# Metastatic chromophobe renal cell carcinoma treated with targeted therapies: a Renal Cross Chanel Group (RCCG) study

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**Abstract**

Background: Treatment of non-clear cell RCC remains controversial despite several recent prospective studies of targeted therapies (TT). Often VEGF and mTOR inhibitors are used, extrapolating the data from use of these agents in clear cell RCC.

Methods: We performed a retrospective data analysis within the Renal Cross Channel Group to determine mChRCC outcomes in the targeted therapy era. The endpoints were overall response, overall survival (OS) and time to treatment failure (TTF). The 2 latter were estimated using the Kaplan-Meier method.

Results: 91 mChRCC patients from 26 centers were included. Median follow-up from date of first metastasis was 6.1 years (range: 0-13.9). Median overall survival was 37.9 months (95%CI: 21.4 to 46.8) from diagnosis of metastatic disease. Among the 61 patients who received TT, 50 (82%) were treated with antiangiogenic (AA) and 11 with mTOR inhibitors. Median TTF and OS in patients receiving a first line of AA was 8.7 months (95%CI: 5.2-10.9) and 22.9 months (95%CI: 17.8-49.2) versus 1.9 (95%CI: 1.0-6.0) and 3.2 months (95%CI: 2.3-Not Evaluable) with mTOR inhibitors, respectively. A stratified log-rank test was used to compare AA and mTOR inhibitors TT while controlling the effect of the IMDC score and no significant difference between AA and mTOR inhibitors was observed for TTF (p= 0.26) or for OS (p=0.55).

Conclusion: We report the largest retrospective cohort of patients with mChRCC treated with TT and no significant difference between AA and mTOR inhibitors was observed for TTF and OS.

Key words: non-clear cell RCC, chromophobe RCC, metastatic, anti angiogenic, VEGF, mTOR

## Introduction

Over the past 12 years, the therapeutic arsenal against renal cell carcinoma (RCC) has widely expanded, with median overall survival increasing to almost 30 months in recent studies[1]. Prospective studies have shown that targeted therapy (TT) increases overall survival (OS) in metastatic clear cell, but the benefit in the other subtypes remains unclear.

Chromophobe renal cell carcinoma (ChRCC) is the second commonest form of non clear cell RCC (nccRCC) (4-6%) after papillary RCC (10-15%)[2]. Systemic therapy targeting VEGF and mTOR pathways have shown some efficacy in nccRCC, but to date little is known about the activity of monoclonal antibody directed against the program death 1 (PD 1)/ program death ligand 1 (PDL 1) pathway[3], and newer VEGF TT[4]. Indeed, two randomized studies investigated targeted therapy in a pool of mixed non clear cell histologies[5,6] and few prospective single arm trial (RAPTOR[7], SUPAP[8]) focus on papillary RCC.

First described by Thoenes in 1985[9], ChRCC probably derived from the intercalated cells of the collecting duct system. Surgical cohorts suggest that localized ChRCC displays a more favorable prognosis than papillary or clear cell RCC (ccRCC) with only 1.5% -8.6% of patients developing recurrence or metastasis[10,11] and a specific mortality around 2%[12,13].

Most of the data about metastatic ChRCC (mChRCC) comes from retrospective small series (3 to 37 patients) or rare phase 2 studies enrolling a heterogeneous population of nccRCC so then no standard of care is defined in ESMO[14] and NCCN guidelines[15] for mChRCC patients. In our study, we identified a large cohort of mChRCC to describe clinical outcomes with the use of TT.

## Methods

### Study design and population

In 2012, we initiated a retrospective chart review of mChRCC patients treated within the French kidney group of the GETUG (Groupe d'Etude des Tumeurs Uro génitales) and the Renal Cross Channel Group (RCCG). Eligibility criteria included adult patients who had measurable disease by RECIST (Response Evaluation Criteria in Solid Tumors) and received TT. ChRCC diagnosis

was performed by local pathology assessment. Standardized chart review collected date of diagnosis, age at diagnosis, gender, date of first metastasis, number and type of metastatic site at the initiation of systemic therapy and prognostic factors according to the IMDC risk model[16]. No central pathology review was provided, imaging was not standardized and response by RECIST was determined locally.

**Statistical Analyses**

The patients' characteristics (sex, age at diagnosis, KPS, number of metastases, IMDC risk model, MSKCC classification, prior nephrectomy and grade) were described (median and interquartile (IQR) for continuous variables and frequency for categorical variables) in TT patients and overall. Median follow-up was estimated by the Schemper's method[17] from the date of first-line therapy for patients treated with TT. For TT patients, the different types of TT classified as anti-angiogenic (AA: sunitinib, sorafenib, pazopanib and bevacizumab) or mTOR inhibitors (temsirolimus, everolimus) and the number of lines of therapy were reported. The patients' characteristics of these 2 groups were also reported and compared. The best response was determined by local assessment every 8-12 weeks according to RECIST 1.1 criteria as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) and the objective response rate (ORR) defined as CR/PR, SD or PD were described. The latter was compared between the 2 classes of targeted therapies by a Fisher's exact test. The time to failure (TTF) was defined as the time from the date of first-line therapy to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death. Patients with no treatment failure were censored at the date of last follow up. Overall Survival (OS) was defined as the time from the first-line therapy to death. Patients alive were censored at the date of last follow-up. These 2 time-to-events were estimated by the Kaplan-Meier (KM) method and median with its 95% confidence interval (CI) was reported. We compared TTF and OS between (i) IMDC prognostic groups (log-rank test) and (ii) targeted therapies (AA and mTOR) (stratified log-rank test). For the latter, no interpretation can be done based on the KM estimation considering the observational type of this study. The cut-off date for the analyses was December 31 2015. The statistical analyses were done with SAS software 9.4. (SAS Institute).

