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ORIGINAL ARTICLE

# Impact of everolimus blood concentration on its anti-cancer activity in patients with metastatic renal cell carcinoma

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**Abstract**
*Purpose* Everolimus has demonstrated its efficacy in metastatic renal cell carcinoma (mRCC). Preliminary studies have shown high variability of everolimus blood concentrations (EBC). In other settings, its activity was correlated with EBC. We therefore decided to monitor EBC in patients treated with mRCC to assess its influence on oncologic outcomes.
*Patients and methods* Our study analyzed first 3 months' trough EBC levels in 42 patients treated in 4 French oncologic centers between March 2010 and August 2013. Patients presented a histologically confirmed diagnosis of mRCC and have failed prior anti-angiogenic (AA) therapies.
*Results* Median follow-up was 25.9 months. A total of 113 EBC were analyzed. The median trough concentration was 14.1 μg/L (range 2.6–91.5). Fourteen patients (67 %) versus 8 (38 %) patients with median EBC above or below 14.1 μg/L were free from progression at 6 months ($p = 0.06$). Median progression-free survival was 13.3 versus 3.9 months (HR 0.66 95 % CI 0.33–1.31; $p = 0.23$), and the median overall survival was 26.2 versus 9.9 months (HR 0.62 95 % CI 0.28–1.37; $p = 0.24$), for patients above or below the median value of trough concentrations, respectively.
*Conclusion* Impact of drug exposure for AA tyrosine kinase inhibitors activity has been demonstrated in mRCC

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setting. Interpatients EBC variability was confirmed in the present study, and the results suggest a relationship between initial EBC within the first 3 months and the drug activity. It underlines the need to prospectively include EBC monitoring in future clinical trials to determine the need of its implementation in routine use.

**Keywords** Renal cell carcinoma · Everolimus · Pharmacokinetic · Monitoring · Activity

## Introduction

Renal cell carcinoma (RCC) accounts for 2–3 % of all malignant diseases in adults. It is the seventh most common cancer in men and the ninth most common in women [1]. Its management has undergone a transformation in the past few years due to the emergence of novel targeted therapies that have dramatically expanded survival for patients with metastatic renal cell carcinoma (mRCC) [2]. Among them, everolimus is an orally administered inhibitor of mammalian target of rapamycin (mTOR), a component of an intracellular signaling pathway regulating cell growth and proliferation, metabolism, and angiogenesis. Abnormal functioning of the mTOR pathway may contribute to the pathogenesis of RCC [3, 4]. In patients with mRCC progressing after anti-angiogenic (AA) therapies, everolimus demonstrated its superiority over placebo in the RECORD1 phase III trial with median progression-free survival (PFS) of 4.9 versus 1.9 months (hazard ratio [HR], 0.33; $p < 0.001$) [5]. This result led to its approval by regulatory authorities in the USA and Europe.

Among studies previously published in patients with cancer or with transplantation, high variability of everolimus blood concentrations (EBC) was observed [6–8]. When used as an immunomodulatory agent to prevent transplant rejection, its efficacy and toxicity were correlated to its blood concentrations leading to advice therapeutic drug monitoring [9, 10]. As well as in tuberous sclerosis treatment, the monitoring of everolimus concentrations to further adapt its dosage has been strongly recommended [11, 12]. An influence of plasma concentration of AAs such as sunitinib or axitinib on treatment activity has been observed in patients with mRCC [13, 14]. Initial axitinib exposure had influence on its activity contrary to exposure thereafter [15]. Significant linear correlation between steady-state trough concentrations and overall everolimus exposure (area under the curve) had been previously observed when the drug was administered daily [16]. Steady-state trough blood levels can be chosen as a convenient monitoring pharmacokinetic (PK) parameter for this exploratory analysis. Therefore, this study monitored everolimus trough concentrations in patients with mRCC to explore its influence on everolimus activity.

