Abstract

Patients diagnosed with non-clear renal cell carcinoma have often been excluded from clinical trials due to the shortage of treatments available, the low incidence of tumours with non-clear histology, and the corresponding diversity of intrinsic molecular features. This approach led to a knowledge gap in finding the optimal treatment for patients diagnosed with non-clear cell renal carcinoma. Cabozantinib, a potent multiple tyrosine kinase receptor inhibitor, has been recently investigated in patients with non-clear cell histologies of renal cell cancer. In this review, we have summarized available data on the use of cabozantinib in non-clear renal cell carcinoma.

Keywords: cabozantinib, non-clear renal cell carcinoma, efficacy, toxicity, tyrosine kinase receptor inhibitor, renal carcinoma, vascular endothelial growth factor receptor

Introduction

Cabozantinib is a potent inhibitor of multiple receptor tyrosine kinases involved in carcinogenesis, angiogenesis, tumour growth and metastasis. The main targets of cabozantinib are vascular endothelial growth factor receptor 2 (VEGFR 2) and MET, and other targets include VEGFR 1 and 3, KIT, AXL and FLT3 [1] (Figure 1). Two large phase III trials have assessed the efficacy and safety profile of cabozantinib in patients affected by clear cell renal cell cancer (CCRCC). The CABOSUN trial [2] compared cabozantinib to sunitinib as first-line therapy and the METEOR trial [3] compared cabozantinib to everolimus in patients who had a progression of disease following an anti-VEGFR targeted therapy. Based on the results of CABOSUN and METEOR trials, and the encouraging results from two small retrospective studies [4,5], plus the lack of treatment available for non-clear cell renal cell carcinoma (NCCRCC), it has been speculated that cabozantinib is a valid option for NCCRCC which accounts for 10 to 20% of all renal cell carcinomas (RCC) [6]. Indeed, cabozantinib was recently demonstrated to be effective in patients diagnosed with renal cell carcinoma with non-clear cell histologies (NCCRCC) [7]. In this mini-review, we have summarized available data on the use of cabozantinib in NCCRCC.

Molecular characteristics of NCCRCC

NCCRCC treatment continues to be controversial due to its genetic features, variable prognosis as well as clinical and morphological characteristics [8,9] (Table 1). Currently, a set of inherited syndromes predispose to histological subtypes of renal cancer such as Von Hippel-Lindau (VHL) syndrome (correlated with specific mutations in the *VHL* gene and clear cell RCC histology), hereditary leiomyoma renal cell carcinoma (RCC) (correlated with mutations in the *fumarate hydratase* gene and papillary RCC type II), hereditary papillary RCC (correlated with mutations in *c-MET* and papillary RCC type I) and Birt-Hogg-Dubé

syndrome (BHD; correlated with alterations in the *BHD* gene and chromophobe RCC) [10][11]. It is well established that genetic or epigenetic alterations in the *VHL* tumour suppressor gene on chromosome 3p25.3 account for nearly 90% of sporadic clear cell RCC tumours [12,13], but this is not common in NCCRCC where only 16% of sporadic cases have been reported with alterations in *VHL* [14]. Despite the rarity of VHL alteration in NCCRCC, differences in the expression pattern for VEGF and mRNA levels of its receptors (VEGFR 1-2) between papillary and clear cell RCC (cRCC) have been reported, with higher levels for tumours with CCRCC histology, potentially explaining the differences in the pathways associated with angiogenesis [15]. In addition, it has been shown that chromophobe and papillary histologies account for around 80% of NCCRCC [8,9]. In chromophobe RCCs, the mammalian target of rapamycin (mTOR) and consequently the tumour suppressor protein 53 (*TP53*), are the commonest pathways implicated in oncogenesis [16–18]. A range of mTOR pathway molecular components such as PTEN, pAkt, p27 and pS6 have been shown to be overexpressed (compared to normal kidney tissue) and permanently activated in CCRCC as well as NCCRCC [19,20]. Solid staining for CD117 (cKIT) plus a CD117 cytoplasmic reactivity for chromophobe RCC has been reported in several studies [21,22]. In contrast, papillary RCCs include type 1, which is considered sporadic and related to MET mutations or alternatively epidermal growth factor receptor (EGFR) mutations [23]; both genes are involved in proliferation, cell survival, angiogenesis and motility. Type 2 papillary RCC is usually more aggressive, frequently hereditary and related to mutations in the *fumarate hydratase* (*FH*), *CDKN2A* and *SETD2* genes and to fusions involving the *TFE3* gene [16,24]. Lastly, collecting ductal carcinoma (CDC), which generates from the renal collecting ducts, is characterized by a very rare and aggressive phenotype with a high rate of tumour infiltrating lymphocytes (TILs) [25]. In the past, different research groups investigated RCC gene expression profile with DNA microarrays, reporting

