Long survival of patients with metastatic clear cell renal cell carcinoma. Results of real life study of 344 patients

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The treatment landscape in metastatic renal cell carcinoma has changed fundamentally over the last decade by the development of antiangiogenic agents, mammalian target of rapamycin inhibitors and immunotherapy. Outside of the context of a clinical trial, the treatments are used sequentially. We describe results under real-life conditions of a sequential treatment strategy, before the era of immunotherapy. All patients were treated according to their prognostic score (either Memorial Sloan Kettering Cancer Center or International Metastatic Renal Cell Carcinoma Database Consortium) for advanced renal cell carcinoma. A treatment strategy involving 1 to 4 lines was determined including a rechallenge criterion for the repeat use of a treatment class. Three hundred forty-four patients were included over 3 years. Overall survival was 57 months in patients with good or intermediate prognosis and 19 months in patients with poor prognosis. In the former group, the proportions of patients treated with 2 to 4 treatment lines were 70%, 38% and 16%, respectively. The best objective response rates for lines 1 to 4 were 46%, 36%, 16% and 17%, respectively. Grade III/IV toxicity did not appear to be cumulative. The recommended strategy was followed in 68% of

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patients. A large proportion of patients with good or intermediate prognosis who progress after two lines of treatment still have a performance status good enough to receive a systemic treatment, which justifies such a strategy. Overall survival of patients with good and intermediate prognosis was long, suggesting a benefit from the applied approach. These results might be used as selection criterion for the treatment of patients in the era of immune checkpoint inhibitors.

What's new?

Metastatic renal cancer is a notoriously relapsing disease that can be treated with anti-angiogenic treatments, tyrosine kinase inhibitors, inhibitors of the mammalian Target of Rapamycin or immune checkpoint inhibitors. The authors performed a "real-life" study testing a sequential strategy of the first three treatments applied to 344 patients with relapsing metastatic renal cancer before the era of immunotherapy. They found that the overall survival of patients with good and intermediate prognosis was long, almost 5 years, and plan a new study including immunotherapy in the future.

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Introduction

Renal cancer accounts for approximately 3% of adult cancers in western countries. It is the seventh most common cancer in men and the ninth most common in women, and approximately 209,000 new cases are diagnosed annually throughout the world. Up to one third of patients present with regional lymphadenopathy or metastases at the time of diagnosis.[1] Approximately 25% of all patients with localized tumors who undergo curative surgery relapse over time.[2–4] The prognosis of patients with metastatic renal cancer varies greatly and largely depends on risk factors.[5,6] The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) classification identifies three subgroups of patients with different prognosis, depending on their number of risk factors (1, 2 or ≥3). The prognostic indicators are the presence of poor general health, the time from diagnosis to initiation of treatment, the presence of anaemia, hypercalcaemia, thrombocytosis and neutrophilia.

Advances in our understanding of the pathogenesis of clear cell renal cell cancer (ccRCC), the most common histological subtype of renal cancer, have led to the development of antiangiogenic treatments (monoclonal antibodies against vascular endothelial growth factor receptors,[7] inhibitors of the vascular endothelial growth factor receptor tyrosine kinases (TKI),[8,9] inhibitors of the mammalian target of rapamycin pathway (imTOR)[10,11] and more recently by the development of immune checkpoint inhibitors.[12] The development of these new treatments modalities has significantly improved patient outcomes in terms of median overall survival. Sequential treatments are recommended depending on patient prognosis.[13] Before the era of immunotherapy, the recommendations which mostly involve the first two lines of treatment[14] were for a first line TKI or the combination of bevacizumab interferon. Because of its toxicity, interleukin 2 was an option. After disease progression on a TKI, second line treatment with everolimus (imTOR) was considered. For patients developing progressive disease who are eligible for oncologic treatment modalities, the only possibility was to offer a treatment class used previously, although there were no specific recommendations about the optimal sequence or type of treatment to be used.

The IVOIRE (étude observationnelle prospectIve évaluant les traitements par Voie Orale contre le cancer métastatIque du REin) working group proposed a decision algorithm to homogenize the treatment of metastatic ccRCC patients and make the choice of sequences from the first up to the fifth line in a period when immune checkpoint inhibitors were not available and published recommendations only concerned the first two lines of systemic treatment.

