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

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Take home messages: Rare subgroup of renal carcinoma should no more be study as a global entity. We would have been able to investigate the really infrequent metastatic ChRCC with collaborative groups. Our study confirms that these patients have very favorable prognosis and that VEGF inhibition is a good option of treatment in clinical practice.

Abstract

Background: Treatment of non-clear cell RCC remains controversial, despite several recent prospective dedicated studies of targeted therapies (TT). Extrapolating the benefit of VEGF and mTOR inhibitors from the others subtype of kidney cancer, patients are routinely treated as clear cell RCC.

Objective: to assess the clinical outcome associated with the use of targeted therapy in metastatic chromophobe (ChRCC) tumors.

Design, setting, and participants: A retrospective data analysis was performed within the Renal cross Chanel group to determine metastatic ChRCC treatment outcomes in the targeted therapy era. Kaplan-Meier and summary statistics were used. Overall survival rates and overall response rates were calculated.

Results and limitations: 91 mChRCC patients from 26 centers in 4 countries had been diagnosed between July1997 and April 2013 with a median follow-up from date of first metastasis of 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 VEGF TT and 11 with mTOR inhibitors. TTF in patients who received a first line antiangiogenic (AA) was 8.7 months (95%CI: 5.2-10.9) and median OS was 22.9 months (95%CI: 17.8-49.2).

Conclusion: We report the largest cohort of patients with mChRCC treated with targeted therapy. Our results highlight the activity of VEGF inhibition in terms of TTF and OS in mChRCC.

Patient summary: Our study focused on a very rare subtype of renal cancer (ChRCC) with metastatic disease. We have collected 91 cases within a European consortium in order to investigate patient's characteristics, prognosis and outcome with currently available systemic therapy.

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

Introduction

Over the past 12 years, therapeutic arsenal against renal cell carcinoma (RCC) has widely expanded, increasing patient survival with median overall survival reaching almost 30 months in recent studies[1]. However, most of the data have been reported in clear cell RCC. Despite several prospective dedicated studies of targeted therapies in non-clear cell RCC, the benefit of target therapies in the others subtypes remains unclear. Chromophobe renal cell carcinoma (ChRCC) is the most common form of non-clear cell RCC (nccRCC) (4 - 6%), after papillary RCC (10 - 15 %)[2]. Many others rare histologies belong to this group, including collecting duct carcinoma (about 1%) and unclassified RCC (4 - 5 %). Various studies have demonstrated some efficacy of systemic therapies targeting VEGF and mTOR pathways, and to date little is known about the activity of more recently monoclonal antibody directed toward the programmed death (PD 1)/ programmed death ligand 1 (PDL 1) pathway[3] as well as dual new tyrosine kinase inhibiting MET and VEGFR2[4] in nccRCC. Recently 2 randomised studies investigated a pool of mixed non-clear cell histologies and few prospective trials focused on papillary RCC (pRCC); nevertheless evidence based recommendations about systemic therapy for metastatic ChRCC (mChRCC) are limited.

First described by Thoenes in 1985, ChRCC probably derives from the collecting duct system from the intercalated cells[5], it has been associated with better prognosis than other subtypes. Large surgical cohorts suggested that localised ChRCC display a more favourable prognosis with fewer metastatic spreading. Patard et al showed that ChRCC patients had a better outcome compared to papillary or clear cell RCC[6]. In this series, only 6 patients out of 396 (1.5%) with ChRCC had distant disease. In another large retrospective database of 291 ChRCC, only 25 patients with ChRCC (8.6%) developed recurrence and 18 (6.2%) died from disease[7]. Similarly, other small cohorts reported a low rate of specific mortality and recurrence of 2% and 6%, respectively in a serie of 50 patients with ChRCC with a mean follow up of 6 years[8]or no recurrence in a 61 patient's cohort with a follow of 4.1 years[9].

