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# Thèse

Pour le

## DOCTORAT EN MEDECINE

Diplôme d'État

par


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**TITRE**

**Analyse finale de l'étude rétrospective du GETUG (Groupe français d'Etude des Tumeurs Uro-Génitales) évaluant l'efficacité du sunitinib suivi de l'évérolimus ou de l'évérolimus suivi du sunitinib en première ligne thérapeutique du cancer rénal de type papillaire métastatique.**

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# SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre
et méprisé de mes confrères
si j'y manque.

**Lists of abbreviations:**

ANC: Absolute Neutrophil Count
BEV-IFN: bevacizumab - interferon-α
ccRCC: clear cell Renal Cell Carcinoma
ccpRCC: clear cell papillary Renal Cell Carcinoma
CDKN2A: Cyclin-Dependent Kinase inhibitor 2A
CIMP: CpG Island Methylator Phenotyp
CNIL: Commission Nationale de l'Informatique et des Libertés
CPP: Comité de Protection des Personnes
CTCAE: Common Terminology Criteria for Adverse Events
FH: Fumarate Hydratase
GETUG : Groupe français d'Etude des Tumeurs Uro-Génitales
HGF: Hepatocyte Growth Factor
HLRCC: Hereditary Leiomyomatosis and Renal-Cell Carcinoma
HPRCC: Hereditary type 1 Papillary Renal-Cell Carcinoma
IMDC database: International Metastatic Renal Cell Carcinoma Database Consortium
KPS: Karnofsky Performance Status
MSKCC: Memorial Sloan-Kettering Cancer Center
mTOR: mammalian Target Of Rapamycin
nccRCC: non-clear cell Renal Cell Carcinoma
NGS: Next Generation Sequencing
NRF2-ARE: Nuclear erythroid 2-Related Factor 2- Antioxidant Response Element
ORR: Objective Response Rate
PDGFR: Platelet-Derived Growth Factor Receptor
pRCC: papillary Renal-Cell Carcinoma
TNM: Tumor Node Metastase
TKI: Tyrosine Kinase Inhibitor
VEGF: Vascular Endothelial Growth Factor
VHL: Von Hippel Lindau
WHO: World Health Organization

**Analyse finale de l'étude rétrospective du GETUG (Groupe français d'Etude des Tumeurs Uro-Génitales) évaluant l'efficacité du sunitinib suivi de l'évérolimus ou de l'évérolimus suivi du sunitinib en première ligne thérapeutique du cancer rénal de type papillaire métastatique.**


**Résumé**

**Introduction:** Le carcinome rénal de type papillaire (pRCC) est la forme de cancer du rein la plus fréquente après le cancer à cellules claires (ccRCC). Le pRCC représente 15% de l'ensemble des cancers du rein. Il n'y a pas de standard thérapeutique en première ligne au stade métastatique chez les patients atteints de cette forme histologique.
Deux essais prospectifs de phase II français ont démontré l'efficacité du sunitinib et de l'évérolimus dans le traitement de première intention de la maladie métastatique pRCC : l'essai RAPTOR (1) et l'essai SUPAP (2). Nous rapportons la première série rétrospective évaluant l'efficacité de chacune de ces molécules ainsi que l'impact de la séquence thérapeutique dans ce type de cancer uniquement.

**Matériel et méthodes**: Étude rétrospective multicentrique française évaluant l'efficacité de l'évérolimus ou du sunitinib chez des patients traités en première ligne métastatique de leur pRCC. Le critère d'évaluation principal était la survie sans progression en première ligne (SSP-1). Les critères d'évaluation secondaires comprenaient la survie sans progression en deuxième ligne (SSP-2), les traitements administrés en deuxième ligne, la tolérance, la survie globale (SG), les facteurs pronostiques et l'influence de la séquence thérapeutique.

**Résultats**: 196 patients ont été inclus dans cette étude et ont été traités entre février 2006 et mai 2015: 28 étaient porteurs d'une tumeur papillaire de type 1 et 166 de type "non-type 1". 158 patients ont reçu le sunitinib en première intention et 38 l'évérolimus. Les données ont été mises à jour le 28 février 2018 avec un recul médian de 26 mois [1- 257]. Il n'y avait pas de différence en termes de SSP-1 entre le groupe sunitinib : 6,1 mois [5,0-7,3] et le groupe évérolimus: 5 mois [2,8-7,3] (HR 0.78; IC 95%, 0.54 à 1.11; p=0.16). La SG médiane était de 16 mois [12,4-19,5] dans le groupe sunitinib et de 17,7 mois [10,8-24,5] dans le groupe évérolimus (HR 1.15; IC 95%, 0.80 à 1.68; p=0.44). La SSP-2 médiane était de: 3,3 mois pour le groupe sunitinib [2,6-3,9] et 3,1 mois [1,1-5,1] dans le groupe évérolimus (HR 1.01; IC 95%, 0.65 à 1.53; p=0.99).
En analyse multivariée, un indice de Karnofsky <80 (IK<80) et le nombre absolu de neutrophiles>8000/mL (PNN>8000) avaient un impact pronostique péjoratif sur la SSP-1 ; en ce qui concerne la survie globale l'IK<80, un taux de PNN>8000 et un délai de moins d'un an entre le diagnostic et les métastases avaient une valeur pronostique péjorative. La séquence thérapeutique évérolimus suivi du sunitinib ou inversement ne modifiait pas l'évolution de la maladie. La SSP-1 était statistiquement meilleure pour les pRCC de type 1.

**Conclusion:** Le traitement par sunitinib ou par évérolimus en première ligne de traitement dans le carcinome rénal de type papillaire métastatique, sont deux options thérapeutiques possibles qui ne semblent pas affecter le pronostic.



**Mots-clés**: Carcinome à cellules rénales, papillaire, pRCC, métastase, sunitinib, évérolimus, séquence thérapeutique.

**Final analysis of a retrospective study of the GETUG (Groupe français d'Etude des Tumeurs Uro-Génitales) group evaluating efficacy of first-line everolimus followed by sunitinib versus first-line sunitinib followed by everolimus in metastatic papillary renal cell carcinoma (pRCC).**


## Abstract

**Background:** Papillary Renal Cell Carcinoma (pRCC) is the second most prevalent type of renal cell carcinoma, after clear cell RCC (ccRCC). pRCCs account for 15%-20% of all renal cancers. There is no first-line therapeutic standard at the metastatic stage in patients with this histological form.
Two French prospective phase II trials have demonstrated the efficacy of both sunitinib and everolimus in first-line treatment of metastatic pRCC: RAPTOR ([1]) and SUPAP ([2]). Most patients will usually receive the alternate drug at progression. We report the first series of drug sequencing in pRCC only, evaluating the effectiveness of each of these molecules as well as the impact of the therapeutic sequence in this type of renal carcinoma.

**Patients and methods**: A French multicentre retrospective study evaluating everolimus or sunitinib as first-line treatment in metastatic pRCC patients. The primary endpoint was progression-free survival in first-line (PFS-1). Secondary endpoints included PFS in second-line (PFS-2), second-line treatments administred, safety, overall survival (OS), prognostic factors, objective response rate (ORR) and drug sequence analysis.

**Results:** 196 patients were included in this study. They were treated between February 2006 and May 2015: 28 with type 1 pRCC and 166 with "non-type 1". 158 patients received sunitinib and 38 everolimus in first-line. Data were updated on February 28, 2018 with a median follow-up of 26 months [1- 257], there was no difference in terms of PFS-1: 6.1 months (95% CI, 5.0-7.3) in the sunitinib group and 5 months (95% CI, 2.8-7.3) in the everolimus group (HR 0.78; 95% CI, 0.54-1.11; p=0.16). OS and PFS 2 were similar in both groups. Median OS was 16 months (95% CI, 12.4-19.5) in the sunitinib group and 17.7 months (95% CI, 10.8-24.5) in the everolimus group (HR 1.15; 95% CI, 0.80-1.68; p=0.44). Median PFS-2 was 3.3 months in the sunitinib group (95% CI, 2.6-3.9) and 3.1 months (95% CI, 1.1-5.1) in the everolimus group (HR 1, 01; 95% CI, 0.65-1.53, p=0.99). In multivariate analysis, Karnofsky Perfomance Status <80 (KPS<80) and the absolute neutrophil count >8000 / mL (ANC>8000) had a poor prognostic impact on PFS-1, moreover KPS<80, ANC>8000 / mL and the delay between diagnosis and metastasis <1 year had a poor prognostic value for overall survival. The therapeutic sequence did not affect prognosis. There was a statistically significant difference for a better prognosis in favour of type 1 pRCC in terms of PFS-1.

**Conclusion:** First-line treatment by sunitinib or everolimus in metastatic papillary Renal-Cell Carcinoma patients are two possible alternative therapeutic options.



**Key words**: Renal cell carcinoma, papillary, pRCC, metastasis, sunitinib, everolimus, drug sequence.

**SUMMARY**

## INTRODUCTION

Kidney cancer accounts for approximately 5% of all adult malignancies. Clear cell renal cell carcinoma (ccRCC) is the most predominant subtype among renal cell carcinomas (RCC) (80%). As presented in the 2016 WHO (World Health Organization) classification ([3-4]), the remaining subtypes refer to non-clear cell RCCs consisting of: papillary type 1 and 2, chromophobe, collecting duct, medullary, translocation associated and unclassified. Papillary renal cell carcinoma (pRCC) is the most common type of non-clear cell RCC (nccRCC) comprising for 10–15% of RCC.

In several series, there was a higher male predominance, with a sex ratio of about 3:1.

The incidence increases between the fourth and seventh decades of life and the mean age distribution (59-63 years) is similar to that of ccRCC patients. Approximately 25% of patients have metastatic disease at initial diagnosis.

pRCCs are genetically and histologically heterogeneous. The first subdivision of pRCCs in two morphologic groups was introduced in the 1990s by Delahunt ([5]). Papillary RCC is a malignant tumour derived from the renal tubular epithelium. It is often a circumscribed carcinoma with a prominent fibrous pseudocapsule. Some tumours show a predominantly tubular morphology. The disease is diverse, with two main histological subtypes: ([6])

- Type 1: prominent small-cell tumours, generally cuboidal with nuclei and scanty pale cytoplasm, arranged in a single layer on the papillary cores.
- Type 2: large-cell solitary tumours with nuclear pseudostratification and eosinophilic cytoplasm.

Necrosis and haemorrhage are frequently observed. The two histological subtypes have different clinical characteristics: pRCC type 1 can sometimes be presented as a multifocal or bilateral tumour with an indolent evolution while pRCC type 2 has a more aggressive behaviour with a higher stage and grade.

The 2016 WHO Urinary System Tumour Classification is presented as an appendix (p1).

Recently, two other pathological subtypes with papillary features have been described ([7]):

- clear cell papillary renal cell carcinoma (ccpRCC) accounts for about 1% of all kidney cancers and is characterized by cuboidal cells with an apical nucleus and clear cytoplasm. CcpRCCs have long been confused with type 1 pRCCs.
- MiT family translocation renal cell carcinomas are characterized by translocation involving *TFE3* or *TFEB*. Histologically it is composed of papillae with clear epithelioid cells with abundant psammoma bodies. The histological appearance may resemble type

2 pRCC. Only a few dozen cases have been reported in the literature. These two entities being very rare and particular, they are not covered in this study. Pathological features and immunohistochemical markers in pRCC are reported in appendix (p2).

At the metastatic stage, pRCCs have a worse prognosis than clear cell renal cell carcinoma ([8]). In particular, some data suggest a worse prognosis for type 2 compared to type 1 ([9]). Recently data from more than 5000 patients in the IMDC database (International Metastatic Renal Cell Carcinoma Database Consortium) were analysed ([10]). pRCC histology was reported in 8% of cases (466 patients). Overall survival (OS) in metastatic pRCC patients was lower than for clear cell RCC patients: 13.8 months vs 21.9 months ($p<0.0001$). Similarly, progression-free survival in first-line (PFS-1) was lower in pRCC than ccRCC: 4.7 months vs 7.3 months ($p<0.0001$). No differences in terms of PFS or ORR were detected between type 1 and type 2 pRCC. Similar data were reported in the study by Steffens ([11]) et al. These latter compared clinical characteristics and prognosis of 565 patients with pRCC and 4346 patients with ccRCC, over the period 1990-2010. Patients with non-metastatic stage T1-4 N0 pRCC had a better prognosis than patients with matched-stage ccRCC, with a 5-year overall survival probability of 90% versus 81.2% ($p<0.001$). However, the 5-year survival of patients with nodal or visceral metastases was worse in the case of pRCC (15.9%) than in the case of ccRCC (22.1%) ($p=0.035$). Multivariate analysis identified the papillary subtype as a significant positive prognostic factor in localised (HR: 0.45) but as a negative prognostic factor in metastatic tumour stages (HR: 1.37).