Materials and Methods
Population

The IVOIRE cohort represents a prospectively assessed real-life study, set up in four regions in the western part of France by the Observatory of Cancer—Observatories for Medicines and Medical Devices and Treatment Innovations (OMEDIT Bretagne and OMEDIT Pays de la Loire). All patients with histologically proven ccRCC aged >18 years (whether in the advanced or metastatic phase) were eligible for registration in the IVOIRE cohort. Patients who required a systemic treatment could be included either in first line or for the second line if they received a treatment as recommended in the treatment strategy defined for the cohort. The patients were distributed by prognosis (good, intermediate or poor) defined by the Memorial Sloan Kettering Cancer Center or IMDC criteria.[5,6] They were following the treatment strategy defined for their prognosis.

The patients were included between September 1, 2011, and September 30, 2014. All were being followed up by their referent oncologist until they died or until the cutoff date of March 15, 2016. An assessment of treatment efficacy was recommended every three treatment cycles. Patients lost to follow-up were censored at the date of last seen.

Treatments and decision algorithm

The treatment strategy was defined in June 2011 during several plenary meetings by an expert committee consisting of ten medical oncologists from the centers in the four administrative regions taking part in the IVOIRE cohort.

When the decision algorithm was constructed, the treatments permitted for use outside of a clinical trial in France were interferon alpha, interleukin 2, sunitinib, sorafenib, bevacizumab, everolimus and temsirolimus. Two amendments were made in November 2011 and April 2013 to include pazopanib and axitinib. Cabozantinib as well as immune checkpoint inhibitors were approved after the end of the study. The patients with good or intermediate prognosis were treated in the same way. The sequential strategy proposed followed the guidelines for the first two treatment lines.[15] For the third and subsequent lines of treatment, the IVOIRE consensus proposed the following recommendation: A class of drug could be offered if it had previously achieved tumor control for 6 months or longer or if the treatment had been stopped because of toxicity. The decision algorithm is summarized in Table 1.

Study data

Collection of information from the IVOIRE cohort was coordinated by the Observatory for Medicines and Medical Devices and Treatment Innovations (Pays de la Loire) and was recorded on an electronic report from the patients' medical records. The data collected included age, sex, main past history, creatinine clearance, histological type and Fuhrman grade, whether or not nephrectomy had been performed, local treatment for metastases (metastasectomy or irradiation) prior to starting the first line of systemic treatment, and for each treatment line the drugs used, treatment start date, best response observed, duration of tumor control (DTC), grade 3/4 toxicities and date of death or date of last news.

No centralized review of the histology or imaging was performed.

The variables were described as mean and standard deviations (or median and range) for quantitative data and by numbers by modality and percentages for qualitative data.

Overall survival was estimated using the Kaplan-Meier method and was defined as the median survival with its 95% confidence interval for the whole cohort depending on the treatment sequence received. This was defined as the time between the date when the first treatment line started and death. The survival curves by treatment sequence were compared by the log rank test and a *p* value of less than 0.05 was deemed to be significant. The best treatment response was assessed using the response evaluation criteria in solid tumors 1.1 criteria. DTC by a line of treatment was defined as the time between starting this treatment and initiation of the next line, patient death or date of last news regardless of intermediary events (transient interruption treatment for toxicity or at the patient's request, metastasectomy, irradiation of the metastases, etc.). The Pearson's chi-squared test (or Fisher's exact test if necessary) was used to compare frequencies and the Mann-Whitney test was used in preference to compare disease control times between the two groups. Adverse effects were reported according to the Common Terminology Criteria for Adverse Events (version 4.0). Only grade III/IV AEs were collected and reported.

All patients received an information letter explaining the aim of our study, the possibility to refuse to participate, type of data collected and the possibility to access, change or refuse personal data collection according to French law. At the date of the design of the study, Institutional Review Board was not mandatory because it was considered as an observational study.

Data availability

The data that support the findings of our study are available from the corresponding author (E.V.) upon reasonable request.