Most of the available data in mChRCC comes from retrospective small series or rare phase 2 enrolling heterogeneous population of non ccRCC. No standard of care is currently proposed for mChRCC patients in both NCCN or ESMO guidelines[A1][10,11]. Extrapolating the benefit of VEGF and mTOR inhibitors to the others subtypes of kidney cancers, patients are routinely treated

similarly to clear cell RCC. In our study, we focused on metastatic ChRCC patients to assess the clinical outcome associated with the use of targeted agents.

Materials and Method

Study design and population

In 2012, the initiative was carried out to conduct a retrospective chart review of mChRCC patients treated within the French kidney group of the GETUG (Groupe d'Etude des Tumeurs Uro genitales) and the Renal Cross Chanel 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[12].

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 from the date of first-line therapy for patients treated with TT. For TT patients, the different types of TT classified as AA (sunitinib, sorafenib, pazopanib and bevacizumab) or mTOR (temsirolimus, everolimus) and the number of lines were reported. The best response (by local assessment) was determined 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 whichever occurred first. 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-event endpoints were estimated by Kaplan-Meier method and compared according IMDC risk group using a log-rank test. Median TTF and median OS with 95% confidence interval (95%CI) were reported for each group. The cut-off date for the analyses was December, 31 2015. The statistical analyses were done with SAS software 9.4. (SAS Institute).

Results

All patients

Patient's characteristics and overall survival

We collected data from 91 mChRCC patients from 26 centers in 4 countries (France, UK, Italy and Australia). One patient was excluded because pathological diagnosis of ChRCC was uncertain (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 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 disease while 75.6% (n=68) were synchronous. Abdominal lymph nodes were the most common site of metastasis (41.6%, n=37) while lung (33.7%, n = 30) and liver metastases (19.1%, n =17) 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 %). The median OS from date of first metastasis was 37.9 months (95%CI 21.4 to 46.8).

Patients treated with targeted therapy

From 90 mChRCC patients, 68 patients received medical treatment, mostly TT (n=64), or other systemic therapy: Interferon alone (n=2), vinflunine or hormonal therapy (one each). In addition, 22 patients never received systemic therapy and were treated with surgery alone on oligometastatic site and/or close follow up only 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 for 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 was in favorable prognosis group, 77.3% (n=34) were in intermediate prognosis group and 20.5% (n=9) in poor prognosis group. The score was not available for 17 patients.

Type of treatment

The different types of TT are reported in table 3. In first line, 50 (82.0%) patients received AA while 11 (18.0%) patients received mTOR. *S*econd line therapy was administered in 30 (49.2%) patients and third line in 11(18.0%) patients. As second line of TT, 14 patients were treated with AA (46.7%) and 16 (53.3%) with mTOR.

Response rate

Response rate among 61 treated patients is described in table 2: CR: 1.9% (n=1), PR: 23.1% (n=12), SD: 44.2% (n=23) and PD: 30.8 (16%) (9 had missing data). The ORR was CR/PR: 25.0 %. The distribution of ORR was not significantly different between AA: CR/PR: 28.9% (n=13), SD: 42.2% (n=19) and PD: 28.9% (n=13) and mTOR: CR/PR: 0.0% (n=0), 7.7% (n=4) and PD: 5.8% (n=3) (p=0.28, Fisher's exact test).

Time to Treatment Failure

Time to Treatment Failure was calculated for 61 patients. The median TTF from date of first-line therapy for mChRCC was 7.2 months (95%CI: 4.1-9.5). Median TTF was 8.7 months (95%CI: 5.2-10.9) and 1.9 months (95%CI: 1.0-6.0) respectively for the group treated with AA and mTOR inhibitors (Figure 2A). Median TTF for patients was 8.0 months (95%CI: 4.1-13.6) and 2.3 months (95%CI: 0.7-8.0) p=0.001, according to IMDC risk model for intermediate and poor prognosis respectively (Figure 2B). We performed a stratified log-rank test to compare the targeted therapies (AA and mTOR) while controlling the effect of the IMDC score. No significant difference between AA and mTOR was observed with p= 0.2589 for TTF.