## Patients and methods

### Patients and treatment modalities

Patients with mRCC treated by everolimus in four French oncologic centers between March 2010 and August 2013 were included in the analysis. All patients presented a histologically confirmed diagnosis of mRCC and have failed prior systemic therapies targeting the vascular endothelial growth factor (VEGF) pathway (either VEGF-receptor tyrosine kinase inhibitor [VEGF-R TKI] or VEGF ligand inhibitor) in the metastatic setting with the exception of one patient who received first-line everolimus in the context of a clinical trial. They were classified according to Heng prognostic risk: favorable risk group (zero risk factor), intermediate risk group (one or two risk factors), and poor risk group (three or more risk factors) [17]. Patients received everolimus according to clinical guidelines and to the French product characteristics and approval. Everolimus was prescribed by the medical oncologist at the standard dose of 10 mg daily; dose suspension and/or reduction could be performed in order to ensure patient safety. The drug was administrated as long as the patient was deriving clinical benefit from the therapy until disease progression or unacceptable toxicity. After completion of the everolimus treatment, patients were treated at the discretion of their physician.

### Pharmacokinetic analysis

Everolimus blood concentration levels were centrally monitored in a pharmacology unit. Pharmacokinetic assessments were regularly performed, while the patient was treated and the steady-state trough blood levels were chosen as a convenient monitoring PK parameter because of the correlation between everolimus AUC and trough concentrations [16]. Everolimus was measured using a validated liquid chromatography coupled to tandem mass spectrometry (LC/MS–MS) method. Briefly, patient's samples (together with standards and controls) were spiked with internal standard, then subjected to protein precipitation with $ZnSO_4$ and extracted by acetonitrile. The range of quantification of the method is between 1.2 (LLOQ) and 100.0 μg/L [18].

Due to the occurrence of early progression under everolimus in mRCC setting with a published median PFS of 4.9 months [5], we therefore decided to explore the influence of early everolimus exposure (EEE) on clinical outcomes. The EEE was defined by the median EBC value,

estimated from the trough values measured within the first 3 months and before the first tumor assessment.

### Response and activity assessments

Efficacy was assessed firstly by a radiologist and then reviewed by the medical oncologist with radiological tumor measurements using RECIST 1.1. Tumor measurements (using a CT scan or MRI) were performed at baseline (≤28 days prior to the start of the study treatment) and repeated 12 weeks (±2 weeks) until the patient presented a radiological disease progression. A bone scan was performed at baseline prior to the start of everolimus treatment in patients with known bone metastasis or if clinically indicated. After everolimus completion, patients were followed to assess survival end point until August 2013.

### Statistical methods

The primary objective of our study was to compare the rate of patients free from progression at 6 months and alive at 12 months according to EEE. Secondary objectives was to assess the overall survival (OS) and PFS of the whole cohort and according to their Heng prognostic group, the influence of EEE on PFS, OS, clinical benefit, overall response rate, and time to treatment discontinuation due to toxicity.

OS was defined as the time from start of everolimus to death from any causes or last date of follow-up for alive patients. Alive patient with or without progression were censored. PFS was defined as the time from start of everolimus to date of progression or date of death for patients who died without progression. In patients alive without progression, PFS was determined as the time from start of everolimu to the date of last news or trial end point. Alive patients without progression were censored.

Clinical benefit was defined as having a stable disease (SD), partial response (PR), or complete response (CR) with everolimus treatment. Time to treatment discontinuation (TTD) due to toxicity was defined as the time from start of everolimus to the time of discontinuation of everolimus secondary to everolimus-related toxicity. Patients with everolimus discontinuation due to progression or death and patient alive without progression were censored.

The rate of patients free from progression at 6 months and alive at 12 months was compared by Chi-squared test. Differences in baseline patient characteristics according to EEE were assessed using Chi-squared or Fisher's exact tests.

OS, PFS, and TTD rates along with standard deviations were estimated using the Kaplan–Meier method. Differences in OS, PFS, and TTD according to EEE were tested for significance using the log-rank test. Association of EEE with ORR was tested by logistic regression and expressed by odds ratio (OR) with their 95 % CI. *P* values were two-sided, with values <0.05 considered statistically significant.

Unadjusted risk ratios along with their 95 % confidence intervals were estimated by means of univariate Cox models and used to describe the relationship between the main prognostic factors and PFS and OS. Multivariate analyses using Cox models were performed for PFS and OS to test the association of EEE after adjusting for other prognostic factors. Because of the number of events (death or progression) described in our cohort and to have a sufficient power for the multivariate analysis, we decided to use a threshold of significance equal to 0.05 to include variables in the multivariate model in order to be more selective. Once the model chosen, we included the variable EEE to test its association with OS and PFS adjusted on others mean prognostic factors. Follow-up was calculated using reverse Kaplan–Meier estimation. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