Concerning prognostic factors, at a metastatic stage, the Heng prognostic model includes 6 independent clinical and biological criteria of poor overall survival: anaemia (<120 g/L), thrombocytosis (>400 G/L), neutrophilia (>7 G/L), corrected calcium above the upper limit of normal (>10.2 mg/dL), Karnofsky performance status less than 80%, and interval from diagnosis to treatment of less than 1 year has been validated in patients who were treated with first-line VEGF-targeted treatment without consideration of the histological RCC sub-types. According to the number of poor prognostic factors, patients were segregated into favourable (no factors), intermediate (one or two factors), and poor (more than three factors) risk groups ([12]).

Smoking, hypertension and obesity are established risk factors for RCC development. There are no specific etiological features for pRCC, but this often happens in patients with end-stage renal disease (ESRD), particularly with acquired cystic disease of the kidney (ACDK) ([13]).

Commonly, most pRCCs are sporadic. Only a small percentage of pRCCs are a complication of hereditary familial disease: Hereditary type 1 Papillary Renal-Cell Carcinoma (HPRCC) associated with activating germline mutation of *MET*; Hereditary Leiomyomatosis and Renal-Cell Carcinoma (HLRCC) caused by inactivating mutations of the *FH* gene and the Birt-Hogg-Dubé syndrome caused by a mutation of the *FCLN* gene ([14]). Recently, Linehan et al. explored genetic alterations that were found in pRCC using whole-exome sequencing, copy number, mRNA, microRNA, methylation and proteomic analyses ([15]). Papillary Renal-Cell Carcinomas type 1 and type 2 are characterized by specific genetic alterations: type 1 tumours were associated with activation of the c-MET pathway and gain of chromosomes 7 and 17 (trisomy or tetrasomy), while type 2 tumours were a heterogeneous entity composed of at least 3 subtypes based on molecular and phenotypic characteristics: activation of the NRF2-ARE (antioxidant response element) pathway, CDKN2A loss and CpG island methylator phenotype (CIMP). The subtypes prompting pathologists to classify these cancers as"non-type 1" pRCCs. Opposite to ccRCC, oncogenic initiator events in nccRCC tumours are not driven by the Von-Hippel-Lindau (VHL) gene. Finally, other abnormalities related to tumour progression, such as trisomy 8, 12, 16 and 20 or a deletion 1p, 4q, 6q, 7, 9p, 13q, Xp, Xq deletion, or loss of the Y chromosome, are possible and conferred them a poor prognosis ([16]-[17]).

Metastatic pRCCs have long been treated in the same way as ccRCC. In the 80s, first by immunotherapy with interferon alpha and/or interleukin-2.

More recently, several drugs that inhibit angiogenesis, cell growth and tumour proliferation via the vascular endothelial growth factor (VEGF) and mammalian Target Of Rapamycin (mTOR) pathways have been approved for metastatic renal cell carcinoma with less favourable response for patients with metastatic pRCC.

Currently available therapies inhibiting the VEGF pathway are: sunitinib, sorafenib, bevacizumab (in combination with Interferon-α), axitinib, pazobanib, cabozantinib and those targeting the mTOR pathway include everolimus and temsirolimus. Medical treatment of non-clear cell metastatic renal cancer is definitely the least studied. Because of the scarcity of this malignancy, most clinical trials have been focused only on clear cell RCC. Thus, for these patients, enrolment into specifically designed clinical trials is recommended ([6],[17]). Non-clear cell subtypes have often been excluded or underrepresented in pivotal randomised clinical trials (RCTs), especially in immunotherapy clinical trials for example to preserve the homogeneity of the studied population.

An important meta-analysis of 49 studies with 7771 patients including 1244 cases of non-clear cell RCC ([18]) showed lower response rates with antiangiogenic and mTOR inhibitors than ccRCC (OR=0.52; 95% CI: 0.40-0.68; p<0.001), as well as poorer progression-free survival (PFS) and overall survival (OS). For patients with nccRCCs treated with targeted agents, the median PFS and OS were 7.4 and 13.4 months, respectively; for patients with ccRCC, these were 10.5 and 15.7 months (p<0.001). Historically, cytoreductive nephrectomy before systemic therapy is generally recommended in patients with a prior potentially surgically resectable tumour mass. Recently, using the IMDC database, a retrospective analysis was performed on patients from the outset with metastatic pRCC treated with (n=109) or without (n=244) cytoreductive nephrectomy. Median OS in patients with cytoreductive nephrectomy was 16.3 months (95% CI, 13.1-19.2), compared to 8.6 months (95% CI, 6.1-12.2; p<0.0001) in the no surgery group after adjustment for risk criteria ([19]). The results of this study are questionable because young patients and in good general condition were obviously more frequently operated. This attitude will be adapted according to the results of the CARMENA study (NCT00930033) showing that in patients with metastatic ccRCC of poor or intermediate prognosis, sunitinib alone was not inferior to nephrectomy followed by sunitinib (HR 0.89; 95% CI, 0.71-1.10) ([20]).

Subsequently, there are two standard-of-care therapies:

Sunitinib is an inhibitor of tyrosine kinases including vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR). The efficacy of this treatment in first-line in metastatic RCC was demonstrated ten years ago with longer PFS and higher response rates. In this study of 750 patients with metastatic renal-cell carcinoma in first-line treatment, the median PFS was significantly longer in the sunitinib group: 11 months than in the interferon alfa group: 5 months (HR 0.42; 95% CI, 0.32-0.54; p<0.001) ([21]).

There is a rationale for using these treatments in renal papillary cancer, indeed there is no difference in VEGF expression among the different RCC types ([22]).

Data derived from retrospective series and expanded access programs (EAPs) suggest that sunitinib may be effective in patients with non-clear cell RCC ([23]).

Everolimus is an orally administered inhibitor of mTOR that demonstrated its efficiency in the RECORD-1 trial for patients with metastatic RCC after progression on VEGF therapy. In this study, 410 patients were included to receive everolimus or placebo; median PFS was significantly longer in the everolimus group: 4 months versus 1.9 month in the placebo group (HR 0.30; 95% CI, 0.22–0.40; p<0.0001) ([24]).

Two phase II studies have shown that both sunitinib and everolimus are efficient in first-line treatment of metastatic pRCC: RAPTOR (NCT00688753) ([1]) that studied the efficacy of everolimus and SUPAP (NCT00541008) ([2]) for sunitinib.
Other studies, including RECORD-3 ([25]) and ESPN ([26]) have evaluated the therapeutic sequences: antiangiogenic followed by treatment with mTOR inhibitor or reverse, though in heterogeneous populations grouping several histological subtypes.
Moreover, due to a lack of biomarkers, current practice is based on empirical sequencing. In daily practice, most patients received both drugs, either in first-line or at progression. We aimed to find the optimum initial approach for metastatic pRCC only.

## PATIENTS AND METHODS

### 1. Study design

This was a multicentre retrospective study which was performed in 23 French centres of the GETUG (Groupe français d'Etude des Tumeurs Uro-Génitales). A total of 196 patients (166 men, 30 women) were enrolled between February, 2006 and May, 2015. To be eligible patients had to have received treatment with everolimus or sunitinib in first-line. A first analysis of the data was carried out a few years ago and we update this data, the database was frozen on 28th February 2018. At this point we updated the data of 49 patients who were still alive at the reference date in 18 hospitals. Ten patients were alive when the data were frozen.

The primary objective was to evaluate PFS of metastatic pRCC patients treated in first-line with sunitinib or everolimus (PFS-1).
Secondary objectives were PFS after second-line treatment (PFS-2), overall survival (OS), drugs given in second-line in the event of progression, sequence analysis: sunitinib-mTOR versus everolimus-TKI. Other secondary endpoints included safety and prognostic factors for response and survival. OS was calculated from the date of start of initial therapy to the date of death. Survival of patients who were lost to follow-up was censored as of the date of last contact. PFS-1 was calculated from initiation of first-line therapy until progressive disease or death from any cause or last follow-up. PFS-2 was calculated from initiation of second-line therapy until progressive disease or death from any cause or last follow-up.

Objective response rate (ORR) was defined by the presence of at least one confirmed complete response (CR) or confirmed partial response (PR) whereas clinical benefit was defined by the presence of at least one confirmed CR or PR or stable disease (SD).

This 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. Patients

Eligible patients were 18 years of age or older, with histologically confirmed type 1 or type 2 pRCC at advanced or metastatic stage and had measurable disease according to RECIST criteria. An additional key criterion was first-line treatment with sunitinib or everolimus. All patients were recorded whatever their response after first-line treatment and whatever the subsequent treatments. Patients who had participated in the RAPTOR ([1]) and SUPAP ([2]) trials were eligible for analysis. The flowchart diagram summarising the different therapeutic sequences possible in the study is reported in appendix (p3). Patients could not have received first-line therapy containing everolimus or sunitinib in combination. Patients were ineligible should they are received treatments in an adjuvant or neoadjuvant setting. Patients with histology other than papillary RCC were excluded.

All pRCC tumours will be confirmed by a centralized pathological revision that is currently underway by Professors Gaëlle FROMONT-HANKARD and Nathalie RIOUX-LECLERCQ.

## 3. Statistical analyses

All analyses were performed using IBM SPSS Statistics version 25.0 and R software. Overall survival and PFSs 1-2 were estimated by the Kaplan–Meier method ([27]) and compared by a log-Rank test. A Cox regression model was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CI). Univariate and multivariate analyses were conducted to correlate clinical-pathological factors with PFS and OS, especially on the Heng score and the histological subtype. Variables were tested in the model when a p-value<0.1 was found in univariate analyses. The variables analysed were: age <70 years, treatment group (sunitinib or everolimus), KPS <80, ANC >8000, hypercalcemia >100

mg/L, anaemia <100g/L, thrombocytosis >400 G/L, the histological subtype and the <1 year delay between diagnosis and the start of treatment (TTMets <1 year).

## RESULTS

### 1. Patient Characteristics

Between February 2006 and May 2015, 196 patients received everolimus (n=38) or sunitinib (n=158) as first-line treatment for metastatic pRCC. Of these patients, 30 had been included in the RAPTOR study in the everolimus group and 56 in the SUPAP study in the sunitinib group (Table 1). The median age was 61 years [range, 20-84 years]. There were 166 men (84.7%) and 30 women (15.3%). Twenty eight patients were metastatic pRCC type 1 (14.3%) and 163 "non-type 1" (83.2%). 143 patients (73%) were treated with radical first nephrectomy, 16 patients (8.2%) with partial nephrectomy and 37 (18.8%) did not undergo renal surgery. Metastatic pRCC was initially metastatic in one organ in 107 patients (54.6%), in two organs in 64 patients (32.7%) and in more than 2 organs in 35 patients (12.7%). A performance status with a KPS <80 was observed in 23 patients (11.7%) and a KPS >80 in 173 patients (88.3%). Out of 154 patients assessed according to the Heng score, 38 patients had a favourable prognostic risk (24.7%), 73 an intermediate risk (47.4%) and 43 a poor prognosis (27.9%). Baseline disease characteristics were balanced between the two groups.

The median follow-up period (period time from diagnosis to death or lost follow-up) was 26 months [1- 257].

Table 1: Baseline Demographic and Clinical Characteristics:

| Variables | All | Sunitinib Group | Everolimus group | P-value |
|---|---|---|---|---|
| N *(evaluable pts)* | 196 | 158 | 38 | |
| Sex male | 166 | 131 | 35 | .21 |
| female | 30 | 27 | 3 | |
| Median age [range] | 61 [20-84] | 61 [20-83] | 59.5 [24-84] | .19 |
| Histological type | | | | |
| 1 | 28 | 19 | 9 | .08 |
| non-1 | 163 | 134 | 29 | |
| unclassified | 5 | 5 | 0 | |
| Prior nephrectomy | | | | |
| no | 37 | 25 | 12 | .08 |
| radical | 143 | 120 | 23 | |
| partial | 16 | 13 | 3 | |
| # metastatic organs | | | | |
| 1 | 107 | 85 | 22 | .89 |
| 2 | 64 | 44 | 10 | |
| >2 | 35 | 29 | 6 | |
| Metastatic organs | | | | |
| lung | 71 | 58 | 13 | .46 |
| mediastinum | 30 | 22 | 8 | .20 |
| liver | 36 | 29 | 7 | .58 |
| bone | 35 | 30 | 5 | .30 |
| lymph nodes | 65 | 65 | 19 | .21 |
| other | 63 | 52 | 11 | .40 |
| KPS <80 | 23 (*186*) | 19 (*149*) | 4 (*37*) | .19 |
| Time from diagnosis to treatment <1 year | 128 | 104 | 24 | .44 |
| Haemoglobin <100 g/L | 9 (*170*) | 7 (*136*) | 2 (*34*) | .57 |
| ANC >8 G/L | 21 (*166*) | 14 (*132*) | 7 (*34*) | .10 |
| Platelets >400 G/L | 41 (*170*) | 34 (*136*) | 7 (*34*) | .38 |
| Calcium >2.6 mmol/L | 4 (*145*) | 2 (*112*) | 2 (*33*) | .22 |
| LDH >ULN | 44(130) | 37 (*103*) | 7 (*27*) | .26 |
| Heng score ([12]) | (*154*) | (*120*) | (*34*) | .49 |
| favourable | 38 | 29 | 9 | |
| intermediate | 73 | 56 | 17 | |
| poor | 43 | 35 | 8 | |
| MSKCC score ([28]) | (*117*) | (*88*) | (*29*) | .43 |
| favourable | 45 | 31 | 14 | |
| intermediate | 59 | 46 | 13 | |
| poor | 13 | 11 | 2 | |
| Prior inclusion in RAPTOR | 30 | | 30 | |
| Prior inclusion in SUPAP | 56 | 56 | | |

**Abbreviations**: KPS, Karnofsky Performance Status; ANC, Absolute neutrophil count; LDH, lactate deshydrogenase; ULN, upper limit of normal; MSKCC, Memorial Sloan-Kettering Cancer Center.