unique expression profiles for different RCC histological subtypes as well as suggesting that each subtype is driven by different tumorigenic pathways such as the overexpression of GST-α, IGFBP-3 and VEGF for CCRCC and the overexpression of cytokeratin 7 (CK7) and CD117 for the papillary and chromophobe NCCRCCs respectively [26–28]. These data have been recently confirmed by different groups employing next generation sequencing (NGS) [7,29]. Differentially expressed genes might be used as specific diagnostic and prognostic markers and lead to novel targeted therapeutic strategies [30].

Clinical efficacy

The rarity of NCCRCC means that available therapies are still inferred from clinical evidence for metastatic clear cell RCC, and only a small number of prospective randomised trials have been performed so far. Retrospective analysis by the International Metastatic RCC Database Consortium (IMDC) in 2013 [31] revealed a worse survival outcome for patients with metastatic NCCRCC (mOS of 12.8 months) compared to patients diagnosed with clear cell RCC (mOS of 22.3 months) ($P<0.001$). Although the chromophobe NCCRCC histotype showed a survival outcome similar to clear cell RCCs, the sarcomatoid subgroup of chromophobe NCCRCCs showed a poorer survival outcome [32].

In 2016, the prospective phase II randomised trials ESPN and ASPEN compared the efficacy of everolimus, an mTOR inhibitor, with sunitinib, a multiple receptor tyrosine kinase inhibitor (TKI). Both studies reported an improvement in terms of progression-free survival (PFS) for patients administered with sunitinib as first-line regimen, but not a clear benefit in terms of overall survival (OS) [33,34]. In the ESPN trial, 68 patients diagnosed with papillary (27), chromophobe (12), not classified (10), translocation (7) and sarcomatoid (12) metastatic NCCRCC were randomized to receive oral everolimus (10 mg/day) or oral sunitinib (50 mg/day) for 4 weeks plus 2 weeks off with crossover at disease progression. In

the ESPN trial, the median PFS (mPFS) was 4.1 months with everolimus and 6.1 months with sunitinib (p=0.6); the median OS (mOS) for everolimus was 10.5 months but not reached for sunitinib (p=0.014). Ultimately, mOS was 14.9 and 16.2 months with everolimus and sunitinib, respectively (p=0.18) [34]. Grade 3 or 4 adverse events (AE) occurred in 88% and 54% of patients who received sunitinib and everolimus, respectively; fatigue was the most common event (36%) followed by neutropenia (27%), diarrhoea (21%), hypertension (18%), and hyponatremia (15%). In the ASPEN trial, 108 patients diagnosed with metastatic papillary, chromophobe or unclassified NCCRCC, with no previous systemic therapy, were randomly assigned (1:1) to receive either 10 mg/day everolimus (57 patients) or 50 mg/day sunitinib (51 patients) orally on days 1 through 28 of each 42-day cycle. Sunitinib improved PFS compared to everolimus (8.3 months [80% CI 5.8-11.4] vs 5.6 months [5.5-6.0] hazard ratio 1.4 [80% CI 1.03-1.92] p=0.16), even though heterogeneity was observed based on the prognostic risk groups and histological subtypes. The OS was similar between the two groups under evaluation (hazard ratio 1.2 [95% CI 0.7-2.1]) and within the subsets of patients (risk group, histology). The most common grade 3 and 4 AE observed were hypertension (24% and 2%), infection (12% and 7%) in the sunitinib and everolimus groups, respectively [33].