## Results

### Patient characteristics and pharmacokinetic assessment

Forty-two consecutive adult patients with mRCC entered into this study. At the time of clinical data cutoff (August 2013), 28 progression events had occurred with 17 deaths. Median follow-up at data cutoff was 25.93 months (95 % CI 17.67–31.90). Patients and disease characteristics are summarized in Table 1. The Eastern Cooperative Oncology Group performance status (ECOG) was <2 for 27 patients (64 %). Most of the patients (98 %) had clear-cell renal cell carcinoma, and 35 patients (83 %) had undergone nephrectomy. Among these patients, 8 (19 %) had low risk, 28 (67 %) had intermediate risk, and 6 (14 %) had poor risk disease according to Heng criteria. Everolimus was mainly administrated as a second-line therapy after one prior systemic therapy targeting the VEGF pathway in 72 % of patients. Dose reduction was necessary for 21 patients. At the time of data cut off, everolimus was stopped for 39 patients (93 %), while everolimus was ongoing for 3 patients. Among the 39 patients who have stopped everolimus, 8 received everolimus as their ultimate line of systemic treatment. Among the 31 patients who received another post-everolimus treatment, all of them received AA targeted therapy. Median OS and median PFS of the whole cohort were 17.2 months (95 % CI 7.15–30.13) and 6.9 months (95 % CI 3.77–15.51), respectively. Patient outcomes differed according to their prognostic group (Heng classification) (Fig. 1).

In order to assess EEE, a total of 113 everolimus trough concentrations were analyzed after steady state.

**Table 1** Patient and disease characteristics of the whole cohort according to everolimus median blood concentration on the first 3 months of treatment

| | Total | | Everolimus median blood concentration on the first 3 months of treatment | | | | *p* |
|---|---|---|---|---|---|---|---|
| | | | <14 | | >14 | | |
| | *n* | % | *n* | % | *n* | % | |
| *Sociodemographic characteristics* | | | | | | | |
| Age (years) | | | | | | | 0.0195 |
| ≤75 | 29 | 69.05 | 11 | 52.38 | 18 | 85.71 | |
| >75 | 13 | 30.95 | 10 | 47.62 | 3 | 14.29 | |
| Missing value = 0 | | | | | | | |
| Sex | | | | | | | 0.0195 |
| Male | 29 | 69.05 | 11 | 52.38 | 18 | 85.71 | |
| Female | 13 | 30.95 | 10 | 47.62 | 3 | 14.29 | |
| Missing value = 0 | | | | | | | |
| *Patient characteristics* | | | | | | | |
| Heng | | | | | | | 0.2454 |
| Good | 8 | 19.05 | 2 | 9.52 | 6 | 28.57 | |
| Intermediate | 28 | 66.67 | 15 | 71.43 | 13 | 61.90 | |
| Bad | 6 | 14.29 | 4 | 19.05 | 2 | 9.52 | |
| Missing value = 0 | | | | | | | |
| Perfomance status ECOG | | | | | | | 0.1074 |
| <2 | 27 | 64.29 | 11 | 52.38 | 16 | 76.19 | |
| ≥2 | 15 | 35.71 | 10 | 47.62 | 5 | 23.81 | |
| Missing value = 0 | | | | | | | |
| *Disease characteristics* | | | | | | | |
| Histology | | | | | | | 1.0000 |
| Clear cell | 41 | 97.62 | 21 | 100.00 | 20 | 95.24 | |
| Others | 1 | 2.38 | 0 | 0.00 | 1 | 4.76 | |
| Missing value = 0 | | | | | | | |
| At least 2 metastatic sites | | | | | | | 0.1623 |
| Yes | 18 | 43.90 | 7 | 33.33 | 11 | 55.00 | |
| No | 23 | 56.10 | 14 | 66.67 | 9 | 45.00 | |
| Missing value = 1 | | | | | | | |
| CNS metastasis | | | | | | | 0.9590 |
| Yes | 4 | 9.76 | 2 | 9.52 | 2 | 10.00 | |
| No | 37 | 90.24 | 19 | 90.48 | 18 | 90.00 | |
| Missing value = 1 | | | | | | | |
| Pulmonary metastasis | | | | | | | 0.7385 |
| Yes | 29 | 69.05 | 14 | 66.67 | 15 | 71.43 | |
| No | 13 | 30.95 | 7 | 33.33 | 6 | 28.57 | |
| Missing value = 0 | | | | | | | |
| Pleural metastasis | | | | | | | 0.9387 |
| Yes | 8 | 19.51 | 4 | 19.05 | 4 | 20.00 | |
| No | 33 | 80.49 | 17 | 80.95 | 16 | 80.00 | |
| Missing value = 1 | | | | | | | |
| Hepatic/liver metastasis | | | | | | | 0.2142 |
| Yes | 7 | 16.67 | 5 | 23.81 | 2 | 9.52 | |
| No | 35 | 83.33 | 16 | 76.19 | 19 | 90.48 | |
| Missing value = 0 | | | | | | | |
| Bone metastasis | | | | | | | 0.0242 |
| Yes | 15 | 35.71 | 11 | 52.38 | 4 | 19.05 | |

