IVOIRE STUDY : Efficacity and safety of Oral Drugs treatment in CCRCC : Focus on each therapeutic line and drugs.

Results of a prospective multicentric non-randomised study

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Observatoire dédié au Cancer Bretagne / Pays de la Loire
http//www.omeditbretagne.fr ; http//www.omedit-paysdelaloire.fr

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Introduction

Sequential targeted therapy is standard in patients (pts) with advanced or metastatic **Clear-Cell Renal Cell Carcinoma** (**CCRCC**). Clinical Practice Guidelines exist only for first and second lines.
Few recommendations exist for third-line treatment and further.

Observatory of Cancer Bretagne Pays de la Loire

- Created in 2003 by Regional Representatives of French ministry of health
- Collects data from both private and public hospitals
- Provides a reflexion on drug management to optimize health care

Methods

- Exploratory recommendations for third line-treatments (ttt) and further have been proposed according to the risk (Memorial Sloan Kettering Cancer Center-MSKCC) :
- In 3rd line, pts who had not received everolimus yet were proposed to receive it. Pts who had failed 2nd line ttt with everolimus were proposed to rechallenge with another Tyrosine Kinase Inhibitor (TKI) **only if they had experimented a disease control ≥ 6 months in first line-treatment with TKI.** Before the approval of axitinib (end of 2010), the probability to respond to a second line TKI was thought to be greater if pts experimented a Disease Control Time (DCT) > 6 months previously. It was not modified then.
- For the 4th line and for further lines, TKI or everolimus were rechallenged according to the same criteria.

Prognosis (Motzer* or Heng*)	L1	L2	L3	L4
GOOD and INTERMEDIATE	IL2 + IFN or IFN + BEVACIZUMAB	TKI	EVEROLIMUS or TKI (if stopped for toxicity)	TKI-R EVEROLIMUS
	TKI	EVEROLIMUS TKI	TKI-R EVEROLIMUS	EVEROLIMUS-R TKI R
POOR	TEMSIROLIMUS TKI	TKI EVEROLIMUS		

* Motzer *et al*, 2004 ; * Heng *et al*, 2009.

IL2: Interleukin-2; IFN: Interferon-alpha; TKI: Tyrosine Kinase Inhibitor; R: re-challenge

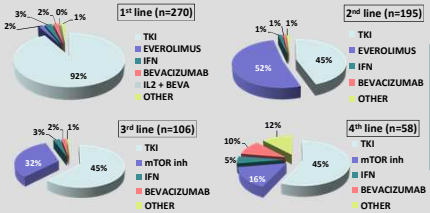
- IVOIRE was a prospective multicentric non randomized study with the main purpose of **evaluating this strategy.**
- Advanced or metastatic RCC pts were included almost during 1st and 2nd line-treatment.
- Secondaries objective were:
  - For each line:
    - **Best response** (RECIST) and Grade III/IV **toxicity**
    - **Disease Control Time** (DCT) : defined as the time from the first day of treatment to the day before the next one, no matter what happened : short break for toxicity, patient wishes, metastasis resection, radiotherapy, …
  - **Overall Survival** (OS): defined as the time from metastatic disease to death.
  - **Optimization** of medical care

Population description

- **270 patients** included between **Sept 2011 and Sept 2014 (17 centers)**
- **Sex ratio :** 196 Men (**72%**) / 74 Women
- **Median age :** 65.5 years [35-90]
- **CCRCC** : 86% ; Fuhrmann grade : I-II : 32%; **III/IV : 54%,** NK : 14%
- **Surgery** of primary tumor **:** 86.3 %

Efficacity of treatment lines/Dose adjustment

- **Description of the 4 first lines**



- **39%** of patients have received a **3rd line-treatment**
- **4th line-ttt : 21%**
- **5th line-ttt : 22 pts** (TKI: 14 ; mTOR Inh: 3)
- **6th line-ttt : 7 pts** (TKI: 2 ; mTOR Inh: 3)

