Everolimus or sunitinib as first-line treatment of metastatic papillary renal cell carcinoma: A retrospective study of the GETUG group (Groupe d'Etude des Tumeurs Uro-Genitales)

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Abstract

Background: Two phase II trials (NCT00688753 and NCT00541008) reported efficacy data of sunitinib and everolimus in first-line treatment of metastatic papillary renal cell carcinoma (mpRCC). Though most patients receive sunitinib or an mTOR inhibitor in first and second line, the optimal strategy remained unknown.

Material and methods: In 23 centers of the GETUG group, after centralized pathological review, we analyzed retrospectively progression-free survival (PFS) of mpRCC patients treated in first-line (PFS-1) with sunitinib or everolimus (primary endpoint), PFS in second-line (PFS-2), overall survival (OS), objective response rate (ORR), disease control rate (DCR), overall sequence and prognostic factors for OS (secondary endpoints).

Results: 138 patients (119 men, 19 women), median age 62.5 years, with mpRCC type 1 (n=24) or non-type 1 (n=114), received first-line sunitinib (n=107) or everolimus (n=31). With a median follow-up of 92 months, we found no significant difference between the treatment groups in terms of PFS-1 (5.5 versus 6.2 months) and DCR (69% versus 83%). 98 patients received a second-line treatment, 69% with mTOR inhibitors after sunitinib and 100% with tyrosine kinase inhibitors (TKIs) after everolimus, with similar DCR (64% versus 58%), median PFS-2 (3.4 versus 4.8 months) and OS (16.0 versus 20.3 months). No factor was prognostic for PFS-1, while leukocytosis, anemia and the time from diagnosis to first systemic therapy (TTST) <1 year were prognostic for OS. We found no prognostic difference between both pRCC subtypes. The IMDC risk factors were prognostic for OS.

Conclusion: sunitinib and everolimus had similar efficacy in first-line treatment of patients with mpRCC.

Key words: Papillary renal cell carcinoma; Metastatic; Sunitinib; Everolimus; First-line treatment; Prognostic factors; Real world; IMDC risk groups

1. Introduction

Papillary renal-cell carcinomas (pRCCs) account for 15-20% of all renal cancers. Two entities have been characterized, based on a common papillary architecture [1]. At a localized stage, pRCCs are surgically curable [2]. Type 1 pRCCs are often multifocal with rather indolent clinical evolution, whereas non-type 1, also designated as type 2, present as single aggressive tumors. Metastatic pRCCs (mpRCCs) are currently treated with the same drugs as metastatic clear cell RCCs (mccRCCs), though in most studies their prognosis is worse than mccRCCs [3, 4]. Only a few prospective studies with targeted therapies have been dedicated to mpRCCs. Two non-randomized phase II trials have shown that both sunitinib and everolimus were active as first-line treatment. The RAPTOR study (NCT00688753) enrolled 92 mpRCC patients (23 type 1, 46 non-type 1 and 3 not specified), with good performance status (PS), treated with everolimus 10 mg daily until progression. The median progression-free survival (PFS) was 7.9 and 5.1 months and the median overall survival (OS) was 28 and 24.2 months, for patients with type 1 and non-type 1 mpRCCs respectively [5]. In the SUPAP trial (NCT00541008), 61 mpRCC patients (15 type 1, 46 non-type 1) were treated with sunitinib 50 mg daily, 4 weeks on / 2 weeks off. Median PFS and OS were 6.6 months and 17.8 months for type-1 patients and 5.5 months and 12.4 months for non-type 1 patients, respectively [6]. In daily practice, most patients with metastatic pRCC have received first-line treatment with either sunitinib or everolimus and the other drug at the time of progression. To the best of our knowledge, there is no study comparing sunitinib and everolimus in this setting. We retrospectively analyzed a cohort of patients with mpRCC who received first-line treatment with sunitinib or everolimus, to provide real-life data, to measure the impact of crossover at progression and to identify prognostic factors.

2. Patients and methods

2.1. Study design and participants

We conducted a retrospective study in 23 centers of the “Groupe d’Etude des Tumeurs Urogénitales” (GETUG). Key-eligibility criteria were 18 years of age or older, histologically proven pRCC, measurable or evaluable metastases according to RECIST criteria [7] and first-line treatment with sunitinib or everolimus. To ensure diagnosis, two expert uro-pathologists (GFH and NRL) performed a centralized pathological review of all patients’ samples. Clinical data of patients who had participated in the SUPAP or RAPTOR trials were updated for the present study.

The study was conducted in accordance with the authorization of French administrative regulatory body (CNIL) and was approved by an independent local ethics review board (CPP Tours). All living patients received an information letter and gave informed consent for the use of their clinical data.

2.2. Outcomes

The primary endpoint was PFS on first-line treatment (PFS-1), assessed by the investigator. The secondary endpoints were the objective response rate (ORR) to first-line treatment, description of second-line treatment, PFS on second-line treatment (PFS-2), OS, and prognostic factors for PFS-1 and OS.

2.3. Statistical analyses

OS was calculated from the start date of first-line treatment until the date of death or last follow-up. PFS-1 and PFS-2 were calculated from the start date of first- and second-line treatment, respectively, until disease progression or death from any cause or last follow-up. ORR was defined by the presence of at least one confirmed complete (CR) or partial (PR) response. The disease control rate (DCR) was defined as the percentage of patients who achieved a response or stable disease (SD).