**Table 1** continued

| | Total | | Everolimus median blood concentration on the first 3 months of treatment | | | | |
|---|---|---|---|---|---|---|---|
| | | | <14 | | >14 | | *p* |
| | *n* | % | *n* | % | *n* | % | |
| No | 27 | 64.29 | 10 | 47.62 | 17 | 80.95 | |
| Missing value = 0 | | | | | | | |
| Lymph node metastasis | | | | | | | 0.5366 |
| Yes | 20 | 47.62 | 9 | 42.86 | 11 | 52.38 | |
| No | 22 | 52.38 | 12 | 57.14 | 10 | 47.62 | |
| Missing value = 0 | | | | | | | |
| Other metastasis | | | | | | | 0.5359 |
| Yes | 17 | 44.74 | 9 | 50.00 | 8 | 40.00 | |
| No | 21 | 55.26 | 9 | 50.00 | 12 | 60.00 | |
| Missing values = 4 | | | | | | | |
| Nephrectomy | | | | | | | 0.2142 |
| Yes | 35 | 83.33 | 16 | 76.19 | 19 | 90.48 | |
| No | 7 | 16.67 | 5 | 23.81 | 2 | 9.52 | |
| Missing values = 0 | | | | | | | |

*CNS* central nervous system

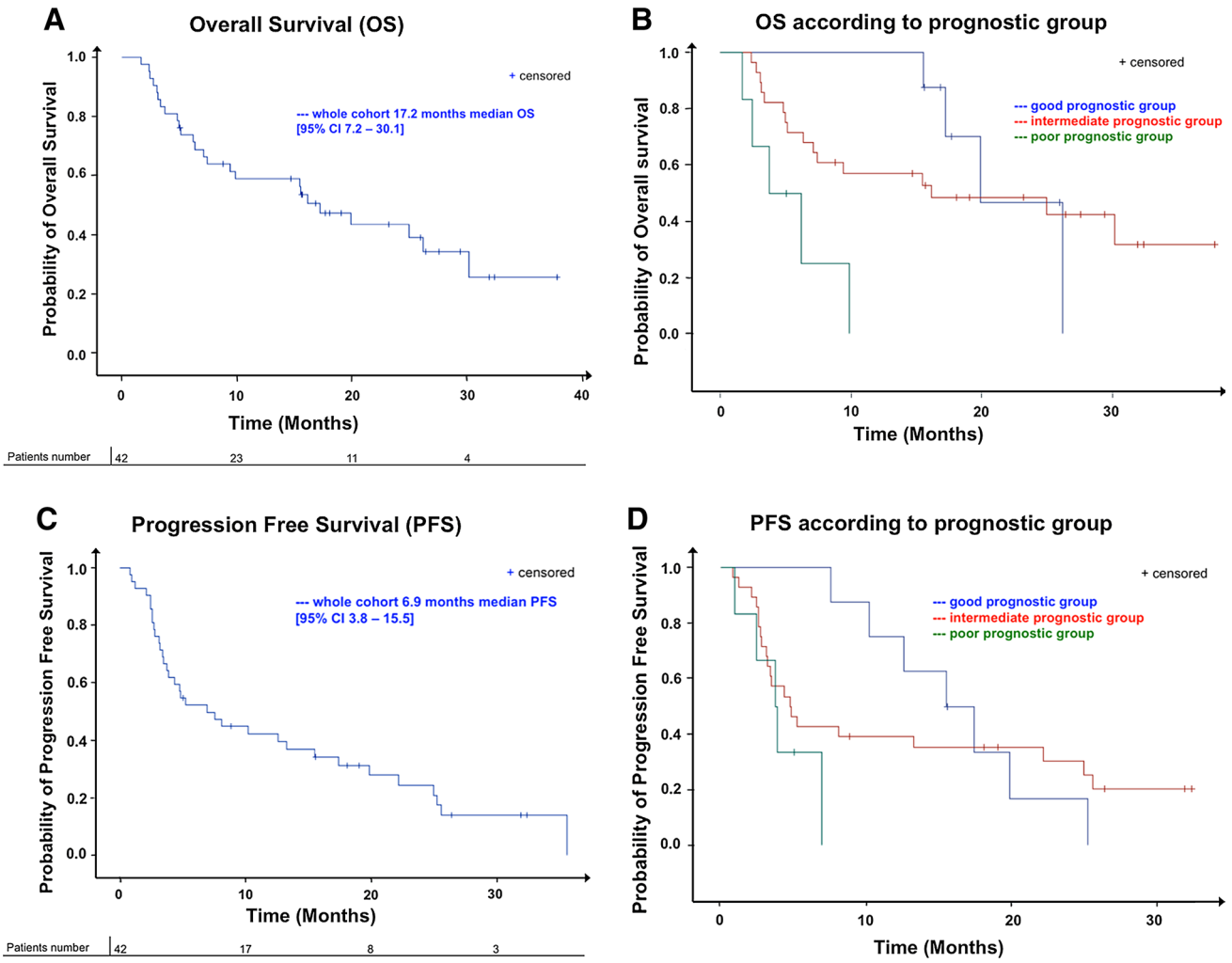