Recently, among a cohort of 1922 patients in the Korean metastatic RCC registry, a retrospective study analysed 156 (8.1%) patients diagnosed with papillary (93), chromophobe (20), collecting duct (18), unclassified (16) and Xp11.2 translocation (9) metastatic NCCRCC. Patients with metastatic NCCRCC were all pre-treated with mTOR inhibitor, cytokines or VEGF-tyrosine kinase inhibitors [VEGF-TKIs], and reported a worse total PFS (median: 6.0 vs 12.0 months, P = 0.0002), first-line PFS (median: 5.0 vs 8.0 months, P = 0.0008) and cancer-specific survival (CSS) (median: 24.0 vs 31.0 months, P = 0.0272) when compared to the patient group with metastatic clear cell RCC [35].

Additionally, the study reported a better survival outcome in terms of total PFS (14.0 vs 24.0 vs 12.0 months), first-line PFS (10.0 vs 18.0 vs 8.0 months) and CSS (58.0 vs 31.0 vs 31.0 months) in the chromophobe, Xp11.2 translocation and clear cell groups, respectively [35]. In contrast, patient groups with papillary, collecting duct and unclassified histology reported poorer survival outcomes than those in the clear cell histology group with a total PFS of 6.0 vs 4.0 vs 4.0 vs 12.0 months, respectively, a first-line PFS of 4.0 vs 4.0 vs 4.0 vs 8.0 months, respectively, and a CSS of 19.0 vs 35.0 vs 10.0 vs 31.0 months, respectively [35].

An American multicentre retrospective study recruited 23 patients diagnosed with metastatic NCCRCC (48% histology subtypes were not classified, 44% were papillary), previously treated with sunitinib (65%), pazopanib (30%) or axitinib (17%) and administered with the anti-PD1 monoclonal antibody nivolumab following disease progression between 12/2015 and 01/2017 [36]. This study demonstrated the safety and efficacy of nivolumab in NCCRCC treatment. Even though the median PFS was 4.2 months and median OS outcome was not reached after 6.5 months of median follow up, among 21 assessable patients, 6 (29%) reported partial response (PR) and 4 (19%) reported stable disease (SD) after radiologic evaluation with a 5.1 months median time to best response [36]; there were no treatment-related deaths. The commonest AE reported were fever (13%) and fatigue (13%) and the commonest grade 3 or 4 AE were fever (7%) and rash (5%). Nivolumab and cabozantinib were both approved as a second-line regimen for RCC. Nivolumab has more recently been shown to moderately improve the outcome in NCCRCC patients in a recent meta-analysis [37] and cabozantinib showed a significant improvement in PFS when compared to nivolumab in a systematic review, even though no difference in OS was reported [38]. In the absence of head-to-head comparison between nivolumab and cabozantinib, however, it remains challenging to identify the better approach for NCCRCC patients.

An interesting result was reported by another American retrospective study where 30 metastatic NCCRCC patients with different histology (17 papillary, 6 chromophobes, 3 unclassified, 2 bearing genetic translocation and 2 sarcomatoid) were administered with 60 mg daily cabozantinib. According to the final report, of the 28 patients with measurable disease, 18 (64%) reported stable disease (SD), 4 (14%) reported partial response (PR) (2 papillary, 1 chromophobe and 1 not classified RCC), 6 (21%) reported progression of disease, accounting for a disease control rate of 78% and an objective response rate of 14%. After a median follow-up of 20.6 months (95% confidence interval [CI]: 11.4-28.8), the median PFS was 8.6 months (95% CI: 6.1-14.7) and median OS was 25.4 months (95% CI: 15.5-35.4) [5]. Of note, 12 patients (57%) required dose reduction due to drug toxicity with fatigue (63%), diarrhoea (57%) and hand-foot skin reaction (37%) as the main AE.