OS and PFSs were estimated by the Kaplan-Meier method [8] and compared by a log-rank test. A Cox regression model was used to calculate hazard ratios (HRs) and their 95% confidence intervals (95% CI)[9]. We tested the following putative prognostic factors for PFS1 and OS: histological subtype (1 *versus* non-1), age >70 years, first-line treatment group (sunitinib or everolimus), performance status (KPS < 80), neutrophil leukocytosis (absolute neutrophil count (ANC) >8 G/L) , hypercalcemia (calcium level > 100 mg/L), anemia (hemoglobin level <100 g/L), thrombocytosis (platelet count > 400 G/L) and time from cancer diagnosis to first systemic therapy (TTST) < 1 year. Variables with a p-value < 0.1 in univariate analysis were tested in the multivariate model. In patients for whom it was available, the impact of the International Metastatic Renal Cell Database Consortium (IMDC) score [10] on OS was analyzed separately. All analyses were performed using IBM SPSS Statistics version 25.0 and R software.

3. Results

3.1. Patients' characteristics (Table 1)

Between February 2006 and May 2015, 196 mpRCC patients were treated in first-line with everolimus (n=38) or sunitinib (n=158). Central pathological review was feasible in 140 cases and identified 24 (17%) type 1 and 114 non-type 1 (83%) pRCCs. Two cases were excluded for misdiagnosis (one collecting duct carcinoma and one tubulocystic carcinoma). Overall, 138 patients with confirmed diagnosis by central review were included in the final analysis. Patients' characteristics were equally balanced between the two groups. The median age was 62.5 years [20-83]. There were 119 men (86%) and 19 women (14%). Twelve patients (9%) had prior partial nephrectomy, 102 (74%) had radical nephrectomy and 24 (17%) had no surgery. At the start of first-line treatment, Karnofsky performance status (KPS) was <80 in 17 of

the 133 evaluated patients (13%). Of 109 patients evaluable for the IMDC score, 27 (25%) were at favorable risk, 53 (48%) at intermediate risk, and 29 (27%) at poor risk. Seventy-six patients (55%) had a single metastatic site, 35 (25%) had 2 sites and 27 (19%) had more than 2 sites. The median follow-up was 92 months [1-112]. Although our series included retrospectively all the patients treated in first-line with sunitinib or everolimus for metastatic pRCCs in the GETUG centers, it differs somewhat from real life because 30 patients in the everolimus group were included in the RAPTOR study and 56 in the sunitinib group were included in the SUPAP study.

Table 1: patients' characteristics.

Variables		Sunitinib group	Everolimus group	P
Number of patients		107	31	
Sex	male	91 (85%)	28 (90%)	0.56
	female	16 (15%)	3 (10%)	
Median age [range]		63 [20-83]	61 [25-78]	0.51
Histology				
	type I	16 (15%)	8 (25%)	0.13
	non-type I	91 (85%)	23 (75%)	
Prior nephrectomy				
	no	14 (13 %)	10 (32%)	0.06
	radical	83 (78%)	19 (61%)	
	partial	10 (9%)	2 (6%)	
Number of metastatic sites				
	1	60 (56%)	16 (52%)	0.73
	2	25 (23%)	10 (32%)	
	>2	22 (20%)	5 (16%)	
Metastatic sites				
	lung	42 (39%)	12 (39%)	0.56
	mediastinum	15 (14%)	8 (25%)	0.10
	liver	18 (17%)	6 (19%)	0.46
	bone	23 (21%)	4 (13%)	0.21
	lymph nodes	45 (42%)	16 (51%)	0.23
	others	12 (11%)	4 (13%)	0.50
KPS < 80 *		15/*103* (15%)	2/*30* (7%)	0.21
Time from diagnosis to first systemic therapy < 1 year		69 (64%)	18 (58%)	0.33
Hemoglobin level < 100 g/l*		3/92 (*3%*)	2/28 (*7%*)	0.33
ANC > 8 x10^9/l*		8/88 (*9%*)	7/28 (*18%*)	0.04
Platelet count > 400 x 10^9/L*		18/92 (*19%*)	5/28 (*18%*)	0.54
Calcium level > 2.6 mmol/l		0 (*0%*)	1 (*3%*)	0.22
LDH level > ULN*		24/72 (*33%*)	7/24 (*29%*)	0.26
IMDC score *				0.66
	favorable	20/82 (20%)	7/27 (26%)	
	intermediate	40/82 (49%)	13/27 (48%)	
	poor	22/82 (30%)	7/27 (26%)	
MKCC score*				0.47
	favorable	24/63 (38%)	13/25 (52%)	
	intermediate	31/63 (49%)	10/25 (40%)	
	poor	8/63 (13%)	2/25 (8%)	
Prior inclusion in RAPTOR trial [5]			30	
Prior inclusion in SUPAP trial [6]		56		

* the number of evaluable patients for the characteristic is less than the number in the column: the ratio of evaluated / evaluable patients (%) is indicated.

3.2. Treatments

Of the 138 patients, 107 received sunitinib (50 mg daily, 4 weeks on / 2 weeks off) and 31 received everolimus 10 mg once daily, as first-line treatment.

At the time of final analysis, the median duration of first-line treatment was 5.5 months (1-51) in the sunitinib group and 5.1 months (1-29) in the everolimus group (p=0.9). The most common reason for first-line treatment discontinuation was disease progression (Table 2).