## 2. Treatment

Of the 196 patients treated in first-line, 151 received the standard 4/2 schedule (4 weeks on and 2 weeks off) of daily sunitinib at the oral dosage of 50 mg, 3 received an alternative sunitinib dosage schedule 2/1 (2 weeks on and 1 week off) and 4 on a continuous basis at 37.5 mg daily. In the second group 37 patients received oral everolimus 10 mg once daily and only one patient had a dose reduction to 5 mg once daily (Table 2).

Table 2: First-line treatments.

| Group | Schedules | Assays | N |
|---|---|---|---|
| Sunitinib | Daily, 4 weeks on / 2 weeks off | 50 mg | 151 |
| | Daily, 2 weeks on / 1 week off | 50 mg | 3 |
| | Daily, continuous | 37.5 mg | 4 |
| Everolimus | Daily, continuous | 10 mg | 37 |
| | | 5 mg | 1 |

The most common reason for treatment termination was disease progression for 106 patients (67%) in the sunitinib group and 24 patients (63%) in the everolimus group. Discontinuation due to AEs (Adverse Events) was 22% (35 of 158 patients) and 24% (9 of 38 patients) for sunitinib and everolimus, respectively (p=0.58) (Table 3). Moreover, dose reductions were reported for 58 patients (37%) in the everolimus group and 15 patients (39%) in the sunitinib group, temporary interruption of treatment for 47 patients (30%) and 18 patients (47%) respectively (Table 4). At the time of final analysis, the median duration of treatment was 5.78 months [0.17- 51] in first-line and 3.20 months [0.03 – 64.6] in second-line, whatever the treatment. When looking at the subgroups, the median durations of treatment with sunitinib and everolimus in first-line were 5.85 months [0.19-53] and 5.1 months [1.36-29], respectively (p=0.39).

Table 3: Cause of first-line treatment discontinuation.

| N (%) | Progression | Toxicity | Unknown | Total |
|---|---|---|---|---|
| Sunitinib group | 106 (67) | 35 (22) | 17 (11) | 158 |
| Everolimus group | 24 (63) | 9 (24) | 5 (13) | 38 |

Table 4: Reduction doses or temporary interruption treatment.

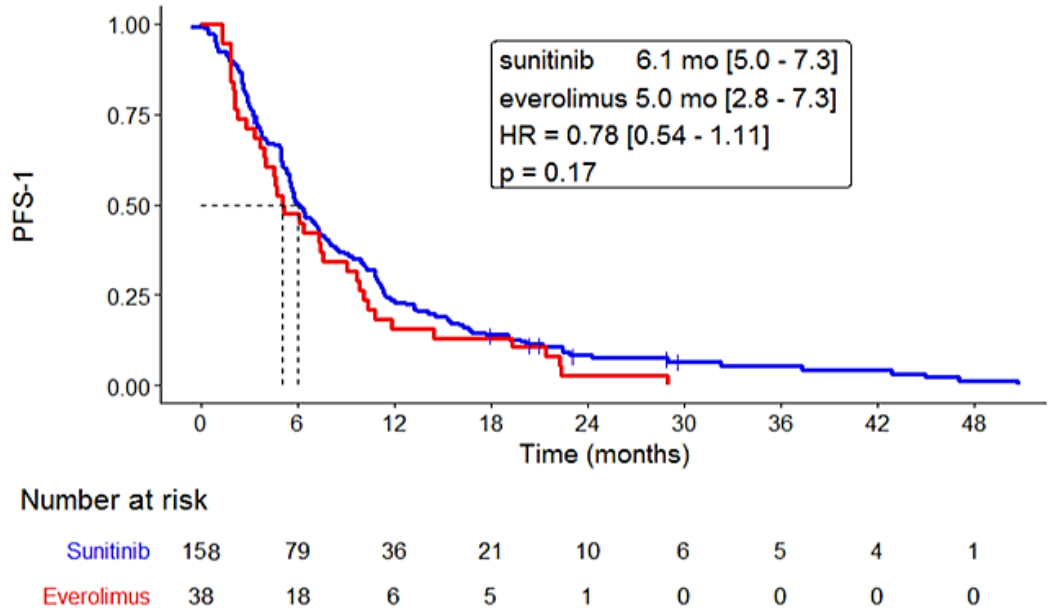
| N (%) | Yes | No | Unknown | Total |
|---|---|---|---|---|
| **Dose reduction** | | | | |
| Sunitinib group | 58 (37) | 98 (62) | 2 (1) | 158 |
| Everolimus group | 15 (39) | 22 (58) | 1 (3) | 38 |
| **Temporary interruption of treatment** | | | | |
| Sunitinib group | 47 (30) | 107 (68) | 4 (2) | 158 |
| Everolimus group | 18 (47) | 18 (47) | 2 (6) | 38 |

### 3. Efficacy

The study's primary endpoint was PFS-1. We found no statistical difference between the two groups: median first-line PFS was 6.1 months [5.0-7.3] for sunitinib and 5 months [2.8-7.3] for everolimus (HR 0.78; 95% CI, 0.54-1.11; p=0.17) (Figure 1.A). There was no difference in terms of overall survival: median OS was 16 months (95% CI, 12.4-19.5) for sunitinib group and 17.7 months (95% CI, 10.8-24.5) for everolimus group (Figure 2) (HR 1.15; 95% CI, 0.80-1.68; p=0.44). Concerning second-line treatments, there was no statistical difference in terms of PFS-2: median PFS-2 was 3.3 months for sunitinib (95% CI, 2.6-3.9) and 3.1 months (95% CI, 1.1-5.1) for everolimus (HR 1.01; 95% CI, 0.65-1.53; p=0.99) (Figure 1.B).

Figure 1. Kaplan-Meier estimates of progression-free survival according to the treatment groups in first-line (A) and second-line (B).

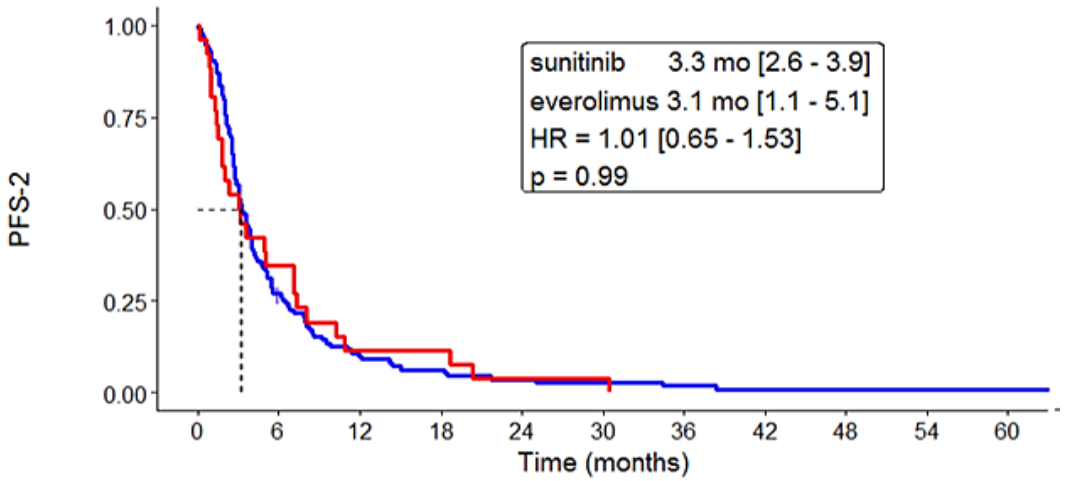
A. Progression-free survival in first-line (PFS-1)




Number at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sunitinib | 158 | 79 | 36 | 21 | 10 | 6 | 5 | 4 | 1 |
| Everolimus | 38 | 18 | 6 | 5 | 1 | 0 | 0 | 0 | 0 |

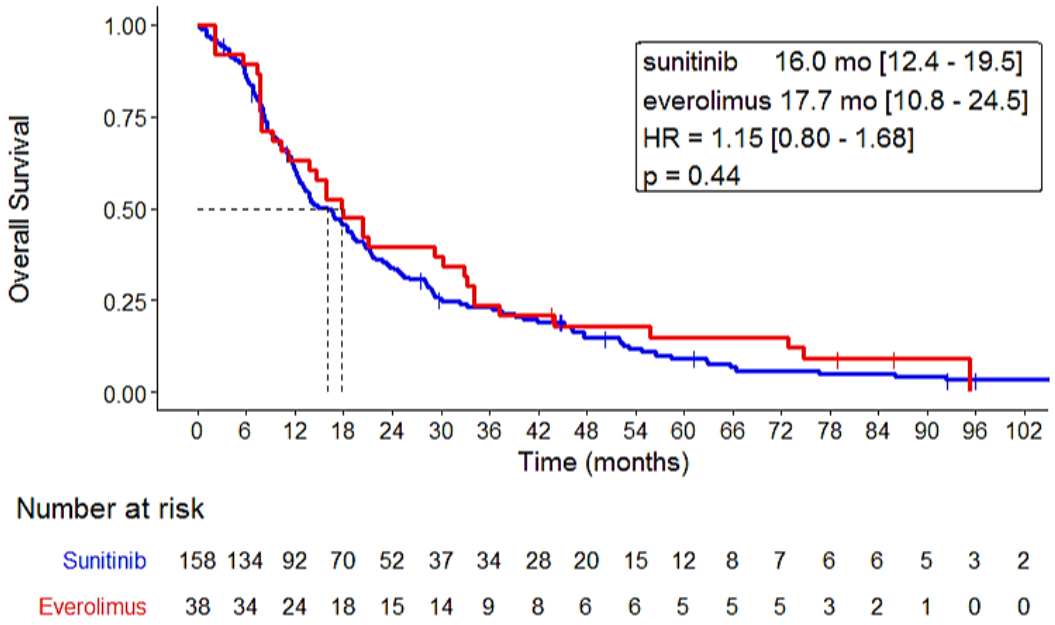
B. Progression-free survival in second-line (PFS-2)




Number at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sunitinib | 113 | 30 | 11 | 7 | 4 | 3 | 2 | 1 | 1 | 1 | 1 |
| Everolimus | 26 | 9 | 3 | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |

Figure 2. Kaplan-Meier estimates of overall survival according to the treatment groups.




## 4. Objective response rate

167 patients were evaluable for objective response rates (ORRs). There was an objective response rate in 18 of 131 patients (13.7%) in the sunitinib group and 5 of 36 patients (13.9%) in the everolimus group (Table 5). Stable disease as the best response was seen in 76 of 131 patients (58%) in the sunitinib group and in 21 of 36 patients (58.3%) in the everolimus group, whereas progressive disease as best response was seen in 37 patients (28.2%) in the sunitinib group and ten (27.8%) patients in the everolimus group. Clinical benefit was defined as complete response, partial response, and stable disease was seen in 94 (71.8%) patients in the sunitinib group and 26 (72.2%) patients in the second group. ORR was of the same order of magnitude in both groups.

Table 5. Best tumour response in first-line

| Response | N (%) | | Total |
|---|---|---|---|
| | Sunitinib | Everolimus | |
| Evaluable | 131 | 36 | 167 |
| *Best overall response* | | | |
| Complete Response (CR) | 1 (0.8) | 1 (2.8) | 2 (1.2) |
| Partial Response (PR) | 17 (13) | 4 (11.1) | 21 (12.6) |
| Stable Disease (SD) | 76 (58) | 21 (58.3) | 97 (58.1) |
| Progressive disease (PD) | 37 (28.2) | 10 (27.8) | 47 ( 28.1) |
| *Composite score* | | | |
| Objective response (CR+PR) | 18 (13.7) | 5 (13.9) | 23 (13.8) |
| Clinical benefit (CR+PR+SD) | 94 (71.8) | 26 (72.2) | 120 (71.9) |

## 5. Prognostic factors

We studied the impact of several other prognostic factors on PFS-1 and OS in univariate and multivariate analysis. Univariate analysis showed thrombocytosis (platelets >400 G/L) neutrophil leukocytosis defined by an absolute neutrophil count (ANC)>8000 cell/µL and the delay between diagnosis and metastasis <1 year were all poor prognostic factors for progression-free survival in first-line. For overall survival in univariate analysis, the delay between diagnosis and metastasis <1 year and anaemia (Hb <10 g/dL) are also factors of poor prognosis. Multivariate analysis, showed a general degraded state according to the Karnofsky Performance Status (KPS <80) and the absolute neutrophil count >8000/mL (ANC>8000) had a prognostic impact on PFS-1, whereas KPS-80, ANC> 8000/mL and the delay between diagnosis and metastasis <1 year were independent poor prognostic factors of OS (Table 6). Other factors studied included: age, calcium level or therapeutic sequence. These were not significant.