Cabozantinib has also been recently investigated in a retrospective, cohort clinical trial carried out in 22 centres with 122 patients enrolled with non-clear cell histology confirmed diagnosis [7]. The vast majority of patients showed papillary histology (59%), followed by Xp11.2 translocation (15%), unclassified histology (13%), chromophobe histology (9%) and collecting duct histology (4%). All patients were previously treated between 2015 and 2018 with any line of therapy available. According to RECIST criteria, radiological complete or partial positive response to the treatment was reported by 30 (27%) patients. With a median of 11 months follow-up, patients reported 12.0 months mOS and 7.0 months mPFS. Cabozantinib discontinuation occurred mostly due to progression of disease (85%) and drug toxicity (7%), leading to a median time to treatment failure (TTF) of 6.7 months. 101 patients (83%) were daily administered with cabozantinib (60 mg) with fatigue (52%), diarrhoea (34%), rash and palmar-plantar erythrodysesthesia (31%), nausea (29%) and hypertension (28%) reported as primary side effects. These side effects were mild to moderate grade, evaluated as acceptable and manageable with no severe clinical implication and in line with

common tyrosine kinase inhibitor (TKI) side effects. 58 patients (48%) were investigated with next generation sequencing (NGS): cyclin-dependent kinase inhibitor 2A (*CDKN2A*) was the commonest mutated gene (22% of cases) among all tumours, followed by mesenchymal-epithelial transitions (*MET*) (20%). According to the authors and considering that 29 patients (24%) were previously administered with three or more chemotherapy regimens, cabozantinib showed promising efficacy and tolerable toxicity profile in the treatment of naïve and heavily pre-treated NCCRCC patients.

Among potential shortcomings of this study, patient recruitment (i.e. heterogeneous histology), clinical background and the retrospective nature of the study represent possible biases. In addition, not every patient was evaluated for cabozantinib efficacy in relation to genomic mutations and not every patient was centrally reviewed for objective response. Although several studies have included MET biomarkers for the identification of patients who might benefit most from HGF/MET single or combined targeted therapies, reliable data on the predictive role of MET aberrations as response markers are lacking [39]. Also, time-to-treatment failure (TTF) endpoint has been reported instead of PFS. This could have led to consideration of treatment discontinuation due to a physician's decisions on drug toxicity rather than documented tumour progression. Lastly, recent real-world data (RWD) analysis of cabozantinib reported PFS data for pre-treated patients with metastatic RCC. It is noteworthy that the PFS of cabozantinib as a second-line and third-line regimen was 7.76 and 11.38 months respectively, with no significant differences between clear cell and non-clear cell histology. This is potentially explained by the higher prevalence of papillary histology tumours in the NCCRCC group [40]. In order to avoid toxicity and unwanted drug discontinuation, liquid chromatography-tandem mass spectrometry could be used to assess cabozantinib in plasma and monitor the exposure levels of patients [41].

Ongoing trials

Currently, cabozantinib is under evaluation in four phase II clinical trials, all in a “recruiting” status with no preliminary results available (Table 2). The NCT03685448 (UNICAB) trial is investigating the effectiveness in terms of objective response rate (ORR), safety and tolerability of 60 mg/day cabozantinib alone (single arm) in 48 patients diagnosed with locally advanced or metastatic NCCRCC who progressed after prior therapy. In the NCT03635892 trial, 57 patients with advanced or metastatic NCCRCC and no prior PD-1/PD-L1 therapy have been administered with 40 mg/day cabozantinib plus 420 mg nivolumab at day 1 and day 15 per cycle. The primary outcome of the study is the assessment of ORR defined by histology across three different cohorts. 84 patients with NCCRCC are expected to be enrolled in the NCT03541902 clinical trial and randomized to receive daily oral cabozantinib or sunitinib malate on days 1-28; PFS within the two cohorts is the primary outcome. Lastly, the NCT03354884 trial (BONSAI) is recruiting 23 patients with collecting duct non-clear cell histology to be orally administered with 60 mg/day cabozantinib in a single arm to define the ORR of cabozantinib. Eligible patients must be affected by unresectable, advanced or metastatic collecting duct NCCRCC, with no prior treatment.