Table 2: treatment after first line

	All (n=138)	Sunitinib group (n=107)	Everolimus group (n=31)
Reason for first-line treatment discontinuation			
Progression	93 (67%)	74 (69%)	19 (61%)
Toxicity	29 (21%)	21 (20%)	8 (26%)
Not stated	16 (12%)	12 (11%)	4 (13%)
Number of treatment lines			
2	98 (71%)	77 (72%)	21 (68%)
3	57 (41%)	45 (42%)	12 (39%)
4	29 (21%)	24 (22%)	5 (16%)
>4	10 7%)	10 (9%)	0 (10%)
Second-line treatment	98 (100%)	77 (100%)	21 (100%)
mTOR inhibitors	53 (54%)	53 (69%)	0
everolimus	37 (38%)	37 (48%)	0
temsirolimus	16 (16%)	16 (21%)	0
TKIs*	44 (45%)	23 (30%)	21 (100%)
sunitinib	21 (21%)	2 (3%)	19 (90%)
other TKI	23 (23%)	21 (27%)	2 (10%)
bevacizumab + IFN	1 (1%)	1 (1%)	0
No treatment	40	30	10

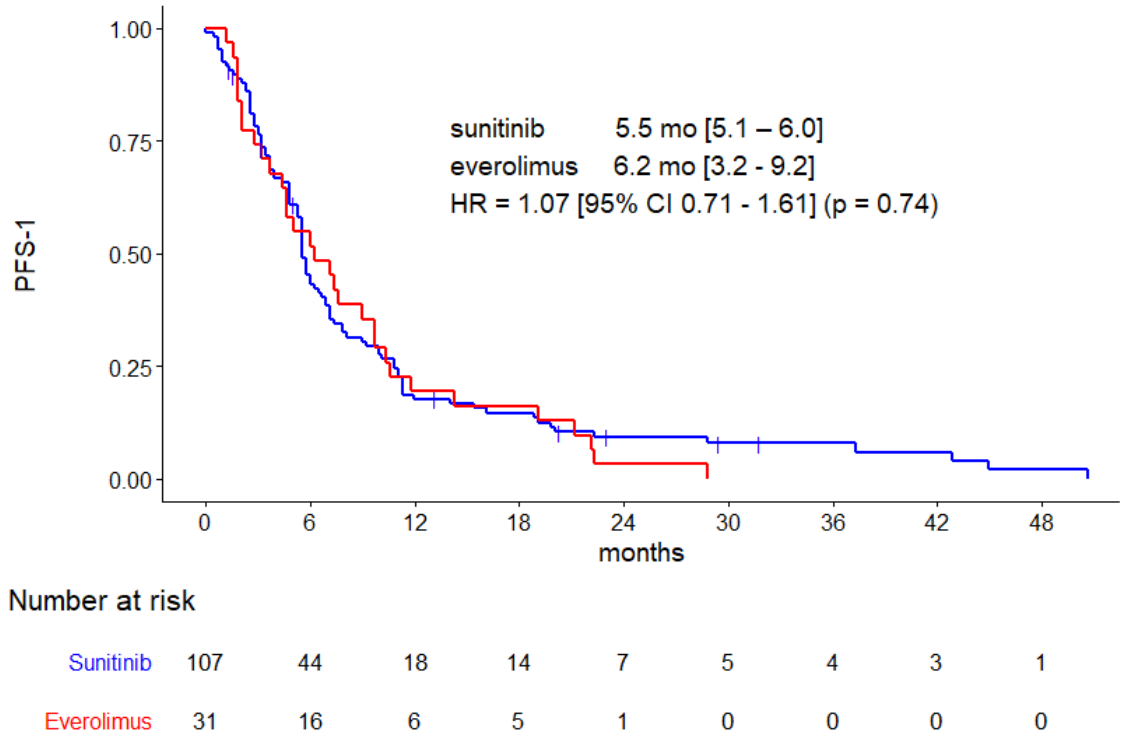
Other second-line TKIs: (*) in the sunitinib group: sorafenib 14, axitinib 4, pazopanib 2, crizotinib 1; in the everolimus group: pazopanib 1, crizotinib 1

Ninety-eight patients (71%) received at least one subsequent systemic therapy after progression. Among the 77 patients who received first-line sunitinib, 53 (69%) switched to mTOR inhibitors (everolimus or temsirolimus), while 23 (30%) received another second-line TKI. All patients who received first-line everolimus received a TKI, mainly sunitinib (19 patients, 90%), as second-line. The median duration of second-line treatments was 3.4 months (0.2-48.1).

3.3. Progression-free survival -1

We found no statistically significant difference between the sunitinib and the everolimus treated patients for PFS-1 (median 5.5 *versus* 6.2 months; HR = 1.07; 95% CI, 0.71-1.61, p=0.74)(Fig. 1).

Figure 1: Kaplan-Meier estimates of progression-free survival after first-line treatment (PFS-1), in patients treated with first-line sunitinib (blue line) or everolimus (red line), with median, HR and 95% confidence intervals.



3.4. Progression-free survival-2 and overall survival

There was no statistically significant difference between the sunitinib and the everolimus groups for PFS-2 (median 3.4 *versus* 4.8 months; HR 1.19; 95% CI, 0.7-2.0, p = 0.49)(Fig. 2) and OS (median OS 16 *versus* 20.3 months; HR 1.10; 95% CI, 0.9-1.30)(Fig. 3).