## Results

### *Overall mChRCC cohort*

We collected data from 91 mChRCC patients from 26 centers in 4 countries (France, UK, Italy and Australia) (Figure 1). Patients had been diagnosed from July 1997 to April 2013. Median follow-up from date of first metastasis was 6.1 years (range: 0-13.9). Patient and tumor characteristics are described in Table 1. Median age at diagnosis was 58 years (IQR: 49.0- 66.6) with a majority of men (64.4%, n= 58). Most patients had a nephrectomy (92%, n=83). Median time from diagnosis to metastasis was 9.4 months (IQR: 0.7-37.7). Median time from metastasis to first-line treatment was 3.5 months (IQR: 1.1-13.4). In our cohort, 24.4% (n=22) had metachronous metastases while 75.6% (n=68) were synchronous. Abdominal lymph nodes were the most common site of metastasis while lung and liver metastases appeared to be less common. International Metastatic RCC Database Consortium (IMDC risk model) prognosis groups were favorable for 10.3% (n=6), intermediate for 69.0% (n=40) and poor for 20.7% (n=12) patients. The score was not available for 32 patients (35.6 %) because of missing data. The median OS from date of first metastasis was 37.9 months (95%CI 21.4 to 46.8) (58 deaths).

### *mChRCC patients treated with targeted therapy*

Sixty eight of the 90 mChRCC patients received medical treatment, mostly TT (n=64), or other systemic therapy: interferon alone (n=2), vinflunine or hormonal therapy (one each). The remaining 22 patients never received systemic therapy, among which 6 were treated with surgery alone on oligometastatic disease, to delay systemic therapy (Figure 1). Among the 64 patients treated with TT, 3 were excluded from the analysis because of missing data. The median follow-up of the 61 treated patients from date of first line of treatment was 4.1 years (range: 1.1-7.7). The IMDC risk model was analyzed in 72.1% (n=44) of 61 patients: 2.3% (n=1) patients were in the favorable prognosis group, 77.3% (n=34) in the intermediate prognosis group and 20.5% (n=9) in the poor prognosis group. Out of the 61 patients, 50 (82.0%) and 11 (18.0%) were treated in first line by AA and mTOR inhibitors, respectively. *S*econd line therapy was

administered in 30 (49.2%) patients: 14 patients were treated with AA (46.7%) and 16 (53.3%) with mTOR and third line in 11 (18.0%) patients. The patients' characteristics treated with AA and mTOR were significantly different except for gender and the number of metastatic sites. It is interesting to note that most of AA patients had intermediate IMDC risk group (n=32, 88.9%) compared to mTOR patients (n=2, 25.0%) ($p<0.001$, n=44) (Table 1). The different types of TT are reported in table 2.

***Response rate***

Among patients treated by targeted therapy, the response were: CR: 1.9% (n=1), PR: 23.1% (n=12), SD: 44.2% (n=23) and PD: 30.8% (n=16) (9 had missing data) (Table 3). The ORR was CR/PR: 25.0 % with no significant difference between AA (CR/PR: 28.9% (n=13), SD: 42.2% (n=19) and PD: 28.9% (n=13)) and mTOR inhibitors (CR/PR: 0.0% (n=0), SD: 57.1% (n=4) and PD: 42.9% (n=3)) ($p=0.28$, Fisher's exact test). Even if the observed numerical difference of ORR between AA and mTOR is important (28.9% vs 0.0%) the statistical test is not significant due a lack of power. However, even if this difference had been significant, caution is necessary in interpreting this result because of the risk of confounding bias due to the observed unbalance of patients' characteristics between AA and mTOR (Table 1). Furthermore, clinical benefit (defined as CR/PR/SD) appears similar in both groups (71.1% vs 57.1% in AA and mTOR, respectively $p=0.66$).

***Time to Treatment Failure***

The median TTF from the date of first-line therapy for mChRCC was 7.2 months (95%CI: 4.1-9.5) with 61 events. Median TTF was 8.7 months (95%CI: 5.2-10.9) and 1.9 months (95%CI: 1.0-6.0) in patients treated with AA and mTOR inhibitors, respectively (Figure 2A). We reported unadjusted Kaplan-Meier curves between these 2 groups only for description. Median TTF was significantly higher in intermediate IMDC group (8.0 months (95%CI: 4.1-13.6)) compared to poor IMDC group (2.3 months (95%CI: 0.7-8.0)) ($p=0.001$) (Figure 2B). The favorable IDMC group was not collapsed with intermediate group. Given the limited number of patients to

construct a model to estimate the treatment effect controlling for several confounders, a stratified log-rank test was used to compare the targeted therapies (AA and mTOR inhibitors) while controlling the effect of the IMDC score. No significant difference between AA and mTOR inhibitors was observed for TTF (p= 0.26).