Overall Survival

Median overall survival was 20.8 months (95%CI: 11.6-35.2) in treated population (70.5%, 43 deaths). Median overall survival was 22.9 months (95%CI: 17.8-49.2) for the group treated with AA and 3.2 months (95%CI: 2.3-Not Evaluable) with mTOR inhibitors (Figure 2C),. As expected, the median overall survival was longer in patients with intermediate prognosis according to IMDC risk model (22.8 months 95CI%:13.7-82.4) compared to patients with poor prognosis (4.3 months 95%CI: 1.1-35.2) (p=0.0043, log rank test) (Figure 2D). We performed a stratified log-rank test to compare the targeted therapies (AA and mTOR) while controlling the effect of the IMDC score. No significant difference between AA and mTOR was observed with p= 0.5520 for OS.

Discussion

We report the largest series of patients with mChRCC treated with TT.

Firstly, observation of the scarcity of mChRCC and overall prognosis for ChRCC is consistent with prior reports both in the localized and metastatic setting. In 2016 a clinical based cohort study with meta-analysis reported a five-year OS rates for ChRCC and ccRCC of 90.3 and 75.3 %, respectively ($p < 0.001$)[13]. Metastatic ChRCC is a very rare entity, according to large surgical cohorts[6–9]. Higher potential for distant metastases has been associated with sarcomatoid change and microscopic tumor necrosis[14].

Secondly, the lack of standardization in mChRCC is related to the fact that for several decades, nccRCC has been considered as a global entity. More recently, three randomized phase 2 trials reported on nccRCC (Supplementary Table 1). Two dedicated randomized phase 2 compared for the first time everolimus and sunitinib in patients with metastatic nccRCC[14,15]. In the first one (ESPN) among 72 patients, median PFS in first-line therapy was 6.1 (95%CI: 4.2-9.4) months with sunitinib and 4.1 (95% CI: 2.7-10.5) with everolimus and median overall survival (OS) was 16.2 (95%CI: 14.2-NA) with sunitinib and 14.8 (95%CI: 8.0-23.4) with mTOR, respectively ($p = 0.18$)[14]. The second one (ASPEN), among 108 patients, with similar design, median PFS of 8.3 (80%CI:5.8-11.4) months with sunitinib versus 5.6 (80%CI:5.5-6.0) months with everolimus; hazard ratio (HR) was 1.41 (80%CI: 1.03-1.92) with no significance difference ($p =0.16$) [15]. Median OS was 31.5 (80%CI: 14.8-NR) months with sunitinib versus 13.2 (80%CI: 9.7-37.9) with everolimus.

In these studies, chromophobe patients accounted respectively for 12/72 and 16/108 patients. RECORD-3, a randomized phase 2 trials in metastatic RCC, comparing the sequence of everolimus followed by sunitinib at progression to the opposite sequence, enrolled both ccRCC and nccRCC patients[16]. In the subgroup analysis of 66 patients with nccRCC, 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), but mChRCC only accounted for 2% and 3% of patients in each arm respectively.

Before these randomized data, seldom phase III enrolled non ccRCC. In 2007, Hudes' study suggested that interesting responses were seen with temsirolimus in nccRCC[17]; among the 73 patients with nccRCC, median OS was 11.6 months (95%CI: 8.4-14.5) vs 4.3 (95%CI: 3.2-7.3) with IFN alone[18]. Most of the activity of TT in nccRCC report was initially reported in Expanded Access Programs (EAPs). Stadler reported in nccRCC subgroup (n=202) analysis of sorafenib EAP a median PFS of 24 weeks[19], and Beck reported a median PFS of 5.7 months (95%CI: 4.5-6.7) for papillary subtype and of 4.0 months (95%CI: 2.8-4.8) for sarcomatoid features (n=241 nccRCC)[20]. Within the Sunitinib EAP (n=4349), Gore reported in nccRCC subgroup (n=588) a median PFS of 7.8 months (95%CI: 6.3, 8.3) vs 10.9 (95%CI: 10.3, 11.2) months with ccRCC and a median OS of 13.4 months (95%CI: 10.7, 14.9) vs 18.4 months (95%CI: 17.4, 19.2) in the entire population[21].