Fig 2: Kaplan-Meier estimates of progression-free survival after second-line treatment (PFS-2), in patients treated with first-line sunitinib (blue line) or everolimus (red line), with median, HR and 95% confidence intervals.

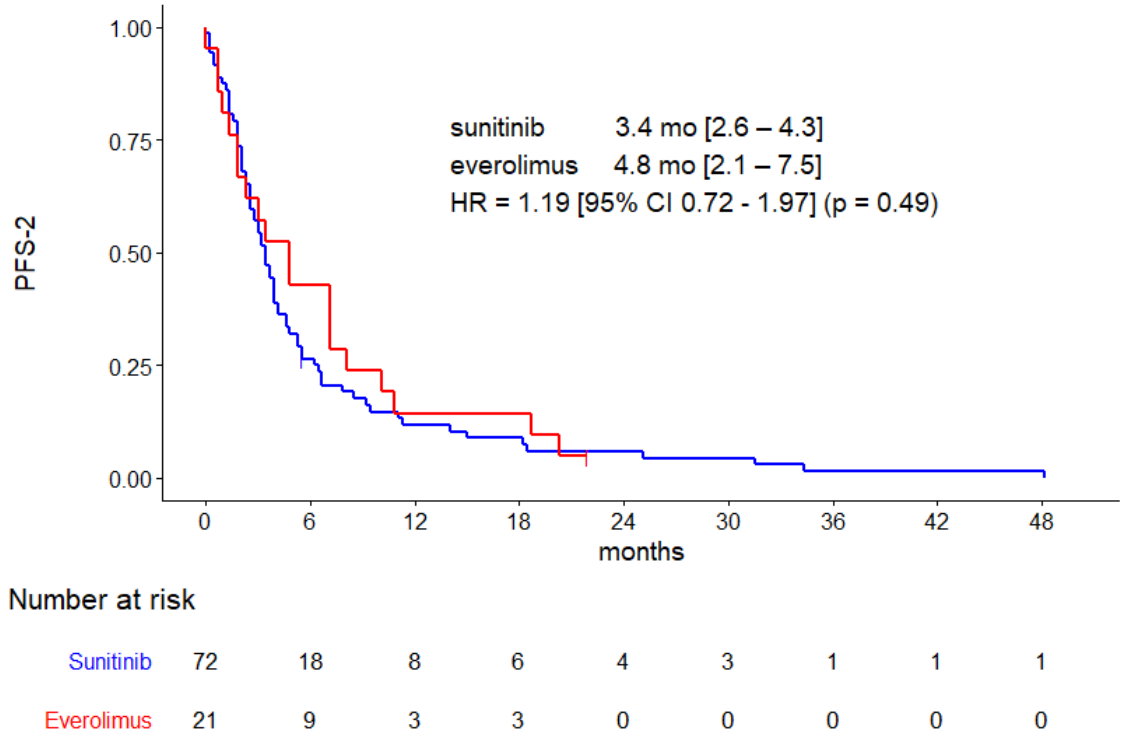
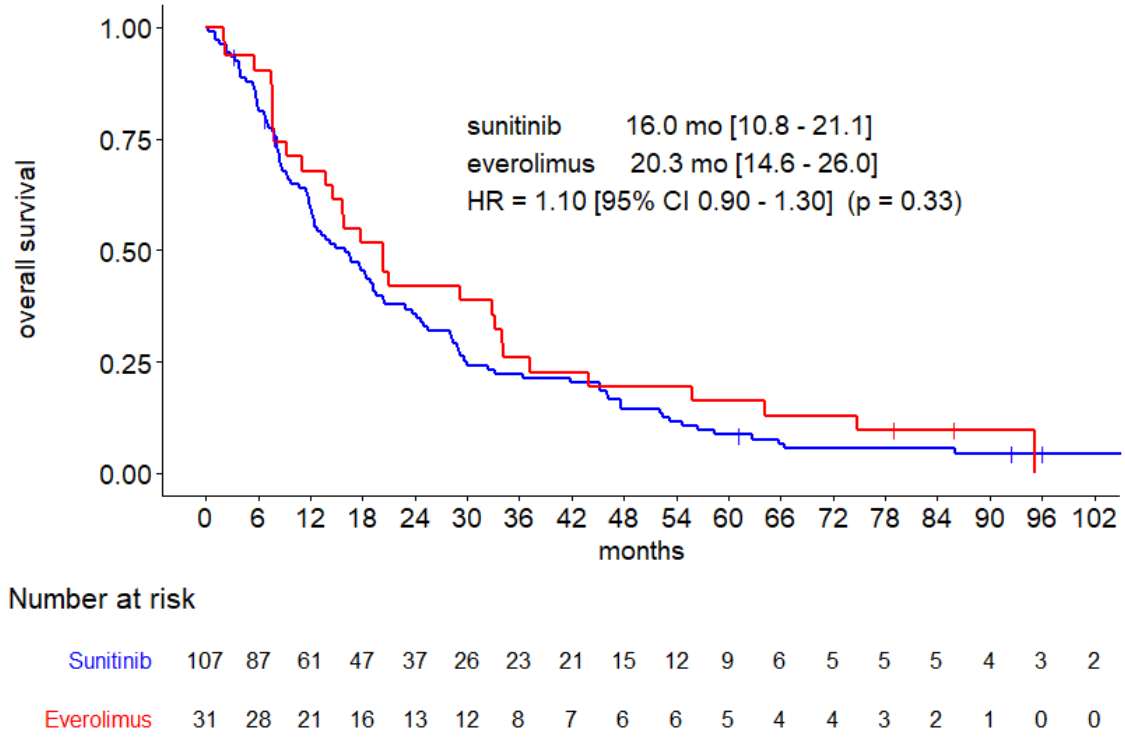


Fig 3: Kaplan-Meier estimates of overall survival in patients treated with first-line sunitinib (blue line) or everolimus (red line), with median, HR and 95% confidence intervals.