Results

Features of the IVOIRE cohort

Thirty-three medical oncologists from 17 centers included at least one patient. A total of 386 patients were included between September 1, 2011, and September 30, 2014; 301 of whom had a good or intermediate prognosis (Memorial Sloan Kettering Cancer Center: 36; IMDC: 43; both: 222) and 43 had a poor prognosis (Memorial Sloan Kettering Cancer Center: 2; IMDC: 1; both: 40). In 42 patients, the prognostic score was missing and these patients were excluded from the study (Fig. 1). Patients' median age was 65 years. Most of them were suffering from ccRCC (good or intermediate prognosis: 88%; poor prognosis: 74%). Median follow-up of good and intermediate prognosis patients at the end point of our study was 37 months and 16 months for poor prognosis

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Table 1. Treatment strategy

Prognosis	L1	L2	L3	L4
Good and intermediate	IL2 + IFN	TKI	Everolimus TKI (if stopped for toxicity in L2)	TKI r Everolimus
	IFN + bevacizumab	TKI	Everolimus	TKI r
	TKI	Everolimus TKI (if stopped for toxicity in L1)	TKI r Everolimus	Everolimus r TKI r
Poor	Temsirolimus	Sunitinib Axitinib		
	Sunitinib	Everolimus		

Abbreviations: IL2, interleukin 2; IFN, interferon alpha; r, rechallenge; TKI, tyrosine kinase inhibitors.
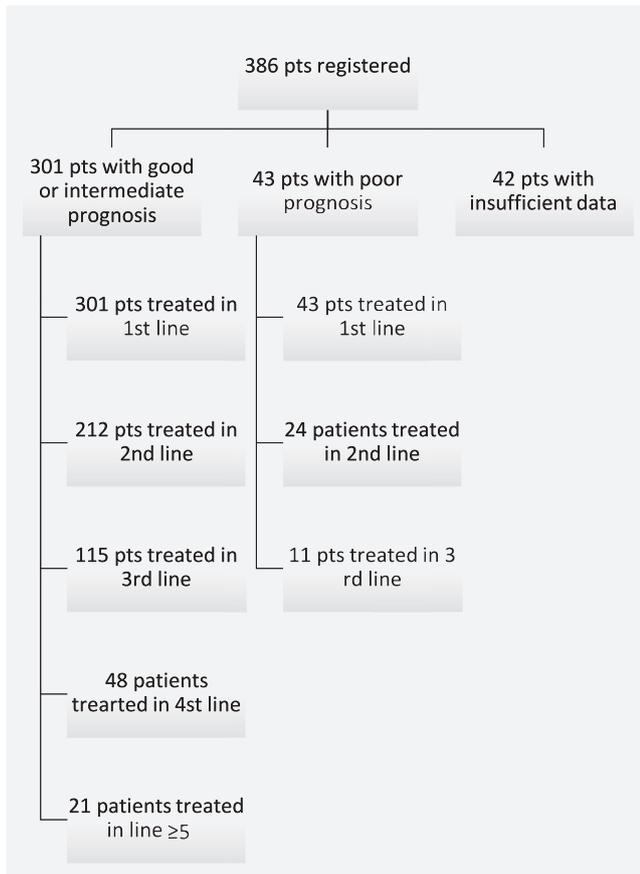
Figure 1. Diagram of patients treated in the IVOIRE study.

patients. The characteristics of the patients are summarized in Table 2.

Treatments

The 301 patients with a good or intermediate prognosis received a first line of treatment, 212 (70%) received a second line, 115 (38%) a third line, 48 (16%) a fourth line and 14 (5%) a fifth line or more (Fig. 1).

Most patients (276 [91.7%]) received a TKI as first-line treatment. Twelve (4%) patients received an imTOR because of a cardiac contraindication to sunitinib ($N = 11$), poor general health ($N = 1$) and one patient to treat a chromophobe carcinoma (practitioner's choice). In second-line treatment, 113 (53%) patients received an imTOR and 96 (45%) patients received a TKI. For third-line treatment, 73 (63%) patients received a TKI and 42 (36%) patients received an imTOR. In fourth-line treatment, 40 (83%) patients received a TKI and 6 (12%) patients received an imTOR.