However overall survival wit nccRCC has previously been reported as widely variable with distinct pathological entities harboring different prognosis. Before the TT era, Motzer reported an overall survival of 9.4 months for all non–clear-cell cohort while it was, 29 months for ChRCC, 11 months for collecting duct, and 5.5 months for papillary subtype[22]. In the TT era, the large report from IMDC real world evidence confirmed this heterogeneity. In the subgroup analyses from Kroeger study, median OS was 12.8 months (95%CI: 11.0-16.1 months) for all non–clear-cell cohort[12]. In ChRCC median OS was 27.1 months (95%CI: 12.6-75.3 months), and it was 14.0 months (95%CI: 10.9-17.1 months), and 10.1 months (95%CI: 5.1-13.2 months) in pRCC and unRCC, respectively. Furthermore, this study demonstrates the applicability of the IMDC prognostic model in nccRCC treated with first line TT (VEGF and mTOR inhibitors): median OS of the 3 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=0.0043, log rank test) (Figure 1D). As only one patient had favorable prognosis risk group, he was excluded from this analysis. For first-line therapy in the Kroeger's study, median TTF for nccRCC treated with TT was 7.8 months (95%CI: 7.2-8.1 months) and 4.2 months (95%CI: 3.7-5.2 months) in ccRCC and nccRCC, respectively. Overall survival from Kroeger's cohort of 37 mChRCC was 27.1 months (95%CI: 12.6-75.3). 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[23].

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

In the current study, we report that patients who received a first line AA have a better median TTF than patients who received mTOR inhibitors as first line (8.7 months vs1.9 months, p=0.0005, log rank test); and similarly they display longer median overall survival outcomes with AA. The short survival of patients with mTOR in this retrospective cohort is explained by the fact that among the 11 patients treated with mTOR inhibitors, 6 belonged to the poor IMDC risk model group, one was intermediate risk and four had missing data about IMDC risk model score. At time of analysis 8/11 (72.8%) had died including 7 deaths within the first month of TT, potentially explaining this extremely short OS.

A very recent cohort from Keizman et al investigated clinical outcome with TT for mChRCC within 36 patients from 10 centers across 4 countries[24]. Metastatic ChRCC patients were individually matched to metastatic ccRCC patients by HENG risk, nephrectomy/smoking status, pre-treatment neutrophil to lymphocyte ratio, use of angiotensinogen system inhibitors, dose reduction/treatment interruption, and hypertension. Treatment outcome was not significantly different between metastatic ChRCC and ccRCC patients: median PFS was 10 versus 9 months (HR: 1.4; p=0.6). Median overall survival was 26 versus 25 months (HR: 1.15; p=0.7).

Our study is not without limitations inherent to its retrospective nature and the major imbalance between AA and mTOR populations that prevents us to draw any conclusion on the specific role of mTOR inhibition in this setting. The vast majority of our mChRCC cohort (81.9%) was treated with AA as first line; this led to this attrition bias related to the fact that a treatment with mTOR in first line was associated to poor prognosis fetaures in our study. Nevertheless, we believe that our cohort (i) provide an exclusive large cohort of mChRCC

treated with TT to a benchmark prognosis for future trial in this rare disease; (ii) highlight the activity of VEGF inhibition in this population in line with recent trials; (iii) illustrate the ability of collaborative groups to investigate rare renal tumors.

Conclusion

Metastatic ChRCC is a rare entity with no specific TT recommended. We provide the largest cohort, to date, of metastatic ChRCC treated with TT, mostly VEGF inhibition and illustrate the ability of academic consortium to investigate rare histologies. Emerging data from the ChRCC genomic landscape may provide insight for more attractive TT in selected patients[25].