Table 6: Univariate and multivariate analyses of first-line progression-free-survival (PFS-1) and overall survival (OS) data.

| **First-line progression-free survival (PFS-1)** | | | | | | |
|---|---|---|---|---|---|---|
| **Variables** | **Univariate** | | | **Multivariate** | | |
| | **HR** | **95% CI** | **p** | **HR** | **95% CI** | **p** |
| age <70 | 1.0 | [0.72 - 1.41] | .97 | | | |
| Trt group Sun vs Eve | 0.77 | [0.54 - 1.10] | .16 | | | |
| **KPS <80** | 1.57 | [0.98 - 2.52] | .06 | **1.55** | **[1.01 - 2.58]** | **.04** |
| Histological type 1 | 0.7 | [0.45 - 1.07] | .1 | .71 | [0.42 - 1.21] | .21 |
| **Platelets >400 G/L** | **1.67** | **[1.16 - 2.40]** | **.006** | 1.37 | [0.89 - 2.12] | .15 |
| Hg <100 g/L | 1.95 | [0.99 - 3.87] | .05 | .78 | [0.33 - 1.85] | .57 |
| Ca >100 mg/L | 2.13 | [0.78 - 5.82] | .13 | | | |
| **ANC >8 G/L** | **1.85** | **[1.15 - 2.97]** | **.01** | **1.86** | **[1.02 - 3.40]** | **.04** |
| **TTMets <1 year** | **1.40** | **[1.03 - 1.91]** | **.03** | 1.15 | [0.78 - 1.67] | .48 |
| **Overall Survival (OS)** | | | | | | |
| **Variables** | **Univariate** | | | **Multivariate** | | |
| | **HR** | **95% CI** | **p** | **HR** | **95 % CI** | **p** |
| Age <70 years | 0.95 | [0.65 – 1.40] | .8 | | | |
| Trt group Sun vs Eve | 1.12 | [0.54 – 1.10] | .16 | | | |
| **KPS <80** | **2.39** | **[1.42 – 4.03]** | **.001** | **2.0** | **[1.07 – 3.67]** | **.03** |
| Histological type 1 | 0.69 | [0.4 – 1.17] | 0.17 | | | |
| **Platelets >400 G/l** | **1.69** | **[1.13 – 2.52]** | **.01** | 1.28 | [0.78 – 2.11] | .33 |
| **Hg <100 g/L** | **1.17** | **[1.02 – 1.35]** | **.004** | 1.32 | [0.52 – 3.30] | .56 |
| Ca >100 mg/ L | 2.38 | [0.87 – 6.52] | .09 | 0.43 | [0.08 – 2.36] | .34 |
| **ANC >8 G/L** | **3.04** | **[1.83 – 5.03]** | **$< 10^{-4}$** | **1.12** | **[1.04 – 1.20]** | **.003** |
| **TTMets <1 year** | **2.29** | **[1.6 – 3.29]** | **$< 10^{-4}$** | **1.74** | **[1.06 – 2.76]** | **.03** |

**Abbreviations:** KPS, Karnofsky Performance Status; ANC, Absolute neutrophil count; Hg, Haemoglobin; Ca, Calcaemia; TTMets <1 year, the delay between diagnosis and metastasis <1 year; Trt: treatment.

Heng prognostic risk factor data were available for a total of 154 patients.

OS was significantly different between patient subpopulations classified as having poor risk (n=43, median OS: 7.6 months), intermediate (n=73, median OS: 16.3 months) and favourable (n=38, median OS: 34.1 months) ($p=10^{-4}$). There was no difference, however, in terms of progression-free survival in first-line between these subgroups, with a median PFS-1 of 4.6 months, 6.9 months and 6.2 months respectively (p=0.11).

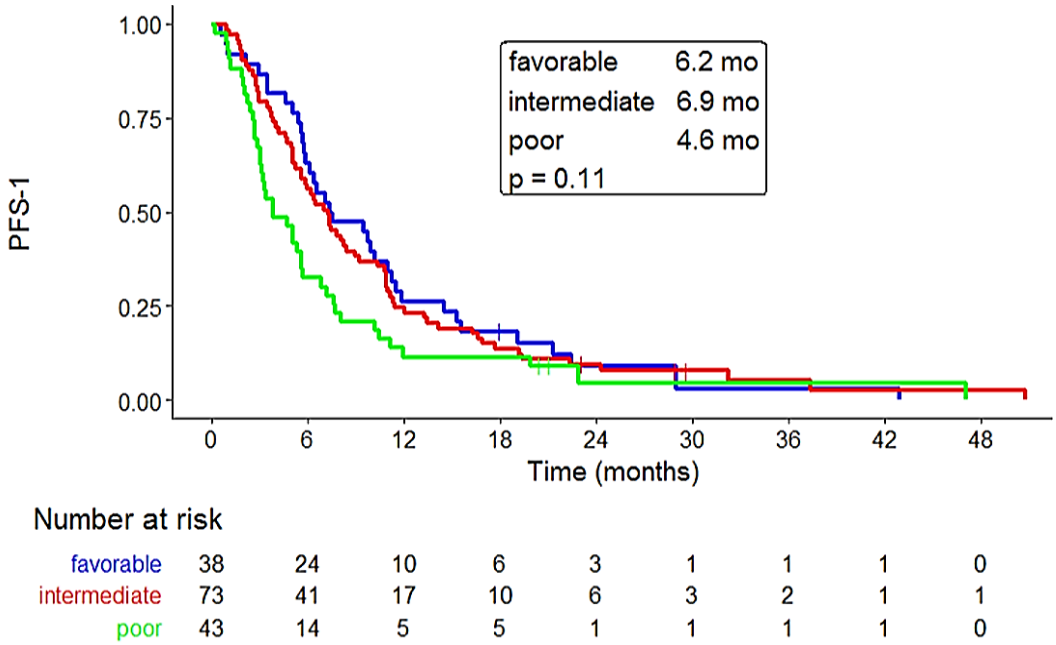
In this study, we observed a statistically significant difference for PFS-1 according to histological subtype: 12.5 months for type 1 pRCC versus 8.7 months for "non-type 1" pRCC (p=0.02). However, the difference was not significant for median OS: 30 months for type 1 and 24.5 months for "non-type 1" (p=0.31) (Table 7 and Figure 3-4).

Table 7. Prognosis according to Heng score and histological subtype.

| **HENG score (n=154)** | **Median OS (months)** | **Median PFS-1 (months)** |
|---|---|---|
| Favourable risk (38) | 34.1 | 6.2 |
| Intermediate risk (73) | 16.3 | 6.9 |
| Poor risk (43) | 7.6 | 4.6 |
| | $p=10^{-4}$ | p=0.11 |
| **Histological subtype (n=191)** | | |
| Type 1 (163) | 30 | 12.5 |
| Non-type 1 (28) | 24.5 | 8.7 |
| | p=0.31 | p=0.02 |

Figure 3. Kaplan-Meier estimates of PFS-1 (A) and overall survival (B) according to Heng prognostic score.

A.




B.

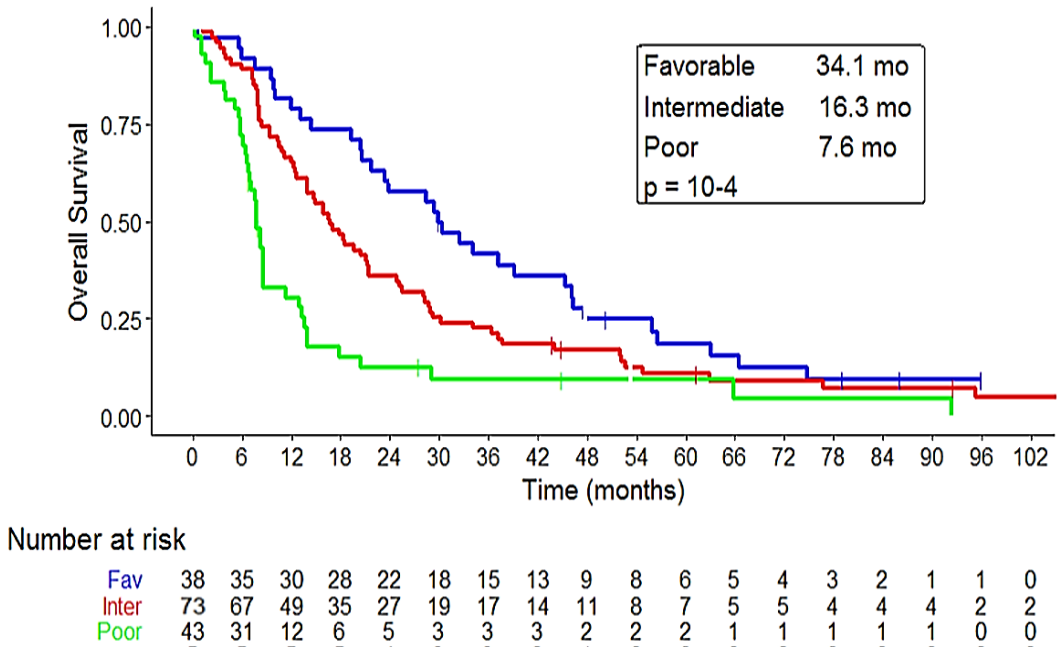
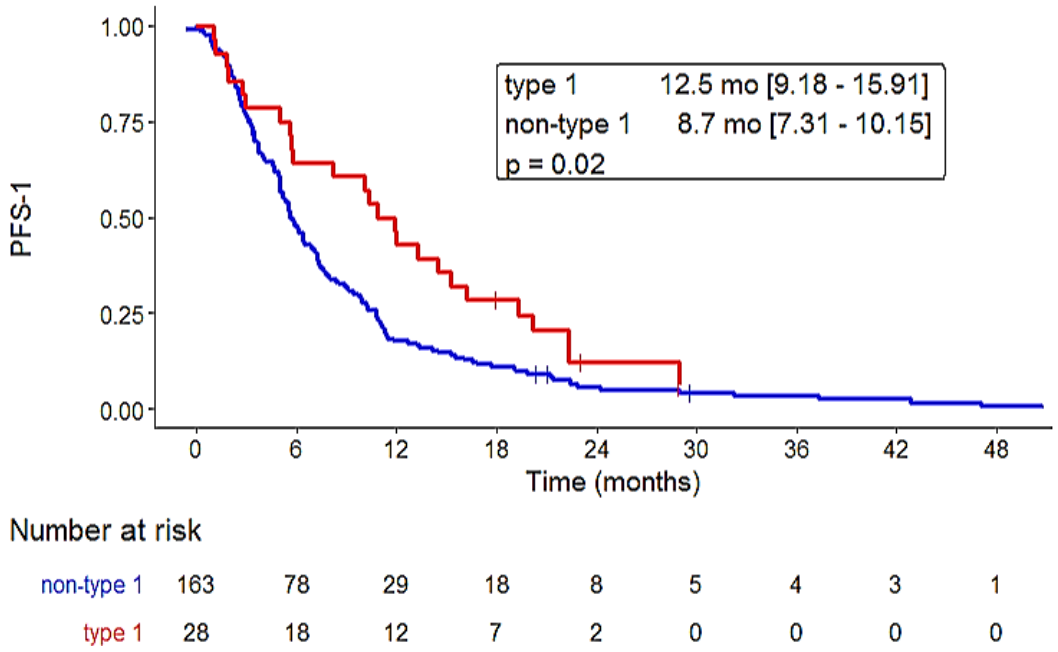
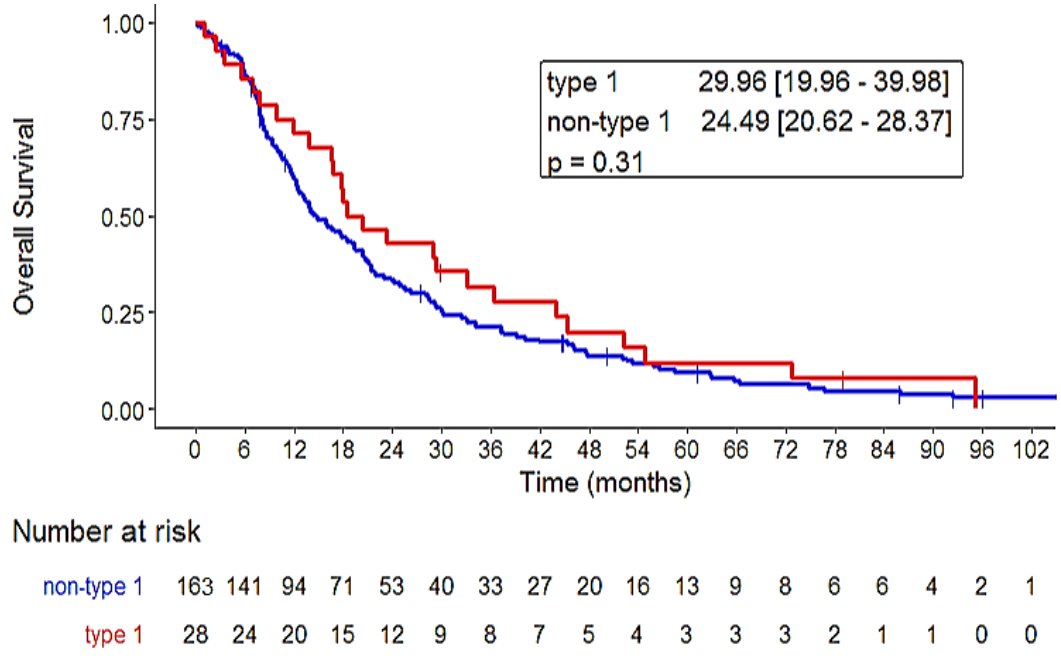


Figure 4. Kaplan-Meier estimates of PFS-1 (A) and overall survival (B) according to histological subtype.