All 43 poor prognosis treatment patients received first-line treatment (TKI: 74%; imTOR: 21%). Twenty-four (55%) patients were treated with a second line (TKI: 50%; imTOR: 50%). Details of the treatments received are summarized in Table 3.

Follow-up, objective response, DTC

One hundred sixty-two of 301 (53.8%) good and intermediate prognosis patients had died at the study end point date. Median overall survival was 57 months (51–70). An objective response was seen on a TKI in 128 (46%), 35 (36%), 12 (16%) and 6 (15%) patients, respectively, for treatment lines 1 to 4. An objective response was achieved with the imTOR in 11 (10%) and 4 (10%) in second- and third-line treatments.

The median DTC from the TKI initiation was 14 months for first-line treatment, 9 months for second-line treatment, 7 months for third-line treatment and 6 months for fourth-line treatment. The imTOR achieved a median DTC of 8 months and 6 months in second and third line use, respectively. These results are summarized in Table 4. It should be noted that the median overall survival after starting fourth-line treatment was 13 months.[8–21]

Of the poor prognosis patients, 29 (67.4%) had died at the study end date. Median overall survival was 19 months (14–63). In first-line treatment, a TKI achieved an objective response rate of 44%, a median DTC of 11.5 months compared to 0% and 9 months respectively for an imTOR. An objective response rate of 33% with a TKI and 0% with an imTOR was found with second-line treatment and a median DTC of 5.5 and 9.5 months, respectively (Table 4).

Analysis of sequences

Overall survival was compared by treatment sequence received in 99 patients who had received at least three lines of treatment including a first-line TKI in the good or intermediate prognosis population. Of these patients, 53 received the TKI > imTOR > TKI sequence and 34 received the TKI > TKI > imTOR sequence. Median survival was 53 months (46–69) and 70 months (55–NA), respectively. This difference was not statistically significant ($p = 0.167$).

The overall survival times in this population were compared according to the duration of first line tumor control. Patients whose DTC on first-line treatment was greater than the median had a significantly longer survival than patients whose DTC was below the median: 70 months (60–100) compared to 33 months (26–69; $p = 0.001$) regardless of sequence received, TKI > TKI > imTOR or TKI > imTOR > TKI.

Rechallenge

Within the proposed strategy, a treatment class which had already been used could be reused if it produced a DTC of over 6 months in patients with good or intermediate prognosis (Table 1). We primarily examined the rechallenge with TKI as third-line treatment. In the other situations, it was not possible to draw a valid conclusion because of the small patient numbers. One hundred fifteen patients received at least three lines of treatment, 99 of whom received a TKI first line. Sixty-three of these patients (64%) were rechallenged with a third-line TKI and 53 (84%) patients had a DTC of ≥6 months in first-line treatment. The objective response and

Table 2. Patient characteristics

	Good or intermediate prognosis		Poor prognosis	
	N = 301		*N* = 43	
Prognosis				
MSKCC	36		2	
IMDC	43		1	
Both	222		40	
Age	66 years (range: 35–90)		65 years (range: 46–86)	
Sex	213 men/88 women (70.8%/29.2%)		29 men/14 women (67.4%/32.6%)	
Renal function (creatinine clearance)	≥60 ml/min	246 (81.4%)	≥60 ml/min	35 (81.4%)
	‹60 ml/min	44 (14.6%)	‹60 ml/min	8 (18.6%)
	Unknown	11 (3.6%)	Unknown	0 (—)
Histology	Clear cell carcinoma	265 (88%)	Clear cell carcinoma	32 (74.4%)
	Tubulo-papillary carcinoma	22 (7.3%)	Tubulo-papillary carcinoma	1 (2.3%)
	Chromophobic cell carcinoma	4 (1.3%)	Chromophobic cell carcinoma	0 (—)
	Sarcomatoid carcinoma	2 (0.7%)	Sarcomatoid carcinoma	3 (7%)
	Other	1 (0.3%)	Other	6 (14%)
	NS	7 (2.3%)	NS	1 (2.3%)
Fuhrman grade	I/II	79 (26.2%)	I/II	10 (23.3%)
	III/IV	168 (55.8%)	III/IV	22 (51.2%)
	NS	54 (17.9%)	NS	11 (25.6%)
Nephrectomy	Yes (no further details)	13 (4.3%)	Yes (no further details)	0 (—)
	Extended	245 (81.4%)	Extended	25 (58.1%)
	Partial	13 (4.3%)	Partial	1 (2.3%)
	No	30 (10%)	No	17 (39.5%)
Median time from diagnosis to systemic treatment	741 days		151 days	
Surgery for metastases	No	188 (62.4%)	No	35 (81.4%)
	Yes	113 (37.5%)	Yes	8 (18.6%)
Radiotherapy for metastases	Yes	37 (12.3%)	Yes	6 (14%)
	No	264 (87.4%)	No	37 (86%)
Inclusion	First line	284 (94.3%)	39 (90.7%)	
	Second line	17 (5.6%)	4 (9.3%)	

