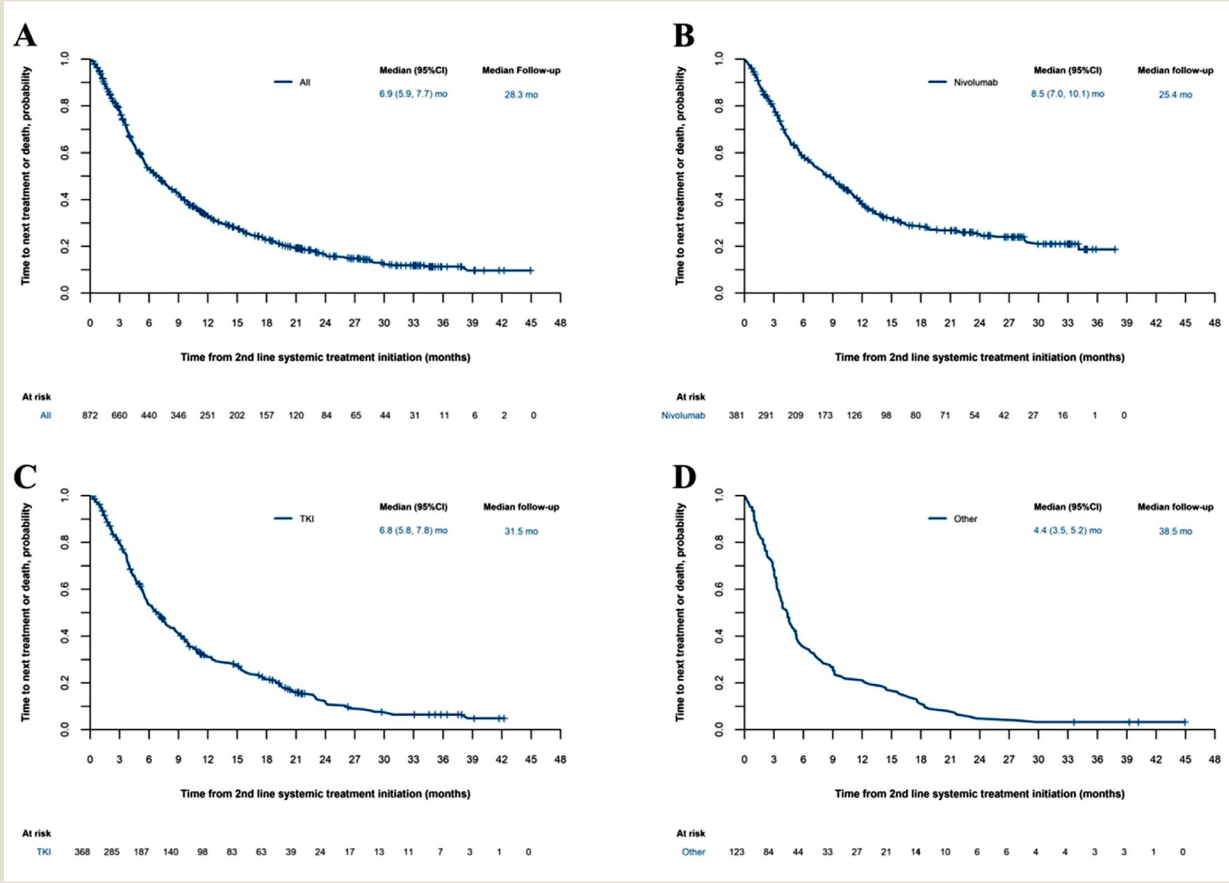
Supplemental Table 1 (*continued*)

ATC Code	Term	UCD Codes	CIP Codes
			3400930153352
			3400930153284
			3400939628110
L01EX07	Cabozantinib	9420005	3400930073520
		9420011	3400930073537
		9420028	3400930073544
L01FF01	Nivolumab	9409469	
		9409452	
		9438979	

Supplemental Figure 2 Time to next treatment or death in patients from first-line treatment initiation, overall and by type of first-line treatment. (A) all patients; (B) patients treated by sunitinib; (C) patients treated by pazopanib; (D) patients treated by other systemic treatments.



Supplemental Figure 3 Time to next treatment or death in patients from second-line treatment initiation, overall and by type of second-line treatment. (A) all patients; (B) patients treated by nivolumab; (C) patients treated by tyrosine kinase inhibitors (TKI); (D) patients treated by other systemic treatments.