**Fig. 1** Survival data of the whole cohort. **a** OS, **b** OS according to prognostic group, **c** PFS, and **d** PFS according to prognostic group

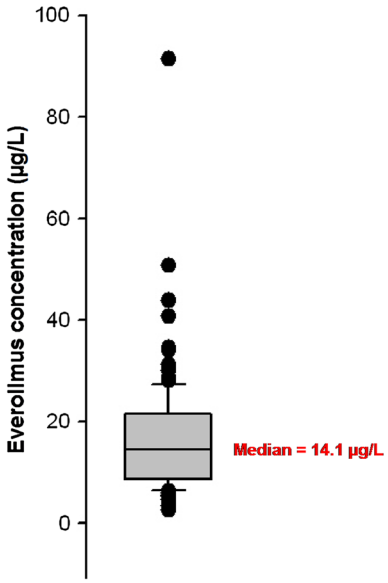


**Fig. 2** Box and whiskers plot showing the variability of the data. The *whiskers* and the *gray box* display, respectively, the 10th and 90th percentiles and the 25th median and 75th percentiles. The *white circles* represent the outliers

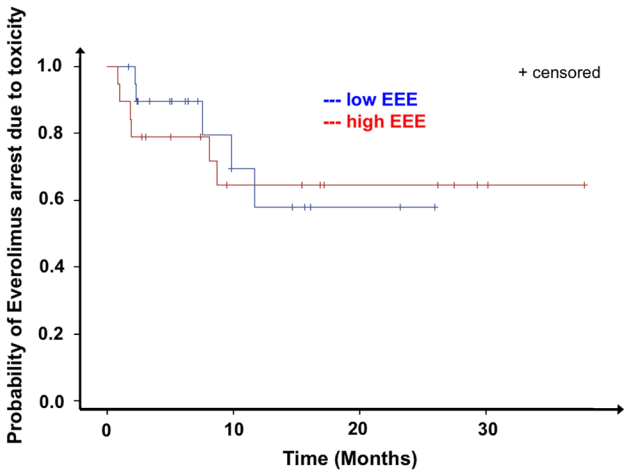


**Fig. 3** Probability or everolimus arrest for toxicity. *EEE* early everolimus exposure

They display large variability (77.2 %) with a median of 14.1 µg/L (range 2.6–91.5) (Fig. 2). Two cohorts were individualized according to EEE: below or above the median concentration of 14.1 µg/L. The 2 cohorts were well balanced with regard to patient characteristics. They only differed for age, sex, and bone metastasis (Table 1). A total of 59 and 54 concentrations were assayed in low and high EEE subgroups, respectively.