mTOR inh : Inhibitor of mammalian Target Of Rapamycine

- **Treatment response and Disease Control Time**

TTT	Criteria	L1 n = 270	L2 n = 195	L3 n = 106	L4 n = 58	L5/6 n=22/7
TKI	n	248	87	66	33	14/2
	Best response	CR+PR : 46% SD : 30 % PD : 16 % NA : 8 %	CR+PR : 28 % SD : 38 % PD : 20 % NA : 14 %	CR+PR : 15 % SD: 39 % PD: 35 % NA : 11 %	PR : 12 % SD: 24 % PD: 30 % NA : 34 %	*PR : 3/0 pts SD: 6/0 pts PD: 2/1 pts* NA : 3/1 pts
	Median DCT Months [Q1-Q3]	12.9 [6.4-23.1]	7.1 [3.4-13.4]	6.2 [3.2-12.1]	3.7 [1.4-9.4]	*Not done*
Everolimus	n	5	101	28	8	3/2
	Best response	*SD : 4 pts PD : 1 pt*	PR : 9 % SD: 44 % PD: 26 % NA : 21 %	PR : 4 % SD: 46 % PD: 36 % NA : 14 %	*SD: 3 pts PD: 2 pts* NA : 3 pts	*PR : 1/0 pts SD: 0/2 pts* NA : 2/0 pts
	Median DCT Months [Q1-Q3]	*Not done*	6.9 [2.8-12.4]	5.3 [2.0-8.1]	1.6 [0.8 - 4.2]	*Not done*
Others ttt	n	17	7	12	17	5/3

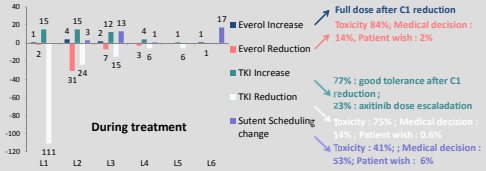
Clinical benefit (CR + PR + SD) : **line 3 :** 54 % for TKI and 51% everolimus
line 4 : 36 % for TKI.

OS: **59 months [50-73].**
Poor risk pts treated by temsirolimus in first line are not presented here.

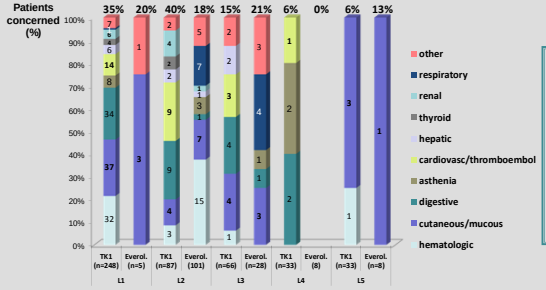
- **Dose adjustment**

Before the beginning of the 1st cycle

%	L1	L2	L3	L4
TKI	13%	14%	20%	30%
Everolimus	1 pts/5	9%	11%	13%



Safety : Grade III and IV Toxicities

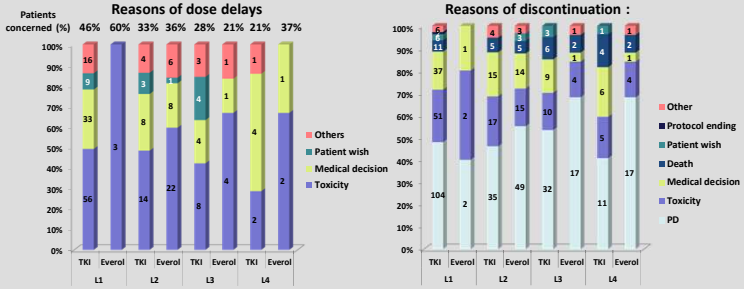


During 1st and 2nd line:
-1/3 patients presented major toxicity with TKI
-1/5 with everolimus

Toxicity previously described : 10% in first line (Motzer 2007, Escudier 2007)

⇒ Real life patients

Dose delays and discontinuations



Conclusion

- Advanced/metastatic CCRCC pts received 1st and 2nd line-treatments according to published guidelines.
- **Toxicity** does not seem to be an obstacle to the use of oral drugs for 3rd and 4th line ttt : in fact the major reason for **treatment discontinuation** was disease **progression**.
- **Substantial clinical benefit** and control disease time could be observed. It seems to be interesting for **patients in good condition to be treated by TKI or mTOR inhibitor in 3rd line or further.**
- With the succession of effective therapeutic lines, **chronicisation** of this disease can be observed.
- These therapeutic lines will be deeply modified with the use of nivolumab or cabozantinib in current practice.

Short-term outlook : Optimization of Care : anticipate side-effects and interaction, improve patient's observance

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