A.

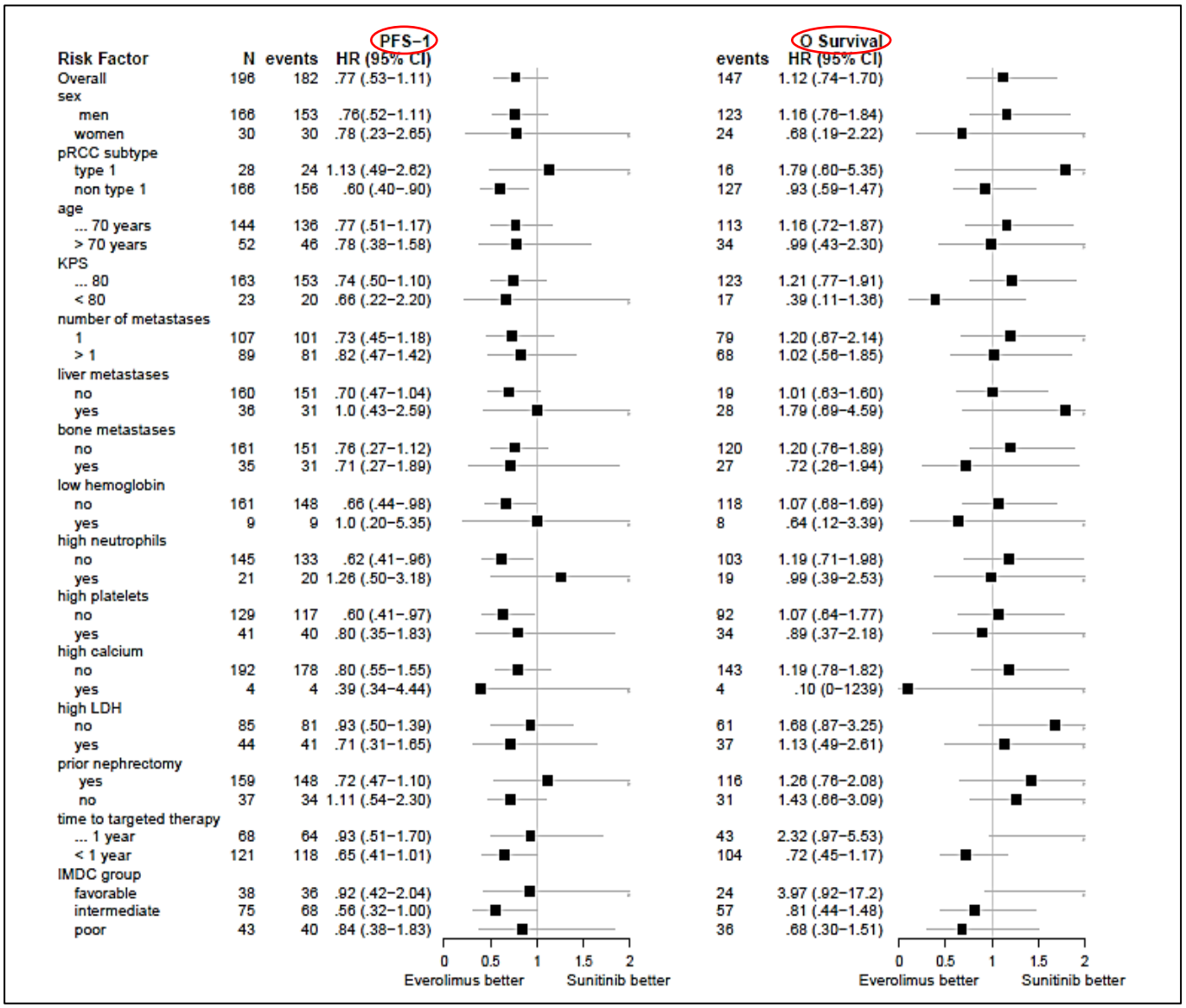



B.



We studied the different prognostic factors according to the treatment group in terms of PFS-1 and OS. In terms of PFS-1, normal haemoglobin, platelets, and neutrophils promote everolimus treatment. In terms of OS, there was no prognostic factors in favour of one of the treatments. These data are summarized in a forest-plot (Table 8).

Table 8. Exploratory forest-plot of PFS-1 and OS according to different prognostic factors.



## 6. Treatment lines

Subsequent therapy after progression was common, patients received several lines of treatment, with 139 patients (70.9%) at least one subsequent treatment for pRCC, three or more for 86 patients (47, 9%) and even five or more for 19 patients (9,7%) (Table 9).

Table 9: Number of lines of treatment according to first-line therapy group.

| Variables | All | Sunitinib group | Everolimus group |
|---|---|---|---|
| Number of treatment lines | | | |
| 1 | 196 | 158 | 38 |
| 2 | 139 | 113 | 26 |
| 3 | 86 | 71 | 15 |
| 4 | 42 | 34 | 8 |
| 5 | 19 | 15 | 4 |
| 6 | 7 | 6 | 1 |
| 7 | 1 | 1 | 0 |

In patients previously treated with sunitinib, crossover to mTOR inhibitors (everolimus or temsirolimus) was noted in 77 (68.1%) of 113 patients and 36 (31.8%) received a second-line of TKIs. One patient (0.9%) received bevacizumab plus interferon alfa-2 as a second-line. Second-line therapy with everolimus after TKIs was reported in 26 (100%) patients, including 23 with sunitinib (88.4%) (Table 10). These data are summarized in a diagram (Figure 5).

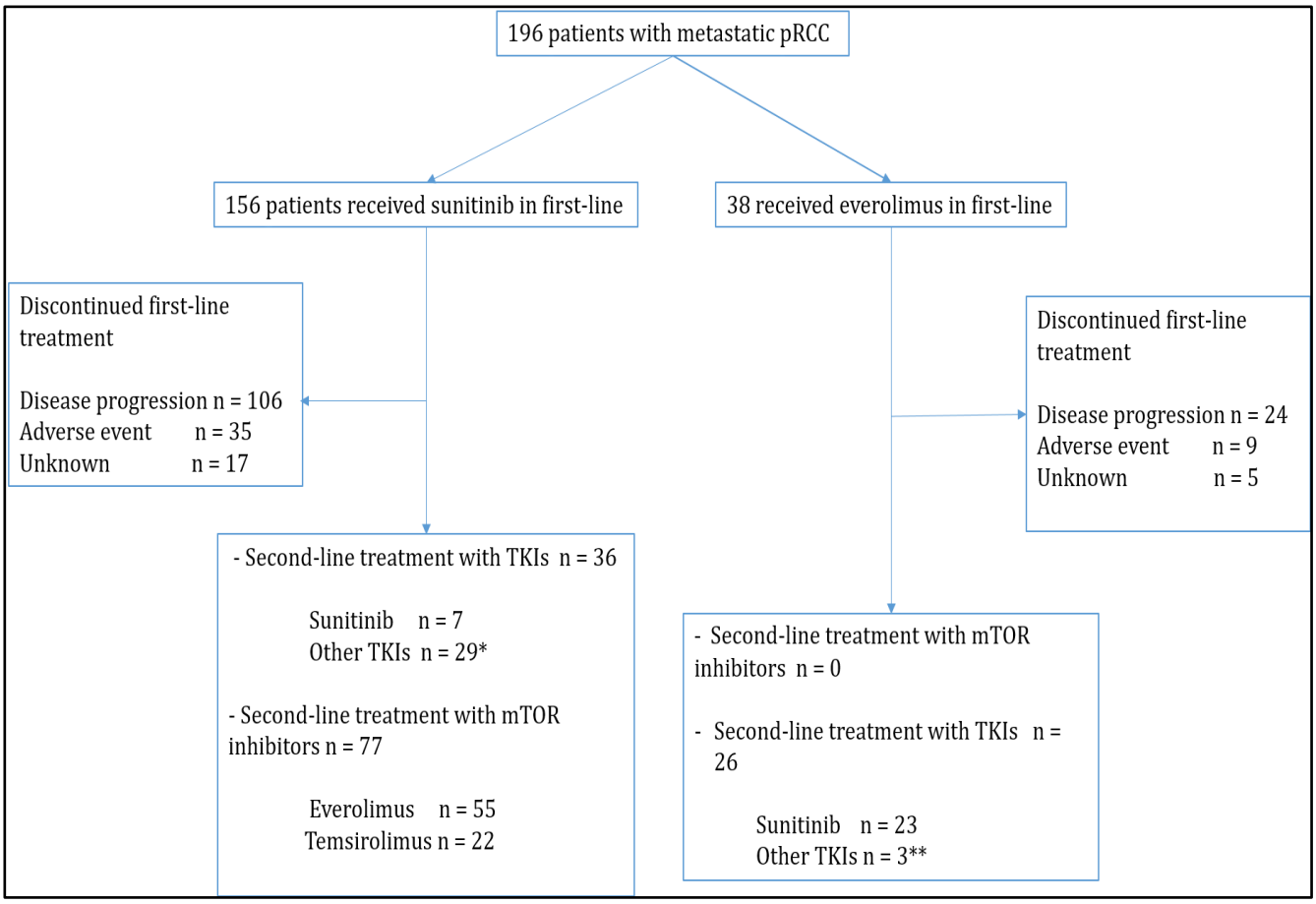
Table 10: Second-line treatments according to first-line treatment group.

| | All | Sunitinib group | Everolimus group |
|---|---|---|---|
| mTOR inhibitors | 77 | 77 | 0 |
| -Everolimus | 55 | 55 | 0 |
| -Temsirolimus | 22 | 22 | 0 |
| TKIs | 62 | 36 | 26 |
| -Sunitinib | 30 | 7 | 23 |
| -other TKIs | 32 | 29* | 3** |
| BEV-IFN | 1 | 1 | 0 |

Other 2nd-line TKIs: (*) in the sunitinib group: axitinib 9, crizotinib 1, sorafenib 19.
(**) in the everolimus group: axitinib 1, crizotinib 1, pazopanib

BEV-INF: bevacizumab - interferon-α

Figure 5. Diagram summarizing the trial.




Nb: one patient in the sunitinib group received bevacizumab in combination with interferon- α in second-line and is not represented on this chart.
Other 2nd-line TKis: (*) in the sunitinib group: axitinib 9, crizotinib 1, sorafenib 19.
(**) in the everolimus group: axitinib 1, crizotinib 1, pazopanib 1.

## 7. Safety

Adverse events (AEs) were reported in 196 patients. 188 patients (95.9%) had at least one AE according to the CTCAE version 4.0 classification. The most common clinical adverse events in both groups were asthenia, mucositis, diarrhoea, nausea, and dysgeusia. In the sunitinib group there was more palmar-plantar erythrodysesthesia (hand-foot syndrome), hypertension, gastro-oesophageal reflux disease and changes in hair colour, while in the everolimus group patients had more limb oedema, skin rash, cough, dyspnoea and non-infectious pneumonitis. Of the 158 patients treated with sunitinib, 15 (9.5%) had grade 3/4 asthenia and 13 (8.2%) had grade 3/4 hand-foot syndrome. Among the 38 patients treated with everolimus, only 4 patients (10.5%) experienced grade 3 or 4 adverse reactions, with the exception of asthenia.