The median duration of treatment was 3.56 months (0.59–25.24) and 7.64 months (0.82–35.57) in patients with low and high EEE, respectively. The main reasons for treatment discontinuation included disease progression, adverse events, and death. Eleven (28 %) patients stopped everolimus due to toxicity with 5 patients and 6 patients with low and high EEE, respectively (Fig. 3). Such arrest occurred earlier within the first 6 months and was rarely observed thereafter as displayed on Fig. 3.

## Survival and response

Fourteen patients (67 %) in the high EEE subgroup were free from progression at 6 months versus 8 (38 %) patients in the low EEE subgroup ($p = 0.06$). Fifteen patients (71 %) in the high EEE subgroup were alive at 12 versus 10 patients (48 %) in the low EEE subgroup ($p = 0.12$). Median PFS in the high EEE subgroup was considerably longer than median PFS in the low-trough subgroup with 13.3 vs. 3.9 months, respectively; hazard ratio (HR 0.66 95 % CI 0.33–1.31; $p = 0.23$) (Fig. 4). Similarly, median OS of 26.2 months in the high-trough concentration group was longer in comparison with 9.9 months in the low-trough concentration group (HR 0.62 95 % CI 0.28–1.37; $p = 0.24$) (Fig. 4).

Clinical benefit (CR + PR + SD) was observed for 24 patients (55 %). Among the six patients (14 %) who had PR, five patients presented higher value of EEE. Two examples of patients with partial responses could be viewed on the online supplementary appendix figure 5. No CR was documented. The influence of EEE on ORR was in favor of higher concentration with an OR of 6.25 [0.66–59.02], nonsignificant ($p = 0.11$).

## Univariate and multivariate analysis

Univariate analysis (Table 2) found 2 significant potential prognostic factors that were associated with shorter PFS: central nervous system (CNS) metastasis ($p = 0.03$) and poor ECOG status ($p = 0.03$). In consequence, these variables were tested in the multivariate model. Once this model tested, the EEE variable was included and adjusted on other factors to test its effect on PFS. In multivariate analysis (Table 3), CNS metastasis and poor ECOG status were associated with lower PFS. When EEE was included in the model, only CNS metastasis remained significant, ECOG status significance disappeared, and a tendency favoring a relation between EEE value and longer PFS was observed.

Univariate analysis (Table 2) shown that 3 potential prognostic factors were significantly associated with shorter OS: CNS metastasis ($p = 0.04$), poor prognostic according to Heng classification ($p = 0.014$), and poor ECOG Status ($p < 0.01$). In consequence, variables tested in the model were Heng classification and CNS metastasis. ECOG status was not included in the model because

**Table 2** Univariate analysis of prognostic factors

| | Influence on PFS | | | | Influence on OS | | | |
|---|---|---|---|---|---|---|---|---|
| | HR | 95 % CI | | *p* | HR | 95 % CI | | *p* |
| Age | | | | | | | | |
| ≤75 versus >75 | 1.58 | 0.73 | 3.45 | 0.25 | 0.86 | 0.37 | 1.96 | 0.71 |
| Sex | | | | | | | | |
| Male versus female | 1.57 | 0.78 | 3.22 | 0.22 | 2.1 | 0.95 | 4.64 | 0.07 |
| Nephrectomy | | | | | | | | |
| No versus yes | 1.95 | 0.79 | 4.8 | 0.14 | 2.07 | 0.77 | 5.6 | 0.15 |
| At least 2 metastatic sites | | | | | | | | |
| Yes versus no | 2.09 | 0.96 | 4.37 | 0.06 | 1.75 | 0.75 | 4.05 | 0.19 |
| CNS metastasis | | | | | | | | |
| Yes versus no | 3.51 | 1.16 | 10.63 | **0.03** | 3.19 | 1.06 | 9.6 | **0.04** |
| Pulmonary metastasis | | | | | | | | |
| No versus yes | 0.791 | 0.374 | 1.675 | 0.54 | 0.82 | 0.35 | 1.91 | 0.64 |
| Pleural metastasis | | | | | | | | |
| Yes versus no | 1.38 | 0.6 | 3.21 | 0.45 | 2.01 | 0.79 | 5.09 | 0.14 |
| Hepatic/liver metastasis | | | | | | | | |
| Yes versus no | 1.98 | 0.76 | 5.1 | 0.16 | 2.03 | 0.71 | 5.77 | 0.19 |
| Bone metastasis | | | | | | | | |
| Yes versus no | 0.99 | 0.49 | 2.02 | 0.98 | 1.03 | 0.45 | 2.31 | 0.95 |
| Lymph node metastasis | | | | | | | | |
| Yes versus no | 1.74 | 0.87 | 3.47 | 0.11 | 1.9 | 0.85 | 4.26 | 0.12 |
| Dose reduction | | | | | | | | |
| Yes versus no | 1.25 | 0.62 | 2.48 | 0.53 | 1.27 | 0.57 | 2.8 | 0.56 |
| HENG | | | | 0.2 | | | | **0.014** |
| Good versus intermediate | 0.84 | 0.35 | 2.02 | 0.7 | 0.7 | 0.23 | 2.12 | 0.52 |
| Poor versus intermediate | 2.35 | 0.84 | 6.64 | 0.1 | 4.38 | 1.47 | 13.05 | **0.01** |
| ECOG | | | | | | | | |
| 2/3/4 versus 0/1 | 2.18 | 1.07 | 4.47 | **0.03** | 4.27 | 1.9 | 9.54 | **<0.01** |