3.5. Objective response rate (ORR) and disease control rate (DCR) (Table 3)

The ORR in the 123 evaluable patients for best response analysis, was 10% for sunitinib and 17% for everolimus (p=0.42) and the DCR was 69% versus 83% (p=0.23), respectively.

Table 3: Response to first-line treatment

	sunitinib	everolimus	Odds ratio	P-value
N	107	31		
Missing data	2	1		
Non evaluable	11	1		
Evaluable	94	29		
CR	1 (1%)	1 (3%)		
PR	8 (8%)	4 (14%)		
SD	56 (60%)	19 (65%)		
PD	29 (31%)	5 (17%)		
ORR (CR+PR)	9 (10%)	5 (17%)	0.51 (95% CI 0.16-1.66)	0.42
DCR(CR+PR+SD)	65 (69%)	24 (83%)	0.47; 95% CI 0.16-1.34	0.23

CR complete response; PR partial response; SD stable disease; PD progressive disease; ORR overall response rate; DCR disease control rate

3.6. Prognostic factors

For PFS-1, in univariate analysis, thrombocytosis and TTST < 1 year were identified as poor prognostic factors. Multivariate analysis retained only thrombocytosis as prognostic factor (p=0.05)(Table 4). For OS, in univariate analysis, anemia, thrombocytosis, neutrophil leukocytosis, TTST < 1 year, bone metastases and nephrectomy were identified as adverse prognostic factors. Multivariate analysis retained anemia, neutrophil leukocytosis and TTST < 1 year as independent poor prognostic factors (Table 5). The IMDC prognostic index could be applied to 109 patients. Median OS was significantly different between subpopulations classified as having poor risk (7.7 months), intermediate risk (16.5 months) and favorable risk (32.4 months) ($p< 10^{-4}$)(Fig.4). We found no difference between the three risk groups in terms of PFS-1, with medians of 4.8, 6.2 and 7.1 months, respectively (p=0.12)(Table 4).

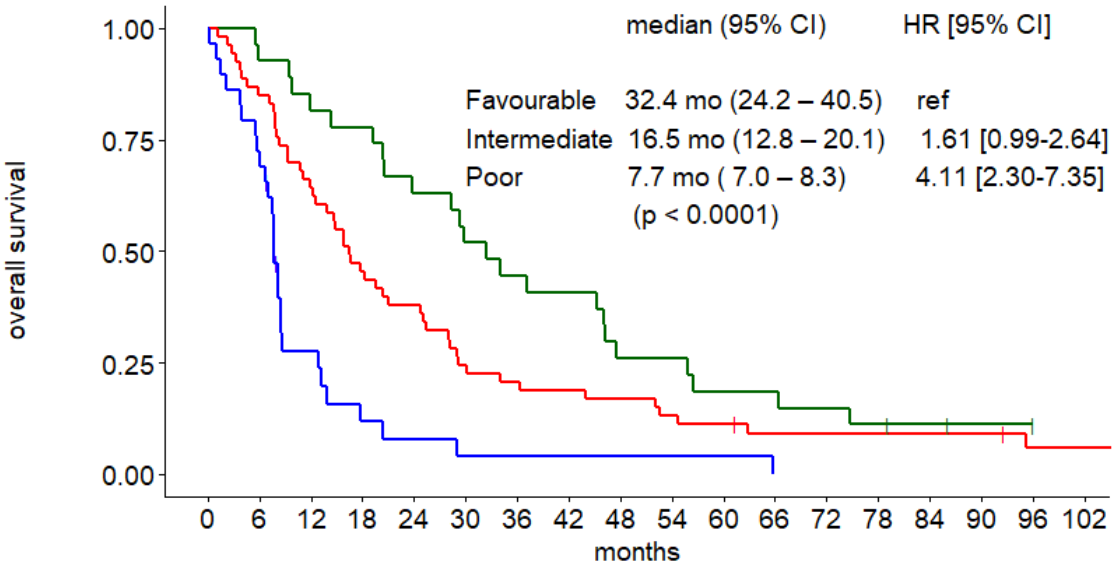
Table 4: univariable and multivariable analyses of first-line progression-free-survival (PFS-1) data.