### *Overall Survival*

Median OS was 20.8 months (95%CI: 11.6-35.2) in the treated population with 43 deaths (70.5%). Median OS was 22.9 (95%CI: 17.8-49.2) and 3.2 months (95%CI: 2.3-Not Evaluable) in patients treated by AA and mTOR inhibitors respectively (Figure 2C). Median OS was 22.8 months (95CI%: 13.7-82.4) and 4.3 months 95%CI: 1.1-35.2) in intermediate and poor prognosis group according to IMDC risk model respectively (p<0.005, log rank test) (Figure 2D), one patient has favorable prognosis. With stratified log-rank test to compare AA and mTOR inhibitors while controlling the effect of the IMDC score, no significant difference between AA and mTOR inhibitors was observed for OS (p= 0.55).

## Discussion

We report a large series of patients with mChRCC treated with TT. For several decades, nccRCC has been considered as a global entity. Recently two dedicated randomized phase 2 trials compared everolimus and sunitinib in patients with metastatic nccRCC (Supplementary Table 1). In the first trial (ESPN), median PFS from first-line therapy was 6.1 months (95%CI: 4.2-9.4) with sunitinib and 4.1 months (95%CI: 2.7-10.5) with everolimus and median overall survival (OS) was 16.2 months (95%CI: 14.2-NA) with sunitinib and 14.8 months (95%CI: 8.0-23.4) with mTOR inhibitors (p= 0.18)[5]. The second trial (ASPEN), median PFS was 8.3 (80%CI: 5.8-11.4) versus 5.6 (80%CI: 5.5-6.0) months with sunitinib and everolimus respectively[6]; hazard ratio (HR) was 1.41 (80%CI: 1.03-1.92), (p= 0.16). Median OS was 31.5 months (80%CI: 14.8-NR) with sunitinib versus 13.2 months (80%CI: 9.7-37.9) with everolimus. Respectively, mChRCC patients accounted for 12/72, and 16/108 patients in ESPN and ASPEN. RECORD-3, a randomized phase 2 trial in metastatic RCC, comparing the sequence of everolimus followed by

sunitinib at progression to the opposite sequence, enrolled both ccRCC and nccRCC patients. In the subgroup analysis of 66 nccRCC patients, everolimus did not yield better results than sunitinib as first line therapy; median PFS were 5.1 and 7.2 months respectively, (HR: 1.54 95%CI: 0.86-2.75), mChRCC accounted only for 2% and 3% of patients in each arm[18]. A very recent systematic review with inter-trial meta-analysis investigated patients with metastatic nccRCC and concludes a trend toward favoring AA for PFS and OS compared to mTOR, but statistical significance was not reached[19].

In 2007, the Global ARCC trial suggested that responses were seen with temsirolimus in nccRCC[20]; among 73 patients with nccRCC, median OS was 11.6 (95%CI: 8.4-14.5) with temsirolimus vs 4.3 (95%CI: 3.2-7.3) with IFN alone[21]. Stadler reported in nccRCC subgroup analysis of sorafenib expanded access program (EAP) (n= 588), a median PFS of 24 weeks (n= 202)[22]. Within the sunitinib EAP (n= 4349), Gore reported a median PFS of 7.8 months (95%CI: 6.3-8.3) compared to 10.9 (95%CI: 10.3-11.2) months for those with ccRCC, and OS was 13.4 months (95%CI: 10.7-14.9) for nccRCC vs 18.4 months (95%: 17.4-19.2) in the entire population[23].

Before the TT era, Motzer reported that median OS was 9.4 months for a nccRCC cohort, with 29 months for mChRCC[24] subgroup. In the TT era, the subgroup analyses from Kroeger et al, reported median OS of 12.8 months (95%CI: 11.0-16.1 months) for all nccRCC cohort[16]; median OS was 27.1 months for mChRCC (95%CI: 12.6-75.3 months), 14.0 months for pRCC (95%CI: 10.9-17.1 months), and 10.1 months (95%CI: 5.1-13.2 months) for unRCC patients. Furthermore, it demonstrated the applicability of the IMDC prognostic model in nccRCC treated with first line TT: median OS of the three IMDC risk groups were 31.4 months (95%CI: 14.2-78.3 months), 16.1 months (95%CI: 12.5-18.7 months), and 5.1 months (95%CI: 2.7-7.1 months) respectively.

In our study, median OS was 22.8 months (95%CI: 13.7-82.4) in intermediate prognosis risk group and 4.3 months (95%CI: 1.1-35.2) in poor prognosis risk group ($p<0.005$, log rank test) (Figure 2D). Similarly, in the retrospective study cohort from Choueiri et al. median OS was 19.4 months in a mixed cohort of pRCC and ChRCC patients treated with sunitinib[25].

In 2016, Keizman et al. investigated retrospectively the clinical outcome with AA for mChRCC within 36 patients from 10 centers[26]. Metastatic ChRCC patients were individually matched to

metastatic ccRCC patients by known prognosis factors. Treatment outcome was not different between metastatic ChRCC and ccRCC patients: median PFS was 10 versus 9 months (HR: 1.4; p=0.6). Median OS was 26 versus 25 months (HR: 1.15; p=0.7).