Impact on PFS (progression-free survival) and OS (overall survival)

Significant *p* values are highlighted in bold characters

*CNS* central nervous system

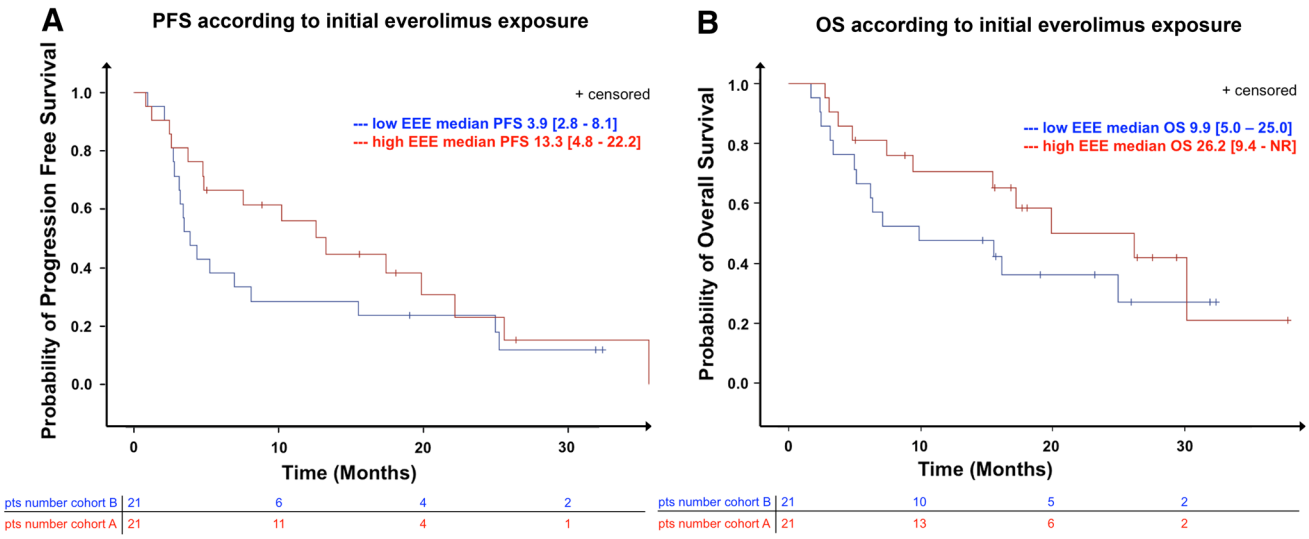


**Fig. 4** Survival data according to the first 3 months median trough everolimus concentration. **a** PFS and **b** OS. *EEE* early everolimus exposure, *pts* patients