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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 (%)	N (%)
Sex		
Male	58 (64.4)	36 (59.0)
Female	32 (35.6)	25 (41.0)
Age at diagnosis (years)		
Median (IQR)	58 (49 – 66)	57 (49 – 63)
KPS		
≥80%	56 (76.7)	40 (75.5)
<80%	17 (23.3)	13 (24.5)
Missing	17	8
Number of metastases		
0-1	45(50.6)	27 (44.0)
>1	44(49.4)	34 (55.7)
Missing	1	0
IMDC Risk model‡		
0	6 (10.3)	1 (2.3)
1-2	40 (69.0)	34 (77.2)
3	12 (20.7)	9 (20.5)
Missing	32	17
MSKCC£		
0	10 (17.5)	4 (9.3)
1	23 (40.4)	20 (46.5)
2	14 (24.6)	12 (27.9)
3	10 (17.5)	7 (16.3)
Missing	33	18
Prior nephrectomy		
No	7(7.8)	4 (6.6)
Yes	83 (92.2)	57 (93.4)
Grade		
1	3(4.4)	1 (2.0)
2	11 (16.2)	9 (18.0)
3	32 (47.1)	23 (46.0)
4	22 (32.4)	17 (34.0)
Missing	22	11

*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.

Table 2: 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
BR**	1/12/19/13	0/0/4/3	1/12/23/16
CR/PR/SD/PD (%)	2.22/26.7/42.2/28.9	0/57.1/42.9	1.9/23.0/44.2/30.8
ORR**	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 3: Type of targeted treatment for 61 treated patients

Targeted treatment	N (%)
Anti angiogenic	50 (81.9)
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 4: Metastatic site for entire cohort at systemic therapy initiation*

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

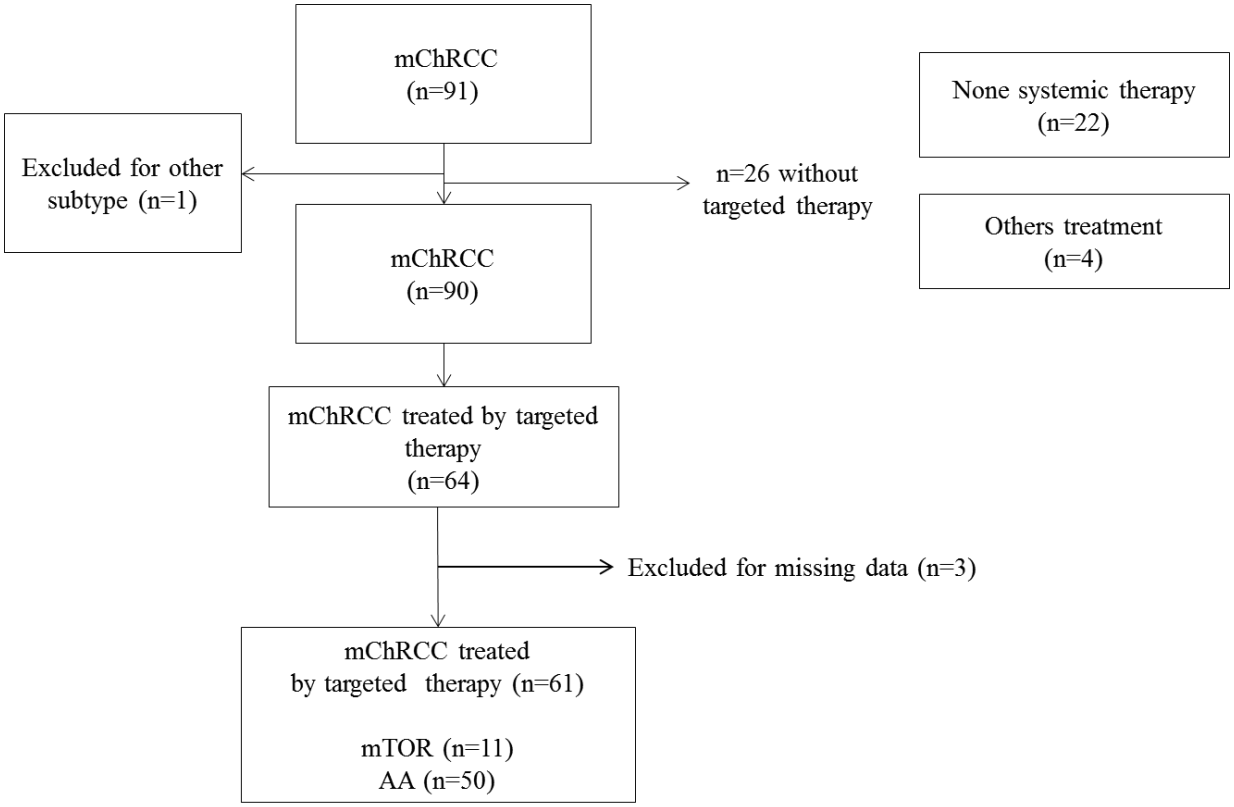
References	Trial design	N mChrcc(%)	Median OS (95% CI) (months)				Median PFS (95% CI) (months)			
			nccRCC		ChRCC		nccRCC		ChRCC	
			AA	mTOR	AA	m TOR	AA	mTOR	AA	mTOR
Motzer RJ et al. **RECORD-3 Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma**. J Clin Oncol 2014	open-label, randomised phase 2	11/207	-	-	-	-	7.2 (5.4-13.8)	5.1 (2.6-7.9)	-	-
Armstrong AJ 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	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 (80% 3.2–19.7)	11.4 (80%5.7–19.4)
Tannir et al **ESPN Everolimus Versus Sunitinib Prospective Evaluation in Metastatic 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 (2.9-20.1)	NA
Kroeger N et al. .**Metastatic non-clear cell renal cell carcinoma treated with targeted therapy agents: characterization of survival outcome 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. **Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial**. Lancet Oncol 2009	Expendanded Acces Program	NA	13.4 (10.7-14.9)	-	-	-	7.8 (6.3-8.3)	-	-	-