In our study, OS was 20.8 months (95%CI: 11.6-35.2) for patients treated with TT, and median OS from diagnosis of metastatic disease for the 90 patients was 37.9 months (CI95%: 21.4-46.8).

Our work is not without limitations inherent to its retrospective nature. Our work is not without limitations inherent to its retrospective nature. Among them, are the lack of central radiological review for the assessment of response and the lack of central pathological review. Given the limited number of patients, no multivariable analyses were performed. Moreover the major imbalance between AA and mTOR populations prevents us from drawing firm conclusions on the specific role of mTOR inhibition in this setting. Indeed, we observed that the majority of our mChRCC cohort (81.9%) was treated with first line AA; this led to an attrition bias because the small number of patients treated with first-line mTOR inhibitors largely had poor prognosis features resulting to a short survival of patients treated with mTOR. Among the 11 patients, 6 belonged to the poor IMDC risk model group, 2 were intermediate risk and 3 had missing data about IMDC risk model score. At the time of analysis 8/11 (72.8%) of patients with mTOR inhibitors had died, including 7 within the first month of TT. This explain the median TTF of 1.9 (95%CI: 1.0-6.0) and OS of 3.2 months (95%CI: 2.3-Not Evaluable). When a stratified log-rank test was used to compare AA and mTOR inhibitors TT in order to control the effect of the IMDC score, no significant difference between AA and mTOR inhibitors was observed for TTF (p= 0.26) and OS (p=0.55).

To our knowledge, our cohort is the largest series of mChRCC treated with TT, providing a benchmark for future trials in this rare disease. Unfortunately, each of the recent prospective trials investigating nccRCC failed to include more than 15 mChRCC[5,6,18]. We report on 61 mChRCC treated with TT within a collaborative groups to provide valuable insight into rare renal tumors. However the weakness of the retrospective design limits results interpretation. Certainly, VEGF inhibition is a reasonable front line and mTOR inhibitors provides clinical benefits to some patients.

## Conclusion

Metastatic ChRCC is a rare entity with no specific TT recommended. We describe the largest cohort, to date, of mChRCC treated with TT and illustrate the ability of an academic consortium to provide unique information on rare histologies. Emerging data from the genomic landscape of ChRCC may provide new insights into novel druggable targets in these patients[27].


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## References


1. Choueiri TK, Figueroa DJ, Fay AP, et al. Correlation of PD-L1 tumor expression and treatment outcomes in patients with renal cell carcinoma receiving sunitinib or pazopanib: results from COMPARZ, a randomized controlled trial. *Clin Cancer Res Off J Am Assoc Cancer Res*. 2015;21(5):1071-1077.

2. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. *Eur Urol*. 2016;70(1):93-105.

3. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial. *J Clin Oncol Off J Am Soc Clin Oncol*. 2015;33(13):1430-1437.

4. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2015;373(19):1814-1823.

5. Tannir NM, Jonasch E, Albiges L, et al. Everolimus Versus Sunitinib Prospective Evaluation in Metastatic Non-Clear Cell Renal Cell Carcinoma (ESPN): A Randomized Multicenter Phase 2 Trial. *Eur Urol*. 2016;69(5):866-874.

6. Armstrong AJ, Halabi S, Eisen T, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. *Lancet Oncol*. 2016;17(3):378-388.

7. Escudier B, Molinie V, Bracarda S, et al. Open-label phase 2 trial of first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis. *Eur J Cancer Oxf Engl 1990*. 2016;69:226-235.

8. Ravaud A, Oudard S, De Fromont M, et al. First-line treatment with sunitinib for type 1 and type 2 locally advanced or metastatic papillary renal cell carcinoma: a phase II study (SUPAP) by the French Genitourinary Group (GETUG)†. *Ann Oncol Off J Eur Soc Med Oncol*. 2015;26(6):1123-1128.

9. Thoenes W. [The science of the kidney]. *Klin Wochenschr*. 1985;63(18):833-834.

10. Patard J-J, Leray E, Rioux-Leclercq N, et al. Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. *J Clin Oncol Off J Am Soc Clin Oncol*. 2005;23(12):2763-2771.

11. Volpe A, Novara G, Antonelli A, et al. Chromophobe renal cell carcinoma (RCC): oncological outcomes and prognostic factors in a large multicentre series. *BJU Int*. 2012;110(1):76-83.

12. Crotty TB, Farrow GM, Lieber MM. Chromophobe cell renal carcinoma: clinicopathological features of 50 cases. *J Urol*. 1995;154(3):964-967.

13. Peyromaure M, Misrai V, Thiounn N, et al. Chromophobe renal cell carcinoma: analysis of 61 cases. *Cancer*. 2004;100(7):1406-1410.

14. Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol Off J Eur Soc Med Oncol ESMO*. 2014;25 Suppl 3:iii49-56.

15. Motzer RJ, Jonasch E, Agarwal N, et al. Kidney cancer, version 3.2015. *J Natl Compr Cancer Netw JNCCN*. 2015;13(2):151-159.

16. Kroeger N, Xie W, Lee J-L, et al. Metastatic non clear cell renal cell carcinoma (nccRCC) treated with targeted therapy agents: Characterization of survival outcome and application of the International mRCC Database Consortium (IMDC) Criteria. *Cancer*. 2013;119(16):2999-3006.

17. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials*. 1996;17(4):343-346.

18. Motzer RJ, Barrios CH, Kim TM, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. *J Clin Oncol Off J Am Soc Clin Oncol*. 2014;32(25):2765-2772.

19. Fernández-Pello S, Hofmann F, Tahbaz R, et al. A Systematic Review and Meta-analysis Comparing the Effectiveness and Adverse Effects of Different Systemic Treatments for Non-clear Cell Renal Cell Carcinoma. *Eur Urol*. 2017;71(3):426-436.

20. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med*. 2007;356(22):2271-2281.

21. Dutcher JP, de Souza P, McDermott D, et al. Effect of temsirolimus versus interferon-alpha on outcome of patients with advanced renal cell carcinoma of different tumor histologies. *Med Oncol Northwood Lond Engl*. 2009;26(2):202-209.

22. Stadler WM, Figlin RA, McDermott DF, et al. Safety and efficacy results of the advanced renal cell carcinoma sorafenib expanded access program in North America. *Cancer*. 2010;116(5):1272-1280.

23. Gore ME, Szczylik C, Porta C, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. *Lancet Oncol*. 2009;10(8):757-763.

24. Motzer RJ, Bacik J, Mariani T, Russo P, Mazumdar M, Reuter V. Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear-cell histology. *J Clin Oncol Off J Am Soc Clin Oncol*. 2002;20(9):2376-2381.

25. Choueiri TK, Plantade A, Elson P, et al. Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. *J Clin Oncol Off J Am Soc Clin Oncol*. 2008;26(1):127-131.

26. Keizman D, Sarid D, Lee JL, et al. Outcome of Patients With Metastatic Chromophobe Renal Cell Carcinoma Treated With Sunitinib. *The Oncologist*. 2016;21(10):1212-1217.

27. Davis CF, Ricketts CJ, Wang M, et al. The somatic genomic landscape of chromophobe renal cell carcinoma. *Cancer Cell*. 2014;26(3):319-330.

Table 1: Patients' and tumor characteristics for all patients (n=90) and for patients treated by targeted therapy (n=61)

| Characteristics | All patients (n=90) | Patients receiving systemic targeted therapy (n=61)* | | | |
|---|---|---|---|---|---|
| | N (%) | All N (%) | Anti angiogenic (n=50) N (%) | mTOR inhibitors (n=11) N (%) | p-value‡ |
| Country | | | | | 0.2847 |
| France | 40 (44.4) | 35 (57.4) | 26 (52.0) | 9 (81.8) | |
| UK | 43 (47.8) | 19 (31.1) | 18 (36.0) | 1 (9.1) | |
| Italy | 6 (6.67) | 6 (9.8) | 5 (10.0) | 1 (9.1) | |
| Australia | 1 (1.1) | 1 (1.6) | 1 (2.0) | 0 (0.0) | |
| Sex | | | | | 0.4999 |
| Male | 58 (64.4) | 36 (59.0) | 28 (56) | 8 (73) | |
| Female | 32 (35.6) | 25 (41.0) | 22 (44) | 3 (27) | |
| Age at diagnosis (years) | | | | | 0.0356 |
| Median (IQR) | 58 (49 – 66) | 57 (49 – 63) | 55 (47 – 62) | 62 (58 – 71) | |
| KPS | | | | | 0.0090 |
| ≥80% | 56 (76.7) | 40 (75.5) | 36 (83.7) | 4 (40.0) | |
| <80% | 17 (23.3) | 13 (24.5) | 7 (16.3) | 6 (60.0) | |
| Missing | 17 | 8 | 7 | 1 | |
| Number of metastases | | | | | 0.7403 |
| 0-1 | 45(50.6) | 27 (44.0) | 23 (46.0) | 4 (36.4) | |
| >1 | 44(49.4) | 34 (55.7) | 27 (54.0) | 7 (63.6) | |
| Missing | 1 | 0 | | | |
| IMDC Risk model‡ | | | | | 0.0003 |
| favorable | 6 (10.3) | 1 (2.3) | 1 (2.8) | 0 (0.0) | |
| intermediate | 40 (69.0) | 34 (77.2) | 32 (88.9) | 2 (25.0) | |
| poor | 12 (20.7) | 9 (20.5) | 3 (8.3) | 6 (75.0) | |
| Missing | 32 | 17 | 14 | 3 | |
| MSKCC£ | | | | | 0.0192 |
| 0 | 10 (17.5) | 4 (9.3) | 4 (11.1) | 0 (0.0) | |
| 1 | 23 (40.4) | 20 (46.5) | 19 (52.8) | 1 (14.3) | |
| 2 | 14 (24.6) | 12 (27.9) | 10 (27.8) | 2 (28.6) | |
| 3 | 10 (17.5) | 7 (16.3) | 3 (8.3) | 4 (57.1) | |
| Missing | 33 | 18 | 14 | 4 | |
| Prior nephrectomy | | | | | 0.0006 |
| No | 7(7.8) | 4 (6.6) | 0 (0.0) | 4 (36.4) | |
| Yes | 83 (92.2) | 57 (93.4) | 50 (100.0) | 7 (63.6) | |
| Grade | | | | | 0.0241 |
| 1 | 3(4.4) | 1 (2.0) | 1 (2.3) | 0 (0.0) | |
| 2 | 11 (16.2) | 9 (18.0) | 8 (18.2) | 1 (16.7) | |
| 3 | 32 (47.1) | 23 (46.0) | 23 (52.3) | 0 (0.0) | |
| 4 | 22 (32.4) | 17 (34.0) | 12 (27.3) | 5 (83.3) | |

| | | | | |
|---|---|---|---|---|
| Missing | 22 | 11 | 6 | 5 |

*Beyond the 64 patients treated by systemic therapy 3 patients were excluded for missing data

IQR: Interquartile range, ‡ IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, £ MSKCC = Memorial Sloan Kettering Cancer Center.