Variables	**PFS-1 (months)**	**Univariable analyses**		**Multivariable analysis**	
	median (95%CI)	HR [95% CI]	P	HR [95% CI]	P
≥ 70 years	5.5 (4.7-6.3)	1.13 [0.77 – 1.66]	0.53		
< 70 years	5.7 (5.1-6.4)	1.0			
sunitinib	5.5 (5.1-6.0)	1.07 [0.71 – 1.61]	0.74		
everolimus	6.2 (3.2-9.2)	1.0			
KPS < 80	3.7 (1.9-5.4)	1.32 [0.75 – 2.31]	0.33		
≥ 80	5.7 (5.2-6.3)	1.0			
pRCC type 1	8.0 (1.7-14.4)	0.68 [0.42 – 1.08]	0.10	0.64 [0.37 – 1.11]	0.11
non-type 1	5.5 (5.0-6.1)	1.0			
Nephrectomy yes	5.5 (1.8-9.2)	0.86 [0.54 – 1.37]	0.54		
no	5.7 (5.2-6.2)	1.0			
TTST < 1 year	5.5 (4.9-6.1)	1.49 [1.04 - 2.14]	0.03	1.27 [0.83 – 1.94]	0.26
≥ 1 year	7.3 (4.3-10.3)	1.0			
Bone mets yes	5.7 (5.0-6.5)	1.24 [0.78 – 1.94]	0.36		
no	5.5 (2.7-8.3)	1.0			
Liver mets yes	5.7 (5.3-6.2)	0.80 [0.50 – 1.28]	0.37		
no	5.5 (0.3-10.8)	1.0			
Hg < 100 g/l	3.7 (0-9.1)	2.13 [0.86 – 5.29]	0.10	1.44 [0.50 – 4.10]	0.49
≥ 100 g/l	5.7 (5.2-6.3)	1.0			
ANC > 8 G/l	3.0 (2.1-3.9)	1.62 [0.92 – 2.86]	0.09	1.58 [0.83 – 3.04]	0.16
≤ 8 G/l	6.2 (5.0-7.4)	1.0			
Plts > 400 G/l	3.4 (2.7-4.1)	2.06 [1.28 – 3.32]	0.003	1.68 [0.99 – 2.86]	0.05
≤ 400 G/l	6.4 (5.3-7.5)	1.0			
Ca > 100 mg/l	5.7 (5.2-6.3)	2.24 [0.31 – 16.33]	0.43		
≤ 100 mg/l	NA				
IMDC groups					
favourable	7.1 (5.7-8.7)	1.0	0.1		
intermediate	6.2 (4.6-7.8)	0.97 [0.60 – 1.56]			
poor	4.8 (2.1-7.5)	1.57 [0.91 – 2.70]			

Table 5: univariable and multivariable analyses of factors associated with overall survival (OS).

Variables	**OS (months)**	**Univariable analyses**		**Multivariable analysis**	
	median (95%CI)	HR [95% CI]	P	HR [95% CI]	P
≥ 70 years	16.6 (10.7-22.5)	1.10 [0.75 – 1.62]	0.60		
< 70 years	16.5 (12.2-20.7)	1.0			
sunitinib	16.0 (10.8-21.1)	1.10 [0.90-1.30]	0.33		
everolimus	20.3 (14.6-26.0)	1.0			
KPS < 80	8.2 (0-16.7)	1.49 [0.83 – 2.65]	0.18		
≥ 80	16.6 (12.3-20.6)	1.0			
pRCC type 1	18.4 (5.0-31.7)	0.85 [0.54-1.33]	0.46		
non-type 1	14.9 (10-19.7)	1.0			
Nephrectomy yes	19.2 (15.7 (22.7)	0.52 [0.29-.93]	0.003	0.84 [0.48 – 1.49]	0.56
no	8.1 (7.0-9.2)	1.0			
TTST < 1 year	12.2 (9.8-14.7)	2.00 [1.39 – 2.89]	$< 10^{-4}$	1.86 [1.18 – 2.90]	0.007
≥ 1 year	29.7 (20.7-38.7)	1.0			
Bone mets yes	8.5 (0-20.5)	1.61 [1.02 – 2.52]	0.039	1.36 [0.82 – 2.25]	0.23
no	16.6 (12.4-20.8)	1.0			
Liver mets yes	16.0 (12.2-19.7)	1.06 [0.68 – 1.67]	0.79		
no	19.2 (9.4-29.0)	1.0			
Hg < 100 g/l	7.0 (6.5-7.5)	3.76 [1.49 – 9.47]	0.005	5.37 [1.81–16.00]	0.003
≥ 100 g/l	16.6 (12.7-20.5)	1.0			
ANC > 8 x10^9/l	7.6 (5.0-10.3)	3.67 [2.06 – 6.55]	$< 10^{-4}$	2.66 [1.38–5.11]	0.003
≤ 8 x10^9/l	19.2 (15.7-22.7)	1.0			
Plts > 400 x10^9/ll	8.1 (7.1-9.1)	1.98 [1.24 – 3.15]	0.004	1.42 [0.86 – 2.35]	0.17
≤ 400 x10^9/l	19.2 (15.0-23.4)	1.0			
Ca > 100 mg/l	16.6 (12.5-20.7)	3.87 [0.53 – 28.32]	0.18		
≤ 100 mg/l	NA	1.0			
IMDC groups					
favourable	32.4 (24.2-40.5)	1.00	$< 10^{-4}$		
intermediate	16.5 (12.8-20.1)	1.61 [0.99 – 2.64]			
poor	7.7 (7.0-8.3)	4.17 [2.30 - 7.35]			

Fig 4: Kaplan Meier estimates of overall survival for the three risk groups as defined by the IMDC criteria: favorable risk (green line); intermediate risk (red line) ; poor risk (blue line). Median, HR and 95% confidence intervals are indicated.