Tannir NMet al. **A phase 2 trial of sunitinib in** **patients 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** **in patients 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. **Phase II trial of sunitinib 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** **treatment of nonclear-cell renal cell carcinoma.** Ann Oncol 2013	Single arm phase 2	8	-	14.0	-	21.6	-	5.2	-	13.1
Keizman D et al Outcome of Patients With Metastatic Chromophobe Renal Cell Carcinoma Treated With Sunitinib The Oncologist. 2016	Retrospective study	36	-	-	26 (HR: 1.15p=0.7)	-	-	-	10 (HR: 1.4; p=0.6).	-
Choueiri TK et al. **Efficacy of sunitinib and** **sorafenib in metastatic papillary and chromophobe renal cell carcinoma**. J Clin Oncol. 2008	Retrospective study	12	19.6	-	NA	-	8.6	-	10.6	-
Voss MH et al. **Treatment outcome with mTOR** **inhibitors for metastatic renal cell carcinoma with nonclear and sarcomatoid histologies.** Ann Oncol 2014	Retrospective study	NA	-	8.7	-	-	-	2.9	-	-
Dutcher JP et al. **Effect of temsirolimus versus interferon-alpha on outcome of patients with**	Exploratory subgroup	12	-	11.6 (8.9-14.5)	-	-	-	7 (3.9- 8.9)	-	-

advanced renal cell carcinoma of different tumor histologies. Med Oncol 2009	analyses from phase 3 ARCC									