‡: p-value was computed using the Fisher's exact for categorical data or the Kruskal-Wallis test for continuous data

Table 2: Type of targeted therapy for 61 treated patients

| Targeted therapy | N (%) |
|---|---|
| Anti angiogenic | 50 (82.0) |
| Sunitinib | 40 (65.7) |
| Pazopanib | 2 (3.2) |
| Sorafenib | 5 (8.2) |
| IFN_bevacizumab | 1 (1.64) |
| Bevacizumab based combination | 2 (3.28) |
| mTOR inhibitors | 11 (18.0) |
| Temsirolimus | 4 (6.7) |
| Everolimus | 7 (11.5) |

Table 3: Best Response Rates, Time to treatment failure and Overall Survival in patients treated by targeted therapy (n=61)

| | Treated patients (n=61)* | | |
|---|---|---|---|
| | AA | mTOR | All |
| Best Response | | | |
| CR/PR/SD/PD (n)** | 1/12/19/13 | 0/0/4/3 | 1/12/23/16 |
| CR/PR/SD/PD (%) | 2.22/26.7/42.2/28.9 | 0/0/57.1/42.9 | 1.9/23.1/44.2/30.8 |
| | | | |
| ORR** | | | |
| CR+PR/SD/PD (n) | 13/19/13 | 0/4/3 | 13/23/16 |
| CR+PR/SD/PD (%) | 28.9/42.2/28.9 | 0/57.1/42.9 | 25.0/44.2/30.8 |
| | | | |
| No of deaths | 35 | 8 | 43 |
| Median TTF (95%CI) | 8.7 (5.2-10.9) | 1.9 (1.0-6.0) | 7.2 (4.1-9.5) |
| Median OS (95%CI) | 22.9 (17.8-49.2) | 3.2 (2.3-NE) | 20.8 (11.6-35.2) |

* Three patients were excluded for missing data, AA: antiangiogenic, mTOR: mTOR inhibitors.

** Nine patients were excluded from BR and ORR analysis for missing data, BR = best response, CR =complete response, PR= partial response, SD = stable disease, PD = progression disease, ORR = objective response rate, CI = confidence interval; NE = not evaluable; TTF = time to treatment failure, OS = overall survival

Table 4: Metastatic site for entire cohort *

| Metastatic site | N=89 (%) |
|---|---|
| Abdominal nodes | 37 (41.6) |
| Lung metastasis | 30 (33.7) |
| Bone metastasis | 20 (22.4) |
| Mediastinal nodes | 17 (19.1) |
| Liver metastasis | 17 (19.1) |
| Brain metastasis | 5 (5.6) |
| Others (peritoneal relapse for majority) | 28 (31.5) |

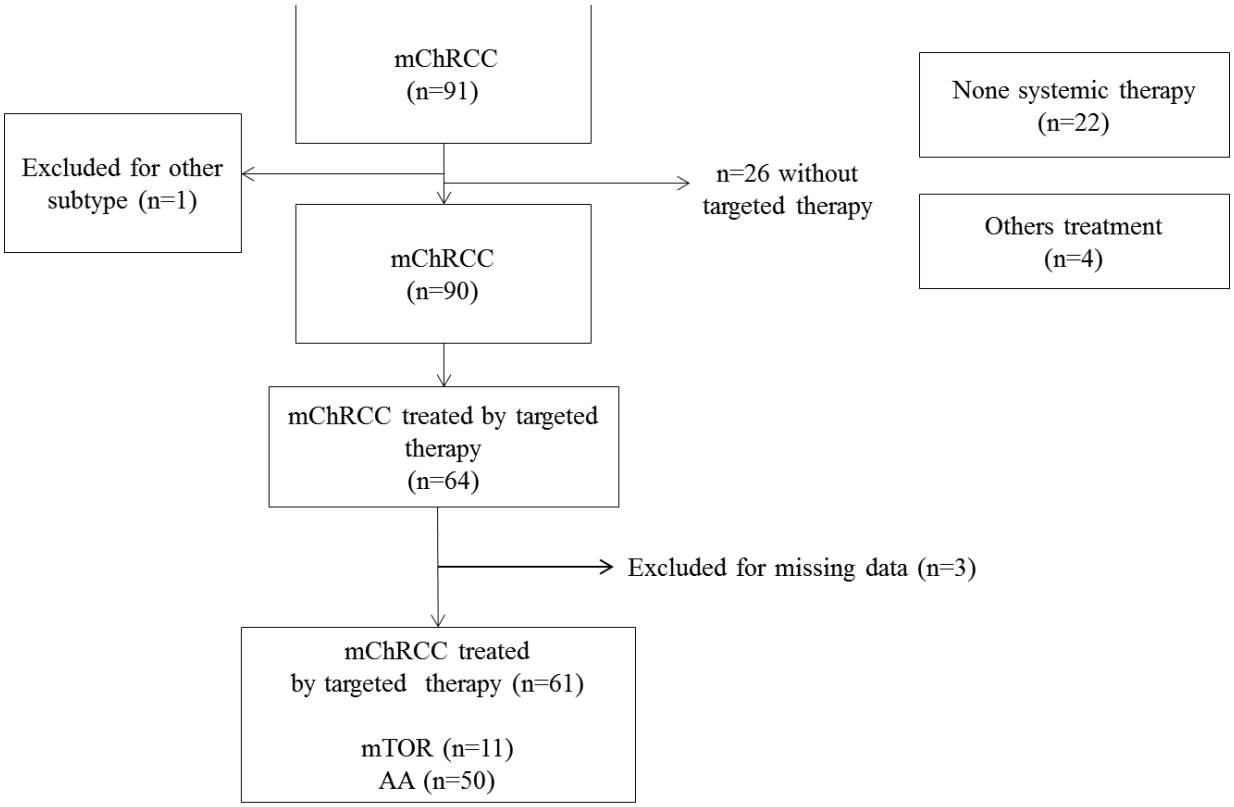
*: 1 patient has missing data for details of metastatic sites

