**Introduction**

Sequential targeted therapy is standard in patients (pts) with advanced or metastatic Clear-Cell Renal Cell Carcinoma (CCRC). Clinical Practice Guidelines exist for first and second lines. Several recent studies have shown promising results for TKI in combination with checkpoint inhibitors (CI).

**Methods**

- **Radiotherapy** (RT): 37 pts (12%)
- **Surgery** of metastasis: 118 pts (38%)
- 1 to 4 surgeries

**Toxicity**

- **TKI**
  - **Weight**
  - **N**
  - **grades 1, 2, 3, 4**
  - **Other**
  - **Median DCT**
  - **TKI and mTOR/other drugs could induce clinical benefit even in line 3 and further.**

**Population description**

- **386 patients** included between May 2011 and Sept 2014 (17 centres)
- First analysis only on 301 good/intermediate prognostic pts
- Sex ratio: 213 Men (71%) / 88 Women
- Mean age: 66 years (35-91) (n=10)
- **CCRC**: 88%; papillary-tubular carcinoma: 7%; chromophobe carcinoma: 1%; others: 2%; Not Known: 2%;
- Karnofsky index: i=1-10; 30%; ii=11-40; 58%, Not Known: NK: 6%, Not Applicable (NA): 5% (no surgery).
- Surgery of primary tumor: 90%
- Median rof of life: 2.3 [17,]

**Treatment Efficacy and Disease Control Time**

- **TKI**
  - **OS**
  - **First line**
  - **TKI-R**
  - **EVEROLIMUS**
  - **EVEROLIMUS TKI-R**
  - **EVEROLIMUS-R**
  - **TKI (if... or IFN + BEVACIZUMAB TKI EVEROLIMUS or TKI (if stopped for toxicity)**
  - **GOOD and INTERMEDIATE**
  - **POOR**

**Results**

**No impact of ttt sequence in the OS of shorter or longer 1st line DCT population**

**Discussion / Conclusion**

Results from a broad prospective multicenter study have been shown here in order to evaluate a sequential treatment strategy for metastatic renal cancer in real life before the development of immunotherapy. It is important to note and keep in mind that the proportion of treated patients decreased between line. 83% and 14% of patients could benefit respectively from a 3rd and a 4th therapeutic line with quite high clinical benefit: around 60% in line 3 (n=151) and 50% in line 4 (n=448). Median DCT has been respectively between 6 and 7 months in 3rd line and 6 months in 4th line. For patients with more than 3 lines, first line DCT seems to condition the overall survival. Patients with longer 1st line DCT (DCT > median DCT) had a better OS than patients with shorter DCT whatever the subsequent lines were used - TKI-TKI-mTOR vs TKI-mTOR-TKI: Grade III and IV toxicities appeared more important than in the literature.

To conclude, some patients could benefit of more than 2 lines of treatment which contributes to chronic disease. 1st line treatment choice seemed to be important because it could condition the overall survival. Treatments sequence will be upset by the arrival of immunotherapy.