**Table 3** Multivariate analysis of prognostic factors

| | HR | 95 % CI | | *p* |
|---|---|---|---|---|
| *Multivariate model with factors associated with PFS without EEE* | | | | |
| ECOG 2/3/4 versus ECOG 0/1 | 2.25 | 1.08 | 4.67 | **0.03** |
| CNS metastasis | | | | |
| Yes versus no | 3.55 | 1.15 | 10.94 | **0.03** |
| *Multivariate model with factors associated with PFS with EEE* | | | | |
| Everolimus blood concentration on the first 3 months of treatment | | | | |
| >14 versus ≤14 | 0.78 | 0.35 | 1.74 | 0.55 |
| ECOG 2/3/4 versus ECOG 0/1 | 2.00 | 0.88 | 4.54 | 0.10 |
| CNS metastasis | | | | |
| Yes versus no | 3.64 | 1.17 | 11.3 | **0.02** |
| *Multivariate model with factors associated with OS without EEE* | | | | |
| CSN metastasis | | | | |
| Yes versus no | 4.07 | 1.28 | 12.93 | **0.02** |
| HENG | | | | |
| Good versus intermediate | 0.61 | 0.19 | 1.93 | 0.4 |
| Bad versus intermediate | 4.57 | 1.51 | 13.87 | **0.01** |
| *Multivariate model with factors associated with OS with EEE* | | | | |
| Everolimus blood concentration on the first 3 months of treatment | | | | |
| >14 versus ≤14 | 0.6 | 0.25 | 1.46 | 0.26 |
| CSN metastasis | | | | |
| Yes versus no | 4.55 | 1.39 | 14.91 | **0.01** |
| HENG | | | | |
| Good versus intermediate | 0.7 | 0.22 | 2.28 | 0.55 |
| Poor versus intermediate | 4.14 | 1.36 | 12.63 | **0.01** |

Impact on PFS (progression-free survival) and OS (overall survival). Results are displayed with or without taking into account of EEE (early everolimus exposure)

Significant *p* values are highlighted in bold characters

*CNS* central nervous system

of colinearity with Heng Classification. Once this model tested, the variable EEE was included to test its association with OS adjusted on others majors prognostic factors. In multivariate analysis (Table 3), poor Heng status and/or SNC metastasis remained associated with lower OS. When EEE was tested in the model, SNC metastasis and bad Heng status remained significant, and a tendency favoring a relation between EEE value and longer OS was observed.

## Discussion

In this study, our population had PFS and OS in line with literature with clear discrepancy according to Heng classification. The median PFS (6.9 months) and OS (17.2 months) of our cohort were comparable to the RECORD1 clinical trial data published by Motzer [5]. Wide variability of EBC with a median of 14.1 µg/L (range 2.6–91.5) was observed. These results underline interpatients EBC variability as shown in Fig. 2, this fact must be taken into account because of the proven impact of this pharmacological parameter on everolimus activity in other pathologies [9, 10]. In the present study, while comparing patients with high EEE versus low EEE, the oncological outcomes differed as displayed in Fig. 4. Our study has shown a trend ($p = 0.06$) for patients to be free from progression at 6 months of everolimus favoring higher EEE. Patients in the higher EEE subgroup had longer median PFS and OS than patients with lower EEE with 13.3 and 26.2 months versus 3.9 and 9.9 months, respectively. The same trend was observed for PRs. When EEE was included in multivariate analysis, a tendency for a relation between treatment concentration and PFS or OS was observed. The small study size did not allow the difference to be significant, nevertheless the tendency of higher efficacy with high EEE may suggest the need to plan a PK monitoring of everolimus.

The impact of drug exposure on its activity has been demonstrated in mRCC setting for 2 AA TKI: sunitinib and axitinib. Pooled analysis of various clinical trials with sunitinib or axitinib has shown PK impact on retrospective analysis [13–15]. Besides Rini et al. underlined the importance of early exposure to axitinib, which was more relevant than overall exposure [15]. Then, a prospective phase II randomized trial confirmed that optimal axitinib exposure has a statistical significant positive influence on ORR [14].

Everolimus is more often administrated beyond the first line of systemic therapy in patients with mRCC. In this second- or third-line setting, expected median PFS are short with 3.6 months for sorafenib in third line in GOLD Trial [19], 5.4 months for everolimus after one prior TKI in RECORD1 trial, 4 months for everolimus after 2 prior TKI in RECORD1 trial [20], and 4.8 months for axitinib in patients previously treated by sunitinib in AXIS trial [21]. Therefore, optimal early exposure is of particular importance: if underexposed, patients may not benefit of the molecule and progress rapidly at first tumor assessment. While regarding PFS according to EEE, we observe many early events in the low EEE subgroup with 62 % of patients progressing within the first 6 months of everolimus and only 33 % in the high EEE subgroup.

Collectively, our results may suggest associations between EEE and everolimus activity in mRCC setting. To be fully validated, this concept must be explored inside larger cohorts of patients and inside prospective pharmacological dedicated clinical trials, such as the one designed by Rini et al. with axitinib [14].

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