Supplemental Table 2 Identification Procedure for Advanced Renal Cell Cancer

Source	Code	Term
ICD-10	C64	Malignant neoplasm of kidney, except renal pelvis
CCAM	JAHB001	*Biopsie du rein, par voie transcutanée sans guidage*
	JAHJ006	*Biopsie du rein sur une cible, par voie transcutanée avec guidage échographique*
	JAHJ007	*Biopsie du rein sur plusieurs cibles, par voie transcutanée avec guidage échographique*
	JAHH002	*Biopsie du rein, par voie jugulaire transcutanée avec guidage radiologique*
	JAHC001	*Biopsie du rein, par coelioscopie ou par rétropéritonéoscopie*
	JAHA001	*Biopsie du rein, par abord direct*

Supplemental Table 3 Identification Procedure for Other Approved Cancers

ATC Code	Term	ICD-10 Codes	Terms
L01XE04	Sunitinib	C16	Malignant neoplasm of stomach
		C17	Malignant neoplasm of small intestine
		C25	Malignant neoplasm of pancreas
L01XE11	Pazopanib	C46	Kaposi sarcoma
L01XE05	Sorafenib	C22	Malignant neoplasm of liver and intrahepatic bile ducts
		C73	Malignant neoplasm of thyroid gland
L01FG01	Bevacizumab	C18	Malignant neoplasm of colon
		C19	Malignant neoplasm of rectosigmoid junction
		C20	Malignant neoplasm of rectum
		C34	Malignant neoplasm of bronchus and lung
		C50	Malignant neoplasm of breast
		C51	Malignant neoplasm of vulva
		C52	Malignant neoplasm of vagina
		C53	Malignant neoplasm of cervix uteri
		C54	Malignant neoplasm of corpus uteri
		C55	Malignant neoplasm of uterus, part unspecified
		C56	Malignant neoplasm of ovary
		C57	Malignant neoplasm of other and unspecified female genital organs
L03AB04	Interferon alfa-2a	C81	Hodgkin lymphoma
		C82	Follicular lymphoma
		C83	Non-follicular lymphoma
		C84	Mature T/NK-cell lymphomas
		C85	Other and unspecified types of non-Hodgkin lymphoma
		C86	Other specified types of T/NK-cell lymphoma
		C91	Lymphoid leukemia
		C92	Myeloid leukemia
		C93	Monocytic leukemia
		C94	Other leukemias of specified cell type
		C95	Leukemia of unspecified cell type
		C43	Malignant melanoma of skin
		C44	Other malignant neoplasms of skin
L01EG01	Temsirolimus	C81	Hodgkin lymphoma
		C82	Follicular lymphoma
		C83	Nonfollicular lymphoma
		C84	Mature T/NK-cell lymphomas
		C85	Other and unspecified types of non-Hodgkin lymphoma
		C86	Other specified types of T/NK-cell lymphoma
L01XE10	Everolimus	C16	Malignant neoplasm of stomach
		C17	Malignant neoplasm of small intestine
		C25	Malignant neoplasm of pancreas
		C34	Malignant neoplasm of bronchus and lung
		C50	Malignant neoplasm of breast
L01EX07	Cabozantinib	C22	Malignant neoplasm of liver and intrahepatic bile ducts
L01FF01	Nivolumab	C81	Hodgkin lymphoma
		C82	Follicular lymphoma
		C83	Non-follicular lymphoma

(*continued on next page*)

Supplemental Table 3 (*continued*)

ATC Code	Term	ICD-10 Codes	Terms
		C84	Mature T/NK-cell lymphomas
		C85	Other and unspecified types of non-Hodgkin lymphoma
		C86	Other specified types of T/NK-cell lymphoma
		C34	Malignant neoplasm of bronchus and lung
		C07	Malignant neoplasm of parotid gland
		C08	Malignant neoplasm of other and unspecified major salivary glands
		C09	Malignant neoplasm of tonsil
		C10	Malignant neoplasm of oropharynx
		C11	Malignant neoplasm of nasopharynx
		C12	Malignant neoplasm of piriform sinus
		C13	Malignant neoplasm of hypopharynx
		C14	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
		C32	Malignant neoplasm of larynx
		C33	Malignant neoplasm of trachea
		C65	Malignant neoplasm of renal pelvis
		C66	Malignant neoplasm of ureter
		C67	Malignant neoplasm of bladder
		C43	Malignant melanoma of skin
		C44	Other malignant neoplasms of skin