Supplementary Table 1: Clinical outcomes described of mChRCC in literature

| References | Trial design | N mChrcc(%) | Median OS (95% CI) (months) | | | | Median PF (95% CI) (mon | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | nccRCC | | ChRCC | | nccRCC | | |
| | | | AA | mTOR | AA | m TOR | AA | mTOR | |
| Motzer RJ et al. **RECORD-3 Phase II randomized trial al first-line everolimus and second-line sunitinib versus first- second-line everolimus in patients with metastatic renal cell carcinoma**. J Clin Oncol 2014 | open-label, randomised phase 2 | 11/207 | - | - | - | - | 7.2 (5.4-13.8) | 5.1 (2.6-7.9) | |
| Armstrong AJ et al **sunitinib for patients with metastatic non-clear cell renal cell PEN): a multicentre, open-label, randomised phase 2 trial.** Lancet Oncol. 2016 | open-label, randomised phase 2 | 16/108 | 31.5 (14.8-NR) | 13.2 (9.7-37.9) | NS | NS | 8.3 (80%5.8-11·4) | 5.6 (80%5.5-6.0) | 5.5 3.2 |
| Tannir et al **rolimus Versus Sunitinib Prospective Evaluation in ic Non–Clear Cell Renal Cell Carcinoma (ESPN): A Randomized Multicenter Phase 2 Trial** | randomized phase 2 | 12/72 | 16.2 | 14.8 | 31.6 (14.2–NA) | 25.1 (4.7–NA) | 6.1 (4.2-9.4) | 4.1 (2.7-10.5); | 8.9 20.1 |
| Kroeger N et al. **lear cell renal cell carcinoma treated with targeted therapy agents: characterization ome and application of the International mRCC Database Consortium criteria.** Cancer 2013 | Retrospective study | 37 | - | - | 27.1 (12.6-75.3) | - | TTF= 4.2 (3.7-5.2) | - | |
| Gore ME et al. **cacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial**. Lancet Oncol 2009 | Expanded Access Program | NA | 13.4 (10.7-14.9) | - | - | - | 7.8 (6.3-8.3) | - | |
| Tannir NMet al. **A phase 2 trial of sunitinib in with advanced non-clear cell renal cell carcinoma.** Eur Urol 2012 | Single arm phase 2 | | 16.8 (10.7-26.3) | - | - | - | 2.7 (1.4-5.4) | - | |
| Lee J-Let al. **Multicenter phase II study of sunitinib tients with non-clear cell renal cell carcinoma**. Ann Oncol 2012 | Single arm phase 2 | 3 | NR but 25.6 (8.4 -42.9) expected | - | - | - | 6.4( 4.2-8.6) | - | |
| Molina AM et al. **unitinib in patients with metastatic non-clear cell renal cell carcinoma.** Invest New Drugs 2012. | Single arm phase 2 | 2 | - | - | - | - | 5.5 (2.5-7.1) | - | |
| Koh Y et al. **Phase II trial of everolimus for the atment of nonclear-cell renal cell carcinoma.** Ann Oncol 2013 | Single arm phase 2 | 8 | - | 14.0 | - | 21.6 | - | 5.2 | |