In summary, while RCC with clear cell histology has been largely investigated with positive results, NCCRCC has been poorly investigated so far due to the shortage of samples available and the genetic, clinical and prognostic heterogeneity. Nevertheless, given the questionable results from studies to date, and uncertainty as to whether NCCRCC patients can be administered with cabozantinib, we would emphasize the need to optimize NCCRCC therapies in the foreseeable future. Given this background, the noteworthy effort made in clinical studies to date could pave the way to new approaches to NCCRCC treatment. An

approach involving a prospective histology- and molecular biology-driven umbrella trial for this category of renal cell cancer is warranted.

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References

1. Kroiss M, Megerle F, Kurlbaum M, Zimmermann S, Wendler J, Jimenez C, et al. Objective response and prolonged disease control of advanced adrenocortical carcinoma with cabozantinib. J Clin Endocrinol Metab. 2020 [cited 13 Jan 2020]. doi:10.1210/clinem/dgz318

2. Choueiri TK, Halabi S, Sanford BL, Hahn O, Michaelson MD, Walsh MK, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: The alliance A031203 CABOSUN trial. J Clin Oncol. 2017;35: 591–597. doi:10.1200/JCO.2016.70.7398

3. Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015;373: 1814–23. doi:10.1056/NEJMoa1510016

4. Prisciandaro M, Ratta R, Massari F, Fornarini G, Caponnetto S, Iacovelli R, et al. Safety and efficacy of cabozantinib for metastatic nonclear renal cell carcinoma: Real-world data from an Italian managed access program. Am J Clin Oncol Cancer Clin Trials. 2019;42: 42–45. doi:10.1097/COC.0000000000000478

5. Campbell MT, Bilen MA, Shah AY, Lemke E, Jonasch E, Venkatesan AM, et al. Cabozantinib for the treatment of patients with metastatic non-clear cell renal cell carcinoma: A retrospective analysis. Eur J Cancer. 2018;104: 188–194. doi:10.1016/j.ejca.2018.08.014

6. Sneed GT, Lee S, Brown JN, Hammond JM. The Role of Pazopanib in Non-Clear Cell Renal Cell Carcinoma: A Systematic Review. Clinical Genitourinary Cancer. Elsevier Inc.; 2019. doi:10.1016/j.clgc.2019.09.001

7. Martínez Chanzá N, Xie W, Asim Bilen M, Dzimitrowicz H, Burkart J, Geynisman DM, et al. Cabozantinib in advanced non-clear-cell renal cell carcinoma: a multicentre, retrospective, cohort study. Lancet Oncol. 2019;20: 581–590. doi:10.1016/S1470-2045(18)30907-0

8. 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: 93–105. doi:10.1016/j.eururo.2016.02.029

9. Ricketts CJ, De Cubas AA, Fan H, Smith CC, Lang M, Reznik E, et al. The Cancer Genome Atlas Comprehensive Molecular Characterization of Renal Cell Carcinoma. Cell Rep. 2018;23: 313-326.e5. doi:10.1016/j.celrep.2018.03.075

10. Lopez-Beltran A, Carrasco JC, Cheng L, Scarpelli M, Kirkali Z, Montironi R. 2009 update on the classification of renal epithelial tumors in adults. International Journal of Urology. 2009. pp. 432–443. doi:10.1111/j.1442-2042.2009.02302.x