Number at risk

Favourable	27	25	22	21	17	14	12	11	7	7	5	5	4	3	2	1	1	0
Intermediate	53	45	34	24	20	13	11	10	9	7	6	4	4	4	4	4	2	2
Poor	29	21	7	3	2	1	1	1	1	1	1	0	0	0	0	0	0	0

3.7. Safety

Discontinuation due to adverse events (AEs) was reported in 21 of 107 patients (20%) and 8 of 31 patients (26%) for sunitinib and everolimus, respectively (p=0.70). Doses reductions were reported for 42 patients (39%) in the sunitinib group and 13 patients (42%) in the everolimus group. Treatment was temporarily held in 15 patients (48%) of the everolimus group and in 34 patients (31%) of the sunitinib group. No unexpected adverse event (AE) was reported and all patients experienced at least one AE according to the Common Terminology Criteria for Adverse Events (CTCAE). The most common reported AEs were hand-foot syndrome, arterial hypertension, hypothyroidism, gastrointestinal disorders and hair whitening in the sunitinib group, whereas skin rashes, cough, dyspnea and non-infectious pneumonitis were the most frequent in the everolimus group. Three toxic deaths possibly related to sunitinib were reported by the investigators; one patient died of acute respiratory distress syndrome, one of multiple organ failure and one of acute pneumonitis.

4. Discussion

This is the first study that compared, though retrospectively, sunitinib and everolimus as first-line treatment in mpRCC patients. Despite the absence of VHL gene alteration in pRCCs, the use of sunitinib was justified by the expression of VEGF-A and its receptors at all stages of the disease, though at lower levels than those seen in ccRCCs [11, 12]. Everolilmus was a good drug candidate in pRCCs since the genetic alteration rate of the PI3K-Akt-mTOR pathway panel components was 28% in the TCGA pRCC dataset [13]. Moreover, the PI3K-Akt-mTOR pathway is activated by MET, that was found to be modified in 81% of type 1 pRCCs and 46% of type 2 pRCCs [14-16] and has been involved the process of resistance to TKIs [17].

Regarding the rarity of the disease, conducting a randomized clinical trial is challenging. The present study provides indirect comparison with a large number of centrally confirmed cases.

mpRCCs account for 60 to 80% metastatic non-ccRCCs, but most of available data relate to all non-ccRCCs indistinctively. In a large expanded-access cohort of 4,564 patients treated with sunitinib, both OS and PFS were shorter in patients with non-ccRCC. Comparison with historical data suggested that sunitinib may improve the prognosis of these patients [18]. In a randomized trial comparing temsirolimus to alpha-interferon, 11% of 626 patients had non-ccRCC and were treated with temsirolimus. Although, overall, non-CCRCC patients had a shorter OS than those with ccRCC, their survival was similar when treated with temsirolimus [19].

Two clinical trials have compared head-to-head sunitinib and everolimus as first-line treatment, in heterogeneous populations of non-ccRCCs. The phase II ASPEN trial randomized 108 metastatic non-ccRCC patients to receive sunitinib or everolimus as first-line therapy. ORR was 18% versus 9%, DCR was 73% versus 62%, median PFS was 6.1 versus 4.1 months, and median OS was 16.2 versus 14.9 months, respectively. However, only 65% of the patients had mpRCC, including 8% type 1 in the sunitinib arm and 4% in the everolimus arm [20]. Similarly, in the ESPN phase II trial, that randomized 68 patients with metastatic non-ccRCC, including only 40% mpRCCs, to receive sunitinib or everolimus as first-line therapy, ORR was 9% versus 3%, DCR 73% versus 77%, median PFS 8.3 versus 5.6 months and median OS 31.5 versus 13.2 months, respectively [21]. A pooled analysis of these two trials and non-ccRCC data from the randomized phase II trial RECORD-3, comparing the two sequences sunitinib-everolimus and everolimus-sunitinib in first and second line [22], showed a trend favoring the sequence sunitinib-everolimus for OS, although statistical significance was not reached (29.5 vs 22.4 months) [23]. Based on these

results, guidelines were amended to recommend, in the absence of clinical trial, sunitinib as the favored option in non-clear cell RCC [24, 25].

Two phase II trials specifically focused on the first-line treatment of patients with mpRCC, one with sunitinib, the other with everolimus. The SUPAP study included 61 previously untreated mpRCC patients, PS 0-1, with a median age of 64 years, of whom 56 are included in our study. Median PFS was 6.6 months and 5.5 months, and median OS was 17.8 months and 12.4 months, for patients with type 1 and non-type 1 respectively [6]. The RAPTOR study included 92 untreated patients, median aged 60, PS 0-1, of whom 30 are included in our study. The median PFS was 4.1 months and the median OS was 21.4 months. Patients with type 1 and non-type 1 mpRCC had a median PFS of 7.9 and 5.1 months and a median OS of 28 and 24.1 months, respectively [5].

Recent IMDC retrospective data have been reported, highlighting the dismal prognosis of mpRCCs (n=466) compared to ccRCCs (n=5,008), the absence of difference in OS between type 1 (n=30, median OS 20.0 months) and non-type 1 mpRCCs (n= 165, median OS 12.6 mo), as well as the added value of the IMDC prognostic model in first line [3].