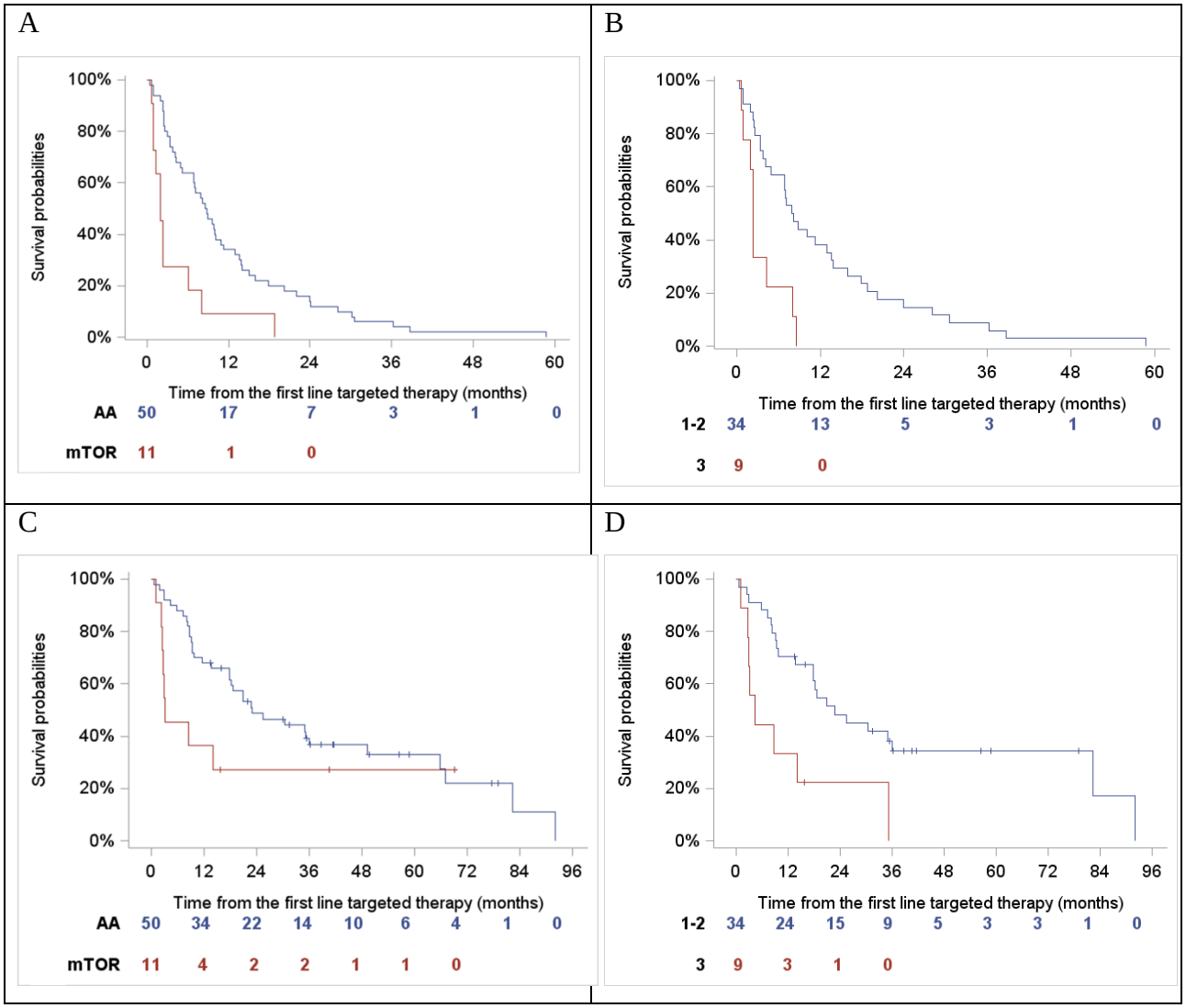
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Keizman D et al<br>s With Metastatic Chromophobe Renal Cell Carcinoma Treated With Sunitinib<br>The Oncologist. 2016 | Retrospective study | 36 | - | - | 26 (HR: 1.15p=0.7) | - | - | - | 10 (<br>1.4;<br>p=0 |
| Choueiri TK et al.<br>**Efficacy of sunitinib and**<br>**tastatic papillary and chromophobe renal cell carcinoma**.<br>J Clin Oncol. 2008 | Retrospective study | 12 | 19.6 | - | NA | - | 8.6 | - | |
| Voss MH et al.<br>**Treatment outcome with mTOR**<br>**or metastatic renal cell carcinoma with nonclear and sarcomatoid histologies.**<br>Ann Oncol 2014 | Retrospective study | NA | - | 8.7 | - | - | - | 2.9 | |
| Dutcher JP et al.<br>**limus versus interferon-alpha on outcome of patients with renal cell carcinoma of different tumor histologies.**<br>Med Oncol 2009 | Exploratory subgroup analyses from phase 3 ARCC | 12 | - | 11.6 (8.9-14.5) | - | - | - | 7 (3.9- 8.9) | |

NA: not assessable; TTF: Time To Treatment Failure; HR: Hazard ratio; NR: not reached; NS: not shown; - : not investigate in the studyFigure 1: Flow-chart



AA: antiangiogenic, mTOR: mTOR inhibitors.

Figure 2: Unadjusted Kaplan-Meier estimates of the failure-free survival in the first line targeted therapy between antiangiogenic (AA) and mTOR inhibitor (panel A), of the failure-free survival in the first line targeted therapy between intermediate IMDC risk model (coded as 1-2) and poor IMDC risk model (coded as 3) (panel B), of the overall survival between antiangiogenic (AA) and mTOR inhibitor (panel C) and of the overall survival between intermediate IMDC risk model (coded as 1-2) and poor IMDC risk model (coded as 3) (panel D) in targeted treated patient (n=61)*




* For IMDC risk model we did not report the TTF and OS for group with favorable prognosis because it represents only one patient.AA: antiangiogenic, mTOR: mTOR inhibitors.