Regarding the biological adverse effects, anaemia was most frequent in both groups, in 36 patients (22.8%) in the sunitinib group and 13 patients (31.6%) in the everolimus group. 26 patients (16.5%) developed hypothyroidism in the sunitinib group. The most frequent AEs (>10%) are summarized in Table 9. Three deaths, partly related to sunitinib, were reported by the investigators. One patient died of acute respiratory distress syndrome, another one due to major hand-foot syndrome complicated by multiple organ failure and the last one to acute infectious pneumonitis.

Table 8. Adverse events (all grades) occurring in more than >10% of patients during first-line therapy according to the CTCAE v 4.0 (Common Terminology Criteria for Adverse Events version 4.0).

| | **Sunitinib ( n=158)** | | | **Everolimus ( n=38 )** | | |
|---|---|---|---|---|---|---|
| *Clinical adverse events, N (%)* | | | | | | |
| | Grades 1/2 | Grades 3/4 | All grades | Grades 1/2 | Grades 3/4 | All grades |
| Asthenia | 80 (50.6) | 15 (9.5) | 95 (60.1) | 26 (68.4) | 4 (10.5) | 30 (78.9) |
| Mucositis/ stomatitis | 63 (39.9) | 6 (3.8) | 68 (43) | 22 (57.9) | 1 (2.6) | 23 (60.5) |
| Diarrhoea | 60 (38) | 5 (3.2) | 65 (41.1) | 16 (42.1) | 0 (0) | 16 (42.1) |
| Hand-foot syndrome | 35 (22.2) | 13 (8.2) | 48 (30.4) | 0 (0) | 0 (0) | 0 (0) |
| Nausea | 36 (22.8) | 1 (0.6) | 37 (23.4) | 14 (36.8) | 0 (0) | 14 (36.8) |
| Dysgeusia | 32 (20.3) | 2 (1.2) | 34 (21.5) | 8 (21) | 0 (0) | 8 (21) |
| Hypertension | 33 (20.9) | 0 (0) | 33 (20.9) | 0 (0) | 1 (2.6) | 1 (2.6) |
| Infection | 24 (15.2) | 4 (2.5) | 28 (17.7) | 8 (21) | 2 (5.3) | 10 (26.3) |
| Gastro-oesophageal reflux disease | 26 (16.5) | 1 (0.6) | 27 (17.1) | 0 (0) | 0 (0) | 0 (0) |
| Limb oedema | 25 (15.8) | 1 (0.6) | 26 (16.4) | 13 (34.2) | 1 (2.6) | 14 (36.8) |
| Decreased appetit | 22 (13.9) | 4 (2.5) | 26 (16.4) | 12 (31.6) | 0 (0) | 12 (31.6) |
| Abdominal pain | 21 (13.3) | 2 (1.2) | 23 (14.6) | 10 (26.3) | 0 (0) | 10 (26.3) |
| Haemorrhage | 18 (11.4) | 2 (1.2) | 20 (12.7) | 4 (10.5) | 0 (0) | 4 (10.5) |
| Dyspnoea | 15 (9.5) | 5 (3.2) | 20 (12.7) | 13 (34.2) | 1 (2.6) | 14 (36.8) |
| Rash | 16 (10.1) | 2 (1.2) | 18 (11.4) | 21 (55.2) | 2 (5.3) | 23 (60.5) |
| Alopecia/hair bleaching | 16 (10.1) | 0 (0) | 16 (10.1) | 1 (2.6) | 0 (0) | 1 (2.6) |
| Musculoskeletal chest pain | 13 (8.2) | 1 (0.6) | 14 (8.9) | 7 (18.4) | 0 (0) | 7 (18.4) |
| Cough | 5 (3.2) | 0 (0) | 5 (3.2) | 13 (34.2) | 0 (0) | 13 (34.2) |
| Non-infectious Pneumonitis | 0 (0) | 0 (0) | 0 (0) | 9 (23.7) | 1 (2.6) | 10 (26.3) |
| *Biological adverse events, N (%)* | | | | | | |
| | Grades 1/2 | Grades 3/4 | All grades | Grades 1/2 | Grades 3/4 | All Grades |
| Anaemia | 29 (18.4) | 7 (4.4) | 36 (22.8) | 12 (31.6) | 1 (2.6) | 13 (34.2) |
| Thrombocytopenia | 23 (14.6) | 5 (3.2) | 28 (17.7) | 6 (15.8) | 0 (0) | 6 (15.8) |
| Hypothyroidism | 26 (16.5) | 0 (0) | 26 (16.5) | 1 (2.6) | 0 (0) | 1 (2.6) |
| Neutropenia | 20 (12.7) | 3 (1.9) | 23 (14.6) | 1 (2.6) | 0 (0) | 1 (2.6) |
| Increased blood creatinine concentration | 13 (8.2) | 4 (2.5) | 17 (10.7) | 5 (13.2) | 0 (0) | 5 (13.2) |

## DISCUSSION

This is the first trial comparing sunitinib and everolimus as first-line treatment of metastatic pRCC only. We found no evidence in the literature suggesting the superiority of either drug in first-line treatment. This is due to the scarceness of these tumours and therefore the difficulty in undertaking prospective randomized clinical trials.

Guidelines for non-clear cell renal cell carcinoma (nccRCC) generally advise inclusion of these patients in therapeutic trials. The ESMO guidelines for this heterogeneous population suggest beginning treatment with sunitinib, based on more available data and reproducible efficacy (II, B) ([6]).These guidelines are based on minor evidence, such as retrospective analyses, and small-scale phase II randomized trials, in particular ASPEN and ESPN studies [[29],[26]].

ASPEN ([29]) and ESPN ([26]) trials compared the efficacy of everolimus and sunitinib in patients with metastatic non-clear cell renal cell carcinoma including: chromophobe, papillary, translocation carcinoma, sarcomatoid differentiation and unclassified subtypes. The pRCC rate was 64.8 % (70 patients) in the first study and 39.7 % in the second (27 patients). Patients were randomized to receive everolimus or sunitinib and crossed over if progression occurred. The ASPEN study showed a longer PFS for first-line sunitinib, with median PFS-1: 8.3 months versus 5.6 months (HR 1.41; 80% CI, 1.03–1.92). For ESPN, no statistically significant difference with median PFS-1: 6.1 months versus 4.1 months (stratified log-rank p value=0.6) was observed. The median overall survival for ASPEN was 13.2 months (95% CI, 9.7–37.9) in the everolimus group and 31.5 months (14.8–not reached) in the sunitinib group, although the results failed to reach statistical significance (HR 1.12; 95% CI, 0.70–2.1; p=0.6). The results were analysed according to the MSKCC risk group, the median PFS was longer in patients treated with sunitinib in patients with intermediate and good risk (6.5 versus 4.9 months and 14 versus 5.7 months). However, patients with poor-risk features had a median progression-free survival of 4.0 months with sunitinib and 6.1 month with everolimus. For ESPN the median OS of patients with metastatic pRCC (central review) was 14.9 months with everolimus and 16.6 months with sunitinib (stratified log-rank p value=0.18). In the statistical analysis, neither papers showed any distinction between papillary type 1 and 2.

A Spanish meta-analysis pooled the results of these two publications, indicating a trend for the superiority of sunitinib over everolimus in terms of PFS-1, though this was not statistically significant (HR 1.30; 95% CI, 0.91-1.86; p=0.15) ([30]).

A recent Italian meta-analysis of four trials was published, comparing TKI to mTOR inhibitors for nccRCC ([31]). This meta-analysis includes the two clinical trials previously mentioned as well as RECORD-3 comparing sunitinib and everolimus in first-line ([22]) and INTORSECT ([32]) who had the distinction of comparing sorafenib (VEGFR) with temsirolimus (mTOR inhibitor) after first-line treatment with sunitinib. RECORD-3 showed that the median PFS was 7.9 months for first-line everolimus and 10.7 months for first-line sunitinib (HR 1.4; 95% CI, 1.2-1.8). For these trials, pRCCs were included in nccRCCs without further details. A total of 332 patients was analysed (164 treated with VEGFR-TKIs and 168 with mTORi). PFS treatment with TKI reduced the risk of progression compared to mTOR inhibitors (HR 0.71; 95% CI, 0.60-0.84; p<0.0001). There was no difference in terms of overall survival (HR 0.86; 95% CI, 0.67-1.12; p=0.27). Clinical data and results are summarized in a table form in the appendix (p4).

It can be seen that these trials all included non-clear cell histological subtypes because of the scarceness of these diseases. We cannot, therefore, conclude on a particular histological subtype.

For trials recruiting only patients with metastatic pRCC, we compared our results to those found in two French phase II studies:

The first is RAPTOR ([1]) including 92 patients (72 males and 20 females) with previously untreated metastatic pRCC, measurable lesions and good general condition (ECOG 0-1 performance status). The median age was 60 (range 23-84). As a reminder of the 92 patients included, 30 patients were included in our study. Patients received oral everolimus 10 mg once daily. A centralized pathological examination was performed in 78% of cases. These were pRCC type 1 in 23 cases, type 2 in 39 cases, and untyped in 30 cases. In this large prospective study, median PFS was 4.1 months (95% CI, 3.6-5.5) and PFS rate at 6 months was 34% (80% CI, 25-45). Median OS was 21.4 months (95% CI, 15.4-28.4). Histological subtype analyses: type 1 or type 2, have shown that median PFS was 7.9 months (95% CI, 2.1-11.0) and 5.1 months (95% CI, 3.3-5.5), respectively, and median OS was 28.0 months (95% CI, 7.6-not estimable) and 24.2 months (95% CI, 15.8-32.8). Regarding the everolimus group, the median PFS-1 was 4.1 months (95% CI, 3.6-5.5) in RAPTOR (1) versus 5 months (95% CI, 2.8-7.3) in GETUG study. Overall survival was also similar, the median OS was 21.4 months (95% CI, 15.4-28.4) in RAPTOR and 17.7 months (95% CI, 10.8-24.5) in the everolimus group of GETUG study.

The second is SUPAP ([2]). Sixty one previously untreated patients were included (51 males and 10 females), with measurable lesions, and good general condition (ECOG 0-1 performance status). A large proportion of these patients, 56 patients, were included in

our retrospective study. The median age was 64 (range 32-81), They received repeated cycles of sunitinib at the standard dose of 50 mg for 4 weeks followed by 2 weeks without treatment. The median first-line PFS was 6.6 months (95% CI, 2.8–14.8) in type 1, and 5.5 months (95% CI, 3.8–7.1) in type 2. Median OS was 17.8 (95% CI, 5.7–26.1) and 12.4 (95% CI, 8.2–14.3) months respectively, in types 1 and 2. The results were consistent with the GETUG study with a median PFS-1 that was 6.1 months (95% CI, 5.0-7.3) for sunitinib group and the median OS was 16 months (95% CI, 12.4-19.5).

Regarding adverse effects, the safety profiles of sunitinib and everolimus are similar to those found in the literature. For everolimus, looking at the original study RECORD-1 ([24]) in patients with metastatic renal cell carcinoma whose disease had progressed under vascular endothelial growth factor-targeted therapy, the most common clinical side effects found were the same: mucositis, asthenia, rash, diarrhoea and anorexia. Biological adverse effects were probably underestimated in our study, with less anaemia, hypercholesterolaemia, hyperglycaemia and elevated creatinine. And this for several reasons: the retrospective nature of our study, with a small number of patients, and in patients treated on the first-line of treatment. Sunitinib tolerance was also similar in terms of clinical adverse events in studies, with asthenia, diarrhoea, mucositis, hand-foot syndrome and hypertension as stated in the article by Motzer et al ([21]). Fewer biological adverse events, however, were identified.

The Heng score, which is a recognized and reproducible prognostic score for the use of TKIs in all kidney cancer subtypes, could not be performed in all patients due to a lack of biological data, including serum calcium and LDH levels. One hundred fifty four patients were classified, mostly in the intermediate risk prognostic group, i.e. 73 patients (47.4%). This prognostic group is also the most represented in therapeutic trials. The survival data according to the prognostic scores are similar to those found in the literature. One study showed medians of OS for the favorable, intermediate and poor prognosis groups of 31.4, 16.1 and 5.1 months in patients treated for nccRCCs. The median PFS was 9.6, 4.9, and 2.1 months, respectively([8]). In the GETUG study, the median OS of the favorable, intermediate, and poor prognosis groups was 34.1, 16.3 and 7.6 months and the median PFS was 6.2, 6.9, and 4.6 months, respectively.

Recent advances in the treatment of metastatic renal cell carcinoma introducing new standards such as nivolumab, a check-point inhibitor, and cabozantinib, which is an oral multipotent inhibitor of VEGF 2, MET, and AXL, may alter treatments used in papillary renal-cell carcinoma. Indeed, MET inhibitors such as cabozantinib will probably be a very good therapeutic option in papillary renal cell carcinoma type 1 (pRCC 1) associated with

*MET* gene alterations. *MET* activation can lead to prolonged survival of tumour cells and increased cell growth and promotes migration, invasion and angiogenesis. pRCC type 1 is conventionally associated with mutations of *MET* exons 16-19, especially in familial forms. In sporadic forms, the frequency of *MET* mutations in type 1 pRCCs was assessed from 15% to 17% in coding regions ([33]). However, broadening the analysis to the entire *MET* gene suggests a greater frequency of abnormalities in non-coding regions and a potential prognostic role of genetic polymorphisms ([34]). In addition to these activating mutations, other anomalies exist allowing the qualification of "tumours controlled by MET" combining: *MET* amplification, chromosome 7 gain and the generation of *HGF-MET* autocrine loop or cofactors activation of MET protein ([15],[35]). At least one of these abnormalities is identified in about 50 to 80% of type 1 papillary renal cell carcinomas. The existence of these anomalies provides a strong rationale for targeting MET especially in pRCC 1.