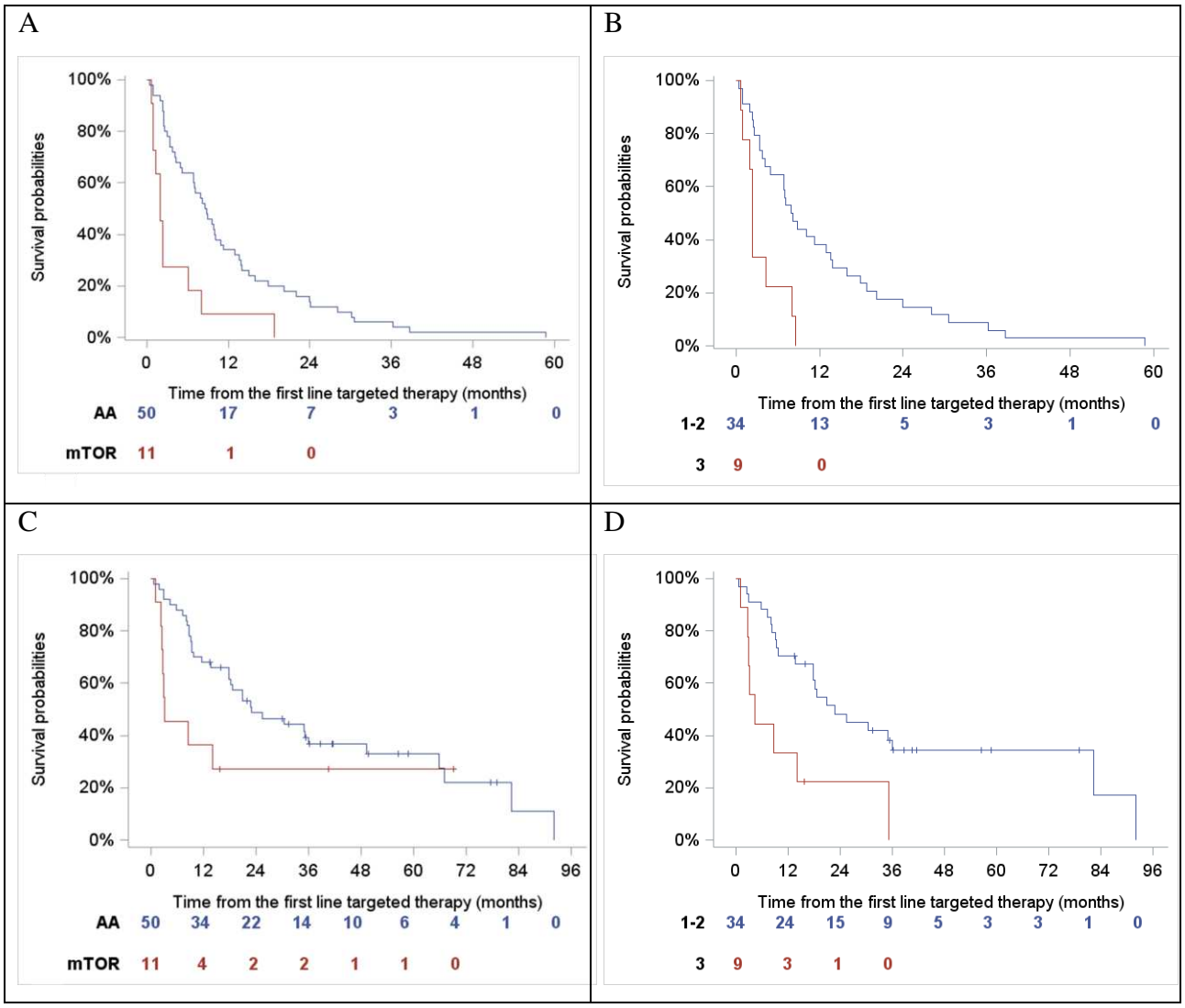
NA: not assessable; TTF: Time To Treatment Failure; HR: Hazard ratio; NR: not reached; NS: not shown.

Figure 1: Flow-chart



AA: antiangiogenic, mTOR: mTOR inhibitors.

Figure 2: Unadjusted Kaplan-Meier estimation of (i) time to treatment failure in the first line targeted therapy according to type of targeted therapy (AA and mTOR) (A) and IMDC risk criteria (B) (ii)overall survival according to type of targeted therapy (AA and mTOR) (C) and IMDC risk criteria (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.