Our study focused on mpRCC patients who received first-line treatment with sunitinib or everolimus, to provide real-life data, to measure the impact of crossover at progression and to identify prognostic factors. There was no clear benefit of one drug over the other. Outcomes were similar in terms of PFS-1 (5.5 and 6.2 months) and OS (16.0 and 20.3 months) irrespective of first-line used agent. Sixty-eight percent of the patients received at least one second-line treatment at disease progression. PFS-2 was comparable for patients receiving second-line treatment after sunitinib or everolimus, with a median PFS-2 of 3.4 and 4.8 months, respectively. The side effects we are reporting in this real life situation were as

expected. In the RECORD-3 trial [26], SAEs were more frequent after sunitinib both in first line (63% versus 47%) and second line (57% versus 47%). However, in our study, treatment suspensions in first line were more frequent with everolimus than sunitinib (48% vs. 31%) as well as discontinuation for toxicity (26% vs. 20%), while dose reduction rates were similar (41 % versus 39%). In the absence of OS and PFS benefits, better safety could favor the use of sunitinib over everolimus as first-line treatment in the absence of a clinical trial.

Despite a response to first-line treatment that appeared to be longer in patients with type 1 mpRCC (median PFS-1 8.1 vs. 5.5 months), the difference did not reach statistical significance and did not translate in OS improvement (median OS 18.4 versus 14.9 months, $p = 0.46$), as in the IMDC data set [3].

In multivariate analysis, we identified no poor prognostic factor for PFS-1. Anemia, neutrophil leukocytosis and time from diagnosis to metastasis < 1 year were adverse prognostic factors for OS. The IMDC prognostic score was available in 109/138 patients. This score was validated for OS in a population of 1,028 patients receiving TKIs, including 13% of non-ccRCC patients [4]. Its prognostic value was confirmed in this population of mpRCC patients, with a median overall survival of 32.4, 16.5 and 7.7 months for the groups with favorable, intermediate and poor prognosis, respectively. The IMDC score had no prognostic value for PFS-1.

Recent comprehensive genomic approach showed that alterations in the MET pathway were associated with type 1 pRCCs. Non-type 1 pRCCs often showed evidence of an activation of the NRF2 anti-oxydant response element (NRF2-ARE) pathway [27]. These findings triggered molecular-based studies, in a first-line setting, including the SAVOIR trial, which randomized, in a MET-driven population, the standard of care compared to savolitinib [28], a specific MET inhibitor (NCT03091192), and a phase II multi-arm trial that compared sunitinib, cabozantinib,

crizotinib and savolitinib (NCT02761057). The SAVOIR study was prematurely discontinued [29]. The SWOG 1500 study was restricted to sunitinib and cabozantinib arms, after futility analysis. Cabozantinib (46 patients) provides a better outcome compared to sunitinib (44 patients) in terms of ORR (23% versus 4%), and PFS (median 9.0 versus 5 6 months, HR 0.60 (0.37–0.97) [30]. This stresses the potential benefit of a dual VEGFR-MET inhibition in this clinical setting.

In ccRCCs, high PD-1 and PD-L1 expression by tumor-infiltrating immune cells was reported to be associated with a poorer response to VEGF-TKI, whereas PD-L1 expression by tumor cells did not affect the efficacy of the treatment [31]. An inverse association between the angiogenesis and PDL-1 pathways has been found in tumor samples from primary ccRCC [32]. In non-ccRCC, patients with PD-L1+ tumors appeared to have worse clinical outcomes, although only PD-L1positivity in tumor cells is associated with higher tumor stage and grade [33]. We had no data about the expression of PD-1 and PD-L1 in our series. Although in the PANZAR consortium series of 374 cases of predominantly localized stage pRCC, PD-1 and PD-L1 were expressed independently of histologic subtype in less than 5% and 8%, respectively, PD- expression 1 and PD-L1 in pRCCs at more advanced stages should be investigated [34]. Little is known about the efficacy of immune checkpoint inhibitors (ICI) in pRCC patients. Recently, a retrospective study of 57 mpRCCs patients treated with ICIs (mostly nivolumab) in first (7%) or latter line(s) (93%) reported an ORR of 11% and a disease stabilization rate of 33%. The median time to treatment failure was 3.1 months and the median OS was 14.6 months. The study population included 16 type 1, 34 no-type 1 and 7 unclassified mpRCCs [35]. A prospective study with pembrolizumab as single agent in first line setting, in 165 non-ccRCC patients (including 118 with mpRCC) reported an ORR of 25.4% and a SD rate of 34.7% in the mpRCC subgroup. Median PFS was 4.1 months and median OS

was not reached at time of analysis for the overall non-ccRCC study population [36]. These conflicting results could be explained by difference in the inclusion criteria, and possibly by different efficacy of ICIs.

Our study has certain limitations, given its retrospective design and the numerical imbalance between the two groups treated with everolimus or sunitinib. However, the centralized pathology review for the diagnosis of pRCC, and the fact that most of these patients were treated in clinical trials for the first line (62%) are guarantees of the quality of the analysis and provide useful data for the specific care of pRCCs.

5. CONCLUSIONS

Little is known about the optimal sequence of systemic therapy in mpRCCs. Though a pooled analysis of randomized phase II trials in non-ccRCC patients, suggested that sunitinib might be more efficient than everolimus, our study identified no difference in terms of PFS, OS or safety between patients receiving either sunitinib or everolimus as first line treatment for pRCC. IMDC risk classification, which has been validated in a population of ccRCC patients, is also a strong prognostic predictor of OS for mpRCC patients. Given the difficulty of diagnosis, referral and histological review should be considered. Furthermore, given the limited activity of standard agents, inclusion in clinical trials should be favored for patients with mpRCC.

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