Abbreviation: NS, not specified.

clinical benefit rates during the rechallenge were not significantly different in patients whose rechallenge criterion determined using the IVOIRE recommendations was met and in those in whom the rechallenge criterion was not met (15% and 57% compared to 10% and 60%, respectively).

Toxicity

Grade III/IV Common Terminology Criteria for Adverse Events (version 4.0) toxicities in patients with good or intermediate prognosis are reported in Table 5. Thirty percent, 31%, 19% and 12% of patients who received a TKI suffered at least one grade III/IV toxicity during lines 1 to 4, respectively. The corresponding figures for the imTOR were 17%, 28%, 14% and 0% for lines 1 to 4, respectively.

Following the study guidelines

Forty-seven (13.7%) patients were included into the cohort despite having a histology that did not reveal ccRCC. The choice of first line was consistent with the guidelines except in 12 good or intermediate prognosis patients (4%) who received an imTOR. In second-line treatment of good or intermediate prognosis patients, repeat use of the TKI was reserved for those who stopped the TKI because of toxicity. Twenty-three of 77 (29.9%) patients who received a second-line TKI after having received a first-line TKI (29.8%) stopped this because of toxicity. The rechallenge criteria for a third-line TKI were met in 84% of patients. A total of 205 (68%) of the 301 good or intermediary prognosis patients met the guidelines for the first four lines of treatment. Regarding poor prognosis patients, 95% followed the guidelines for first-line treatment and 70% for the second line.

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Table 3. Treatments received

Good or intermediate prognosis patients

	L1 *N* = 301	L2 *N* = 212	L3 *N* = 115	L4 *N* = 48	L ≥ 5 *N* = 21
Sunitinib	224 (74.4%)	16 (7.5%)	8 (7%)	8 (16.7%)	5 (23.8%)
Pazopanib	28 (9.3%)	12 (5.7%)	11 (9.6%)	9 (18.8%)	3 (14.3%)
Sorafenib	24 (8%)	21 (9.9%)	27 (23.5%)	15 (31.2%)	2 (14.3%)
Axitinib	-	47 (22.2%)	27 (23.5%)	8 (16.7%)	4 (19%)
Bevacizumab-IFN	6 (2%)	-	-	-	-
Everolimus	6 (2%)	113 (53.3%)	42 (36.5%)	6 (12.5%)	5 (23.8%)
Temsirolimus	6 (2%)	-	-	-	-
IFN	3 (1%)	-	-	-	-
IL2+IFN	3 (1%)	-	-	-	-
IL2	1 (0.3%)	-	-	-	-
Other	-	3 (1.4%)	-	2 (4.2%)	2 (9.5%)

Poor prognosis patients

	L1 *N* = 43	L2 *N* = 24	L3 *N* = 11
TKI	32	12	10
imTOR	9	12	1
Other	2		

Discussion

The treatment landscape in metastatic ccRCC has changed fundamentally over the last decade by the development of targeted antiangiogenic agents, mTOR-inhibitors as well as immunotherapy. These treatments are used sequentially although studies of combinations of two immunotherapies,[16] of a TKI and immunotherapy,[17,18] of an anti-vascular endothelial growth factor antibodies and immunotherapy are either ongoing or have recently been reported. It is important to establish which treatment sequences are the most appropriate for our patients.

ccRCC patients in clinical trials are not always representative of the real-life population.