The subgroup analysis in the CABOSUN study, comparing cabozantinib to sunitinib as first-line therapy for patients with metastatic renal cell carcinoma, showed a higher objective response rate (ORR) in MET overexpressing patients, corresponding to 39% ( n=62) of randomized patients in favour of cabozantinib (HR 0.32; 95% CI, 0.16-0.63) ([36]). A phase 2 study CREATE, with 23 patients treated with crizotinib (another molecule that inhibits several tyrosine kinases, in particular MET, ALK and ROS-1), has shown good efficacy with significant objective response rates and extended responses in patients with *MET* mutations or amplification, treated for metastatic pRCC type 1 (ORR 50%; 95% CI, 6.8-93.2) ([37]). There were also sporadic responses in patients not overexpressing MET, suggesting the presence of other gene abnormalities or alternative pathways. Likewise, this article showed the importance of anatomopathological proofreading because, as 1/4 of patients did not finally present with pRCC type 1. These data were further confirmed in a phase 2 trial with 109 patients including a majority of pRCC type 2 (62%) in which another MET tyrosine kinase inhibitor was tested: savolitinib. Median progression-free survival for patients with MET-driven and MET-independent pRCC was 6.2 months (95% CI, 4.1-7.0) and 1.4 months (95% CI, 1.4-2.7), respectively (HR 0.33; 95% CI, 0.2-0.5; p=0.001) ([38]).

As in ccRCC, PD-L1 or PD-1 inhibitors have been tested in pRCC. The immune checkpoint inhibitor, PD-L1 was expressed in 10.9 % of non-clear cell RCCs compared to 24.2 % of clear cell Renal Cancer Carcinomas (p=0.002), according to a meta-analysis by Iacovelli et al., including 1313 cases among which 111 had non-clear cell histology ([39]).

This same meta-analysis seems shown that a higher level of PD-L1 expression is a factor of negative prognosis (HR 2.05; 95 % CI, 1.38–3.05; p< 0.001).

In parallel, a Korean study evaluated the expression of PD-L1 and PD-L2 in 425 patients with Renal Cell Carcinoma, including 201 papillary subtypes and analysed according to the clinical-immunohistochemical pathological status and several oncogenic protein statuses. PD-L1 and PD-L2 expression were identified in 6.0% (n=12) and 66.2% (n=133) of all pRCCs, respectively. In this study, this expression had no influence on the prognosis of patients. It should be noted that positive PD-L1 was linked to the presence of EGFR (p=0.007) and positive PD-L2 was correlated with VEGF expression (p<0.001)([40]). A small retrospective analysis (n=41) demonstrated an ORR of 20% with nivolumab in a heterogeneous population of patients previously treated for metastatic non-clear cell RCC including 16 patients (39%) with pRCC ([41]). In another retrospective study (n=43), 14 patients (33%) with papillary renal cell carcinoma were treated with PD-1/PD-L1 inhibitors (75% monotherapy and 25% a combination of PD-1/PD-L1 with anti-VEGFR or anti-CTLA4), ORR for the total cohort was 19% (13% for PD1/PDL1 monotherapy patients) ([42]). ORR was 29 % (n=4/14) in patients with pRCC. In small retrospective series, ORRs appear similar to those found in ccRCC.

The GETUG study is limited by its retrospective nature. The two treatment arms are imbalanced with significantly fewer patients treated with everolimus in the first-line which corresponds to current therapeutic practices.

In contrast to clinical trials, patients may not have been followed at regular intervals for clinical, biological or radiological levels to monitor progress. Some information may thus be missing, including for analyses, which may limit the ability to calculate some result parameters.

A retrospective high-throughput molecular analysis of tumour tissue will be performed using next-generation sequencing (NGS) and will determine the MET status of these tumours by analysing *MET* kinase domain mutations, *MET* amplifications, *HGF* amplifications or gains in chromosome 7, locus of *MET* and *HGF* genes. This will allow us to determine the impact of MET status on the evolution of pRCC and the response to the different treatments used. Clinical data and tissue samples will be obtained from three groups: the GETUG (Groupe français d'Etude des Tumeurs Uro-Génitales), the IMDC (International Metastatic Renal Cell Carcinoma Database Consortium) and the Asan GU Cancer Center (about 280 patients in total).

Several clinical trials are currently in progress (>50) and we will perhaps be able to improve the management of these metastatic pRCC tumours. For example the SAVOIR

trial (NCT03091192), which uses *MET* alteration as a selection criterion for randomization to savolitinib (inhibitor of c-Met) versus sunitinib (NCT03091192), or a phase II randomized multi-arm trial testing efficacy of multiple tyrosine-kinase inhibitors such as cabozantinib S-Malate, crizotinib, volitinib and sunitinib (NCT02761057).

## CONCLUSION

In conclusion, in metastatic pRCC, everolimus and sunitinib have proven but modest anti-tumour activity and remain at the present time a first choice therapeutic option. There was no difference in terms of PFS-1. OS and PFS 2 were similar in both groups. There was a statistically significant difference for a better prognosis in favour of type 1 pRCC in terms of PFS-1. A prospective randomized comparative study seems unnecessary in this case. For the future, beyond the conventional treatment according to histological subtype, it seems more judicious to treat patients according to the molecular characteristics of their tumours in order to clarify this unmet medical need. Collaboration between medical centres is important for sharing rare data and for better management of these cancers.

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**Appendix Supplementary data**

Supplementary Table 1. The 2016 WHO Classification of Tumours of the Urinary System.

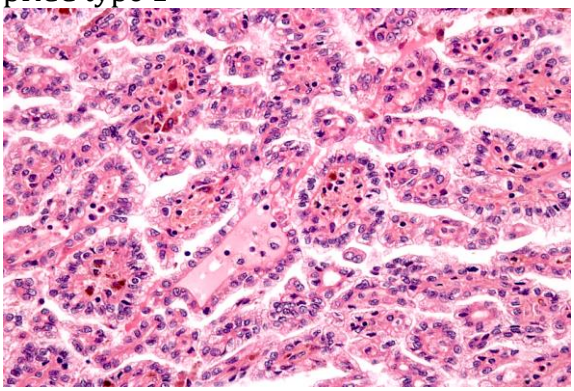
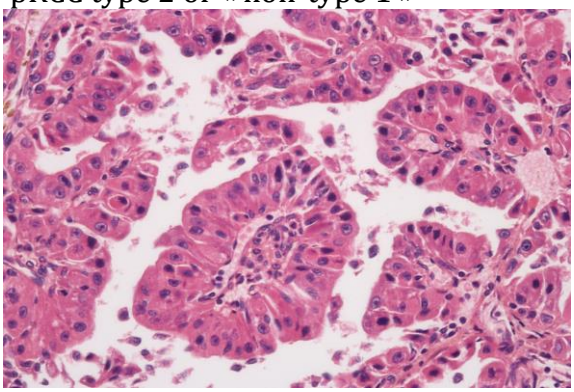
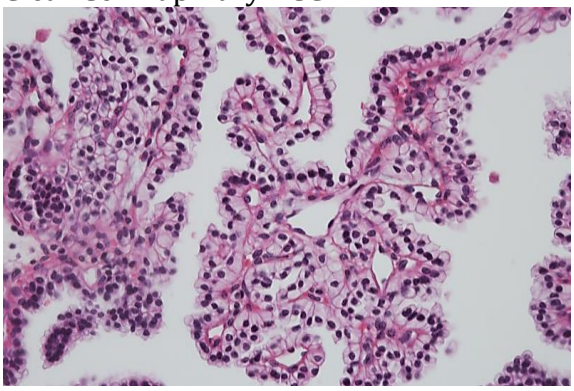
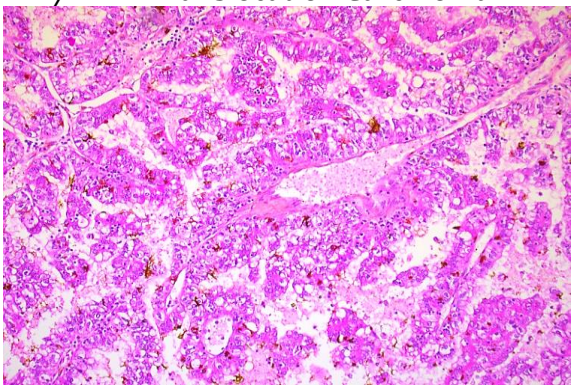
## WHO classification of tumours of the kidney

| | |
|---|---|
| **Renal cell tumours** | |
| Clear cell renal cell carcinoma | 8310/3 |
| Multilocular cystic renal neoplasm of low malignant potential | 8316/1* |
| Papillary renal cell carcinoma | 8260/3 |
| Hereditary leiomyomatosis and renal cell carcinoma–associated renal cell carcinoma | 8311/3* |
| Chromophobe renal cell carcinoma | 8317/3 |
| Collecting duct carcinoma | 8319/3 |
| Renal medullary carcinoma | 8510/3* |
| MiT family translocation renal cell carcinomas | 8311/3* |
| Succinate dehydrogenase–deficient renal carcinoma | 8311/3 |
| Mucinous tubular and spindle cell carcinoma | 8480/3* |
| Tubulocystic renal cell carcinoma | 8316/3* |
| Acquired cystic disease–associated renal cell carcinoma | 8316/3 |
| Clear cell papillary renal cell carcinoma | 8323/1 |
| Renal cell carcinoma, unclassified | 8312/3 |
| Papillary adenoma | 8260/0 |
| Oncocytoma | 8290/0 |
| **Metanephric tumours** | |
| Metanephric adenoma | 8325/0 |
| Metanephric adenofibroma | 9013/0 |
| Metanephric stromal tumour | 8935/1 |
| **Nephroblastic and cystic tumours occurring mainly in children** | |
| Nephrogenic rests | |
| Nephroblastoma | 8960/3 |
| Cystic partially differentiated nephroblastoma | 8959/1 |
| Paediatric cystic nephroma | 8959/0 |
| **Mesenchymal tumours** | |
| **Mesenchymal tumours occurring mainly in children** | |
| Clear cell sarcoma | 8964/3 |
| Rhabdoid tumour | 8963/3 |
| Congenital mesoblastic nephroma | 8960/1 |
| Ossifying renal tumour of infancy | 8967/0 |
| **Mesenchymal tumours occurring mainly in adults** | |
| Leiomyosarcoma | 8890/3 |
| Angiosarcoma | 9120/3 |
| Rhabdomyosarcoma | 8900/3 |
| Osteosarcoma | 9180/3 |
| Synovial sarcoma | 9040/3 |
| Ewing sarcoma | 9364/3 |
| Angiomyolipoma | 8860/0 |
| Epithelioid angiomyolipoma | 8860/1* |
| Leiomyoma | 8890/0 |
| Haemangioma | 9120/0 |
| Lymphangioma | 9170/0 |
| Haemangioblastoma | 9161/1 |
| Juxtaglomerular cell tumour | 8361/0 |
| Renomedullary interstitial cell tumour | 8966/0 |
| Schwannoma | 9560/0 |
| Solitary fibrous tumour | 8815/1 |
| **Mixed epithelial and stromal tumour family** | |
| Cystic nephroma | 8959/0 |
| Mixed epithelial and stromal tumour | 8959/0 |
| **Neuroendocrine tumours** | |
| Well-differentiated neuroendocrine tumour | 8240/3 |
| Large cell neuroendocrine carcinoma | 8013/3 |
| Small cell neuroendocrine carcinoma | 8041/3 |
| Phaeochromocytoma | 8700/0 |
| **Miscellaneous tumours** | |
| Renal haematopoietic neoplasms | |
| Germ cell tumours | |
| **Metastatic tumours** | |

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) [917A]. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification [756A], taking into account changes in our understanding of these lesions.
*New code approved by the IARC/WHO Committee for ICD-O.

