BACKGROUND
Sunitinib, a potent multi-tyrosine kinase (TK) inhibitor, is a standard first-line treatment for metastatic renal cell carcinoma (mRCC). Sunitinib is known to have immune-modulating properties especially on regulatory T-cells and tumor-infiltrating lymphocytes. However, data is sparse about sunitinib impact on peripheral lymphocytes.

OBJECTIVES
To investigate the ex vivo effect of sunitinib and its active metabolite SU12662 on peripheral blood mononuclear cells (PBMC) from naïve mRCC patients using a high throughput kinomic profiling method.

METHODS
1- Retrospective study
- 88 mRCC patients under sunitinib therapy from June 2006 to January 2015
- Baseline clinical and biological parameters were collected
- Haematological specifications were gathered at Day 0 and Day 21 (expressed as a ratio D21/D0) of the first cycle of treatment
- Progression Free Survival (PFS) was estimated with the Kaplan-Meier method
- Factors with a p-value lower than 0.10 in univariate cox model were entered into a multivariate analysis.

2- Kinomic study
- 21 naïve mRCC patients and 12 healthy volunteers
- TK activity profiles of PBMC lysates were generated on TK PamChip® microarrays (Figure 1)
- The ex vivo effect of sunitinib and its active metabolite SU12662 were determined in PBMC from mRCC patients.
- All data were analyzed using BioNavigator® software.

RESULTS
1- Association between increased D21/D0 total peripheral lymphocytes ratio and shorter PFS
- Median PFS : 234 days (confidence interval, C.I[95%], 179-289).
- Lymphocyte D21/D0 ratio; ECOG 0-1 and Body Mass Index (BMI) were independently associated with PFS (Table 1).

2- Basal TK activity in PBMC from naïve mRCC patients
- Large Interindividual variability in patients' kinomic profiles (Figure 2).
- Phosphorylation level in PBMC from mRCC patients was lower than healthy volunteers for 74 peptides (p<0.05).

3- Ex vivo sunitinib effect was associated with Heng prognostic model and D21/D0 lymphocytes ratio in patients
- Sunitinib and SU12662 decreased phosphorylation level for majority of peptides.
- Sunitinib had a stronger inhibitory effect than SU12662 for 80 peptides (p<0.05).
- A lower ex vivo sunitinib inhibition was significantly (p<0.05) correlated with:
  - a poor prognosis according to Heng score (Figure 3A) for 53 peptides.
  - an increased D21/D0 lymphocytes ratio (Figure 3B) for 16 peptides.

CONCLUSIONS
These preliminary results suggest that kinomic profiling of PBMC, could be a promising approach
- To investigate and decipher molecular mechanisms involved in sunitinib-induced immunomodulatory effects.
- To seek future biomarkers.

Further investigations are ongoing to determine the involvement of signaling pathways contributing to the inter-individual variability in kinomic profiles of PBMCs from mRCC patients treated with sunitinib.