We present the results of an assessment of a sequential treatment strategy in 344 patients before the era of immunotherapy. It was a real-life study driven in unselected patients. Inclusion criteria were intentionally very wide with the aim to include patients usually not included in clinical trials. Rules to guide sequences after second-line treatment were clear and took into account the limited number of treatments available at that time. For good or intermediary prognosis patients, the sequential treatment proposed followed the guidelines for the first two treatment lines.[15] For the third and subsequent lines of treatment, we proposed to rechallenge a class of drug if it had previously achieved tumor control for 6 months or longer or if the treatment had been stopped because of toxicity.

In this cohort of patients treated homogeneously, no statistical hypothesis has been done. We aimed to describe the proportion of patients treated with each treatment line and for each of them response rates, DTC, toxicity and finally to report overall survival.

We decided to assess the DTC rather than progression-free survival as we felt this was closer to our daily clinical practice. Cancer treatments are occasionally continued despite tumor progression if this is asymptomatic and a practitioner deems that continuing the treatment is beneficial to the patient. Cancer treatments are occasionally continued after local treatment of only one progressive metastasis.

Patients could be included either in first line or for the second line if they have received a treatment as recommended in the treatment strategy. Some rapidly progressive patients could have not been included for the second line creating a potential bias. It must be highlighted that only 5.6% of good or intermediary prognosis patients have been included after the first line.

Physicians sticked to these wide recommendations for the first four lines of treatment for 205 (68%) of the 301 good or intermediary prognosis patients. For poor prognosis patients, 95% followed the guidelines for first-line treatment and 70% for the second line. Thus, no definitive conclusions could be drawn with regard to the optimal sequence.

As expected, the Memorial Sloan Kettering Cancer Center and IMDC prognostic indicators[5,6] identified two populations with very different overall survivals: 57 months (51–70) for good or intermediate prognosis patients and 19 months (14–63) for poor prognosis patients.

Overall survival appeared to be longer in good and intermediate prognosis patients than in patients treated during the same period of the study which compared pazopanib to sunitinib as first-line treatment and were 42.5 and 43.6 months, respectively, in good prognosis patients and 26.9 and 26.1 months, respectively, in intermediate risk patients.[19]

Table 4. Response and duration of tumor control

Treatment		Good or intermediate prognosis patients						Poor prognosis patients		
		L1 (N = 301)	L2 (N = 212)	L3 (N = 115)	L4 (N = 48)	L5 (N = 14)	L6/7 (N = 7)	L1 (N = 43)	L2 (N = 24)	L3 (N = 11)
TKI	N	276	97	73	40	10	3/1	32	12	10
	Best response (CR + PR)	128 (46%)	35 (36%)	12 (16%)	6 (15%)	1 (10%)	0/0	14 (44%)	4 (33%)	1 (10%)
	Clinical benefit (CR + PR + SD)	220 (80%)	72 (74%)	42 (58%)	18 (48%)	4 (40%)	0/0	22 (69%)	5 (42%)	6 (60%)
	Progression disease	51 (18%)	19 (20%)	27 (37%)	18 (45%)	4 (40%)	3/0	9 (28%)	5 (41%)	3 (30%)
	Median DTC Months [min–max]	14 [0–111]	9 [0–112]	7 [0–45]	6 [0–33]	0 [0–15]	1 [1–8]/ 2	11.5 [0–58]	5.5 [2–46]	4.5 [1–41]
imTOR	N	12	113	42	6	3	1/1	9	12	1
	Best response (CR + PR)	2 (17%)	11 (10%)	4 (10%)	1 (17%)	0	0/0	0 (–)	0 (–)	0 (–)
	Clinical benefit (CR + PR + SD)	9 (75%)	66 (58%)	25 (60%)	3 (50%)	0	1/0	2 (22%)	7 (58%)	0 (–)
	Progression disease	2 (17%)	43 (38%)	14 (33%)	3 (50%)	2 (67%)	0/0	3 (33%)	5 (42%)	1 (100%)
	Median DTC Months [Q1; Q3]	12 [1–51]	8 [0–44]	6 [0–41]	5.5 [0–19]	1 [1–10]	19/1			
Other	N	13	2	0	2	1	1/0			
	Best response (CR + PR)	4 (31%)	0	-	0	0	0			
	Clinical benefit (CR + PR + SD)	10 (77%)	0	-	0	0	0			
	Progression disease	3 (23%)	0	-	2 (100%)	1 (100%)	1/0			
	Median DTC Months [Q1; Q3]	25 [3–113]	23.5 [12–35]	-	6 [2–10]	2	2			