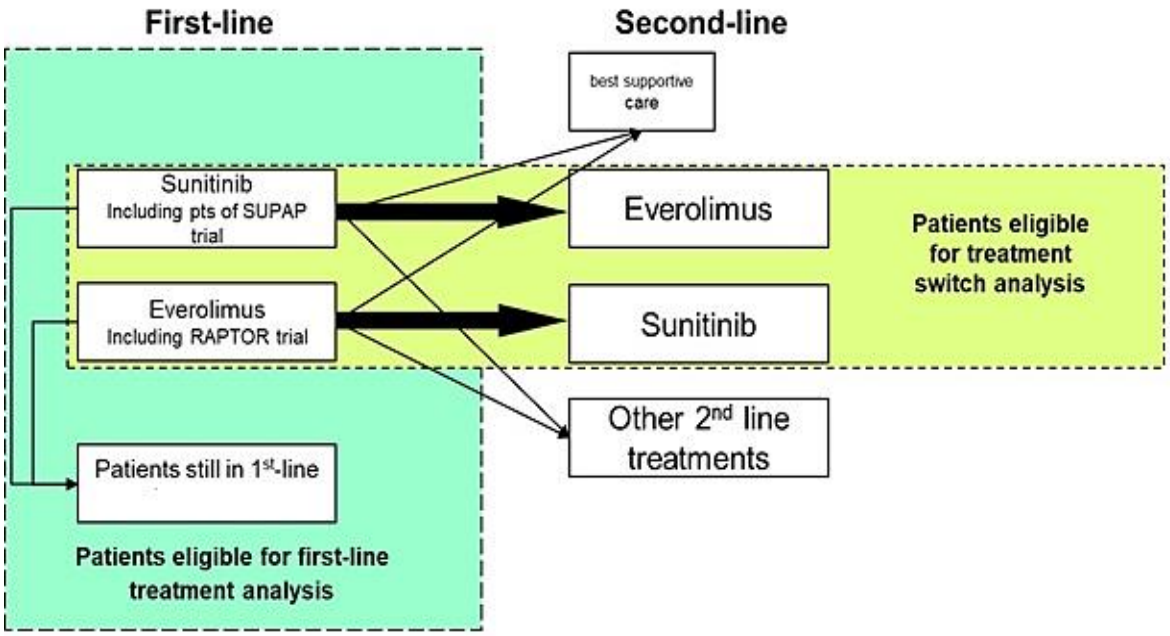
*Moch et Al. European Urology* Volume 70, Issue 1, Pages 93-105 (July 2016)

Supplementary Table 2. Pathological features and immunohistochemical markers in pRCC.

| | CA IX | CD10 | CK7 | P504S | *TFE3/TFEB* |
|---|---|---|---|---|---|
| A. pRCC type 1  | +/- | + | + | + | - |
| B. pRCC type 2 or « non-type 1 »  | +/- | + | +/- | + | - |
| C. Clear Cell Papillary RCC  | + | +/- | + | - | - |
| D. *TFE/MiTF* Translocation Carcinoma  | +/- | +/- | - | +/- | + |

*Courtesy of G.FROMONT-HANKARD*

Supplementary Table 3. Possible therapeutic sequences in the study.



Supplementary Table 4. Prospective trials in non–clear cell RCC comparing treatment by VEGFR or mTORi.

| Trial | ASPEN | ESPN | RECORD-3 | INTORSECT |
|---|---|---|---|---|
| Treatment (control arm versus experimental arm) | Sunitinib vs Everolimus | Sunitinib vs Everolimus | Sunitinib vs Everolimus | Sorafenib vs Temsirolimus |
| Author and Year | Armstrong et al. 2016 | Tannir et al. 2016 | Motzer et al. 2014 | Hutson et al. 2014 |
| Phase of study | II | II | II | III |
| Line of treatment | first-line | first-line | first-line | second-line (after sunitinib) |
| Number of patients | 108 pts | 68 pts | 471 pts | 512 pts |
| Histology type | nccRCC | nccRCC | nccRCC and ccRCC | nccRCC and ccRCC |
| Patients with pRCC histology (%) | 70 pts (64.8%) | 27 pts (39.7%) | nccRCC=66 pts pRCC=NS | nccRCC=90 pts pRCC=NS |
| Median PFS-1 (months) | 8.3 vs 5.6 HR 1.41 [CI 1.03–1.92] p=0.16 pRCC : 8.1 vs 5.5 | 6.1 vs 4.1 (p=0.6) pRCC : 5.7 vs 4.1 | 10.7 vs 7.9 HR 1.43 [CI 1.15-1.77] nccRCC : 7.2 vs 5.1 | 3.9 vs 4.3 HR 0.87 [CI 0.71-1.07] nccRCC : NS |
| Median OS (months) | 31.5 vs 13.2 HR 1.12 [CI 0.7-2.1] p=0.6 | 16.2 vs 14.9 (p=0.18) pRCC : 16.6 vs 14.9 | 29.5 vs 22.4 HR 1.1 [CI 0.9–1.4] nccRCC : 16.8 vs 16.2 | 12.6 vs 16.6 HR 1.31 [CI 1.05-1.63] nccRCC : NS |
| ORR (%) | 18 vs 9 | 9 vs 3 | 26 vs 9 | 8 vs 8 |

**Abbreviations**: CI, Confidence Interval; ccRCC, clear cell renal cell carcinoma; HR, hazard ratio; nccRCC, non-ccRCC; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; NS, not specified; pts,patients.

Supplementary data 5. Information letter sent to patients.

**INFORMATION PATIENT**

**Étude rétrospective française sur l'efficacité du sunitinib et / ou de l'everolimus dans le traitement des patients atteints de carcinome rénal papillaire avancé ou métastatique.**

Madame, Monsieur,

Votre médecin participe à une étude nationale destinée à étudier le traitement du cancer du rein de type papillaire, chez 250 malades. Les deux traitements les plus largement utilisés actuellement sont l'everolimus (Afinitor®) et le sunitinib (Sutent®). Afin d'améliorer la prise en charge de cette maladie, nous souhaitons mieux connaître l'efficacité de chacun de ces médicaments pris séparément et, le cas échéant, de leur administration séquentielle. Dans ce but, sauf désaccord de votre part, votre médecin recueillera, de manière rétrospective, un certain nombre d'informations sur vos caractéristiques générales et sur votre maladie. Ces données sont issues de votre dossier médical et portent sur les points suivants :

- Age, sexe, état général, antécédents
- Diagnostic et caractéristiques du cancer du rein
- Traitements médicaux et chirurgicaux reçus pour le cancer du rein
- Votre réponse aux différents traitements et l'évolution de votre maladie
- Les effets secondaires éventuels liés aux traitements

Votre participation à cette étude n'influencera en aucun cas le déroulement de votre prise en charge. Aucun examen ou prise de sang supplémentaires ne sont prévus en plus de ceux qu'aurait normalement prescrit votre médecin.

Votre participation à cette étude est entièrement volontaire. Vous êtes libre d'accepter ou de refuser de participer, sans avoir à vous justifier et sans que cela ne modifie la relation avec votre médecin, la nature de votre traitement et de votre suivi.

Afin d'assurer la collecte des données médicales requises par le protocole et la qualité de l'étude, votre médecin pourra permettre l'accès à votre dossier médical à une personne astreinte au secret professionnel. Les données de santé recueillies feront l'objet d'un traitement informatique en garantissant la sécurité et la confidentialité.

Conformément aux articles 39 et 40 de la loi du 6 janvier 1978 modifiée, relative à l'informatique, aux fichiers et aux libertés, vous disposez à tout moment, par l'intermédiaire de votre médecin, d'un droit d'accès et de rectification des données à caractère personnel vous concernant, dans le cadre de cette étude.

Cette étude a reçu un avis favorable du Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS) et une autorisation de la Commission Nationale de l'Informatique et des Libertés (CNIL).

En vous remerciant de votre attention, nous vous prions d'agréer, Madame, Monsieur, l'expression de toute notre considération

Supplementary Table 6. List of participating centres.

GETUG
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1. BORDEAUX - CHU St André, Dr GROSS-GOUPIL
2. CLERMONT-FERRAND – Centre Jean Perrin, Dr MAHAMMEDI
3. CRETEIL - Henri Mondor, Dr SALDANA
4. LILLE – Centre Oscar Lambret, Dr PENEL
5. LYON - CHU Sud, Dr TARTAS
6. LYON – Centre Léon Bérard, Dr FLECHON
7. MARSEILLE - CHU Timone, Dr DEVILLE
8. MARSEILLE - Institut Paoli Calmettes, Dr GRAVIS
9. DIJON - Centre Georges François Leclerc, Dr ZANETTA
10. PARIS - APHP St Louis, Dr BAUMERT
11. POITIERS – CHU, Pr TOURANI
12. RENNES - Centre Eugène Marquis, Dr LAGUERRE
13. SAINT PRIEST EN JAREZ - Institut de Cancérologie de la Loire, Dr GUILLOT
14. STRASBOURG – CHU, Pr BARTHELEMY
15. SURESNES - Hôpital Foch, Dr THEODORE
16. TOULOUSE – Institut Universitaire du Cancer de Toulouse, Dr CHEVREAU
17. TOURS – CHU, Pr LINASSIER
18. VILLEJUIF – Institut Gustave Roussy, Dr ESCUDIER
19. PARIS – APHP HEGP, Pr OUDARD
20. PARIS – APHP Hopital Cochin, Pr GOLDWASSER
21. REIMS – Institut Jean Gaudinot, Dr EYMARD
22. NANTES et ANGERS – Institut de Cancérologie de l'Ouest, Dr ROLLAND et Dr DELVA
23. CAEN – Centre Francois Baclesse, Dr MOISE

**Vu, le directeur de Thèse**

**Vu, le Doyen**
**De la Faculté de Médecine de Tours**
**Tours, le**

**BLONZ Cyriac**

49 pages – 12 tableaux – 4 figures – 7 graphiques

**Résumé :**
**Introduction:** Le carcinome rénal de type papillaire (pRCC) est la forme de cancer du rein la plus fréquente après le cancer à cellules claires (ccRCC). Le pRCC représente 15% de l'ensemble des cancers du rein. Il n'y a pas de standard thérapeutique en première ligne au stade métastatique chez les patients atteints de cette forme histologique. Deux essais prospectifs de phase II français ont démontré l'efficacité du sunitinib et de l'évérolimus dans le traitement de première intention de la maladie métastatique pRCC : l'essai RAPTOR et l'essai SUPAP. Nous rapportons la première série rétrospective évaluant l'efficacité de chacune de ces molécules ainsi que l'impact de la séquence thérapeutique dans ce type de cancer uniquement.
**Matériel et méthodes**: Étude rétrospective multicentrique française évaluant l'efficacité de l'évérolimus ou du sunitinib chez des patients traités en première ligne métastatique de leur pRCC. Le critère d'évaluation principal était la survie sans progression en première ligne (SSP-1). Les critères d'évaluation secondaires comprenaient la survie sans progression en deuxième ligne (SSP-2), les traitements administrés en deuxième ligne, la tolérance, la survie globale (SG), les facteurs pronostiques et l'influence de la séquence thérapeutique.
**Résultats**: 196 patients ont été inclus dans cette étude et ont été traités entre février 2006 et mai 2015: 28 étaient porteurs d'une tumeur papillaire de type 1 et 166 de type "non-type 1". 158 patients ont reçu le sunitinib en première intention et 38 l'évérolimus. Les données ont été mises à jour le 28 février 2018 avec un recul médian de 26 mois [1- 257]. Il n'y avait pas de différence en termes de SSP-1 entre le groupe sunitinib : 6,1 mois [5,0-7,3] et le groupe évérolimus: 5 mois [2,8-7,3] (HR 0.78; IC 95%, 0.54 à 1.11; p=0.16). La SG médiane était de 16 mois [12,4-19,5] dans le groupe sunitinib et de 17,7 mois [10,8-24,5] dans le groupe évérolimus (HR 1.15; IC 95%, 0.80 à 1.68; p=0.44). La SSP-2 médiane était de: 3,3 mois pour le groupe sunitinib [2,6-3,9] et 3,1 mois [1,1-5,1] dans le groupe évérolimus (HR 1.01; IC 95%, 0.65 à 1.53; p=0.99). En analyse multivariée, un indice de Karnofsky <80 (IK<80) et le nombre absolu de neutrophiles>8000/mL (PNN>8000) avaient un impact pronostique péjoratif sur la SSP-1; en ce qui concerne la survie globale l'IK<80, un taux de PNN>8000 et un délai de moins d'un an entre le diagnostic et les métastases avaient une valeur pronostique péjorative. La séquence thérapeutique évérolimus suivi du sunitinib ou inversement ne modifiait pas l'évolution de la maladie. La SSP-1 était statistiquement meilleure pour les pRCC de type 1.
**Conclusion:** Le traitement par sunitinib ou par évérolimus en première ligne de traitement dans le carcinome rénal de type papillaire métastatique, sont deux options thérapeutiques possibles qui ne semblent pas affecter le pronostic.

**Mots-clés**: Carcinome à cellules rénales, papillaire, pRCC, métastases, sunitinib, évérolimus, séquence thérapeutique.

**Jury:**

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**Directeur de thèse: Professeur Claude LINASSIER**
**Membres du Jury: Professeur Gilles CALAIS**
**Docteur Bérangère NARCISO**
**Docteur Hélène VEGAS**

Date de soutenance : 28/09/2018