Abbreviation: DTC, duration of tumor control.

Table 5. Grade III/IV toxicities in good or intermediate prognosis patients

		L1	L2	L3	L4
TKI	Number of patients	276	97	73	40
	Number of patients with 1 grade III/IV toxicity	106 (38%)	30 (31%)	14 (19%)	5 (12%)
	Total number of grade III/IV events	148	41	26	9
mTOR	Number of patients	12	113	42	6
	Number of patients with 1 grade III/IV toxicity	2 (17%)	32 (28%)	6 (14%)	0
	Total number of grade III/IV events	5	40	7	0

Approximately 55% of patients in our study received a second line of treatment. The number of patients who received other treatment lines was not evaluated.

The observed relatively long overall survival in our study confirms the effectiveness of this sequential strategy and moreover the beneficial effects of a rechallenge with a molecule regardless of the duration of initial tumor control.

The benefit of these strategies which were constructed on a collegiate basis can be used to study a cohort of patients treated in a consistent manner and allow all patients to benefit from the recent treatments. The practitioners involved adhered closely to this plan as 386 patients were included over 3 years in 17 centers.

These real-life condition studies are essential and complementary to clinical trials as they provide results for unselected patients. Marschner et al.[20] reported on the survival of 737 metastatic renal cell carcinoma patients in the German Clinical RCC Registry according they were "trial eligible" or "trial ineligible" (patients were classified as "trial ineligible" when ≥1 of the following criteria had been documented: Karnofski index <80%, haemoglobin less than the lower limit of normal and/or nonclear cell carcinoma histology). Progression free and overall survivals of "trial ineligible" patients were lower than "trial eligible" patients. It is difficult to compare the population of this study and our cohort. In the German registry there was twice more nonclear cell histology. In "trial ineligible" patients 8.7% were poor prognosis patients. Those patients were treated separately in our study. "Trial eligible" patients' overall survival was 26 months (22.1–29.6), which is much shorter than the overall survival of good or intermediary prognosis patients of our cohort. This difference is partly related to the older age of the patients (median 70 vs. 65) and the fact that they received a maximum of two treatment lines.

We demonstrate that the proportion of treated patients falls by approximately 50% with each line of treatment from second line and that a further 15% of good or intermediate prognosis patients receive a fourth line or beyond. We also show that in contrast to what may have been feared, grade III/IV toxicites did not appear to be cumulative. There are several reasons which may explain this, the main one of which is that when treatment is restarted, the initial doses were reduced. In the advanced phase, the emphasis is placed on patients' comfort of life and the treatment is stopped promptly if adverse effects occur without waiting for these to worsen. Axitinib and pazopanib that are mostly used as higher (>3) treatment lines demonstrate a different tolerability profile compared with sunitinib.[21]

In conclusion, regarding our large cohort of metastatic ccRCC patients, we were able to achieve overall survival rates of almost 5 years with an intelligent and stringent sequencing of the available treatment lines. We can reasonably hope that the incorporation of immunotherapy treatment modalities will help to further increase survival rates in patients with advanced or metastatic ccRCC.

The treatment sequences described here have already been profoundly changed by the arrival of the immune checkpoint inhibitors. A study of new sequences or combinations will need to be considered promptly. This is an important challenge for the coming years and is the aim of the IVOIRE two study.

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