11. Linehan, W. Marston, Walther MM ZB. The genetic basis of cancer of the kidney. J Urol. 2003;170 (6 Pt.

12. Gnarra JR, Tory K, Weng Y, Schmidt L, Wei MH, Li H, et al. Mutations of the VHL tumour suppressor gene in renal carcinoma. Nat Genet. 1994;7: 85–90. doi:10.1038/ng0594-85

13. Banks RE, Tirukonda P, Taylor C, Hornigold N, Astuti D, Cohen D, et al. Genetic and epigenetic analysis of von Hippel-Lindau (VHL) gene alterations and relationship with clinical variables in sporadic renal cancer. Cancer Res. 2006;66: 2000–2011. doi:10.1158/0008-5472.CAN-05-3074

14. Moore LE, Nickerson ML, Brennan P, Toro JR, Jaeger E, Rinsky J, et al. Von Hippel-Lindau (VHL) inactivation in sporadic clear cell renal cancer: Associations with germline VHL polymorphisms and etiologic risk factors. PLoS Genet. 2011;7. doi:10.1371/journal.pgen.1002312

15. Ljungberg BJ JJ. Different vascular endothelial growth factor (VEGF), VEGF-receptor 1 and -2 mRNA expression profiles between clear cell and papillary renal cell carcinoma. BJU Int. 2006.

16. Durinck S, Stawiski EW, Pavía-Jiménez A, Modrusan Z, Kapur P, Jaiswal BS, et al. Spectrum of diverse genomic alterations define non-clear cell renal carcinoma subtypes. Nat Genet. 2015;47: 13–21. doi:10.1038/ng.3146

17. Davis CF, Ricketts CJ, Wang M, Yang L, Cherniack AD, Shen H, et al. The somatic genomic landscape of chromophobe renal cell carcinoma. Cancer Cell. 2014;26: 319–330. doi:10.1016/j.ccr.2014.07.014

18. Malouf GG, Monzon FA, Couturier J, Molinié V, Escudier B, Camparo P, et al. Genomic heterogeneity of translocation renal cell carcinoma. Clin Cancer Res. 2013;19: 4673–4684. doi:10.1158/1078-0432.CCR-12-3825

19. Lin F, Zhang PL, Yang XJ, Prichard JW, Lun M, Brown RE. Morphoproteomic and molecular concomitants of an overexpressed and activated mTOR pathway in renal cell carcinomas. Ann Clin Lab Sci. 2006;36: 283–293.

20. Pantuck AJ, Seligson DB, Klatte T, Yu H, Leppert JT, Moore L, et al. Prognostic relevance of the mTOR pathway in renal cell carcinoma: Implications for molecular patient selection for targeted therapy. Cancer. 2007;109: 2257–2267. doi:10.1002/cncr.22677

21. Yamazaki K, Sakamoto M, Ohta T, Kanai Y, Ohki M, Hirohashi S. Overexpression of KIT in chromophobe renal cell carcinoma. Oncogene. 2003;22: 847–852. doi:10.1038/sj.onc.1206153

22. Krüger S, Sotlar K, Kausch I, Horny HP. Expression of KIT (CD117) in renal cell carcinoma and renal oncocytoma. Oncology. 2005;68: 269–275. doi:10.1159/000086783

23. Hung MS, Chen IC, Lin PY, Lung JH, Li YC, Lin YC, et al. Epidermal growth factor receptor mutation enhances expression of vascular endothelial growth factor in lung cancer. Oncol Lett. 2016;12: 4598–4604. doi:10.3892/ol.2016.5287

24. Linehan WM, Spellman PT, Ricketts CJ, Creighton CJ, Fei SS, Davis C, et al. Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma. N Engl J Med. 2016;374: 135–145. doi:10.1056/NEJMoa1505917

25. Becker F, Junker K, Parr M, Hartmann A, Füssel S, Toma M, et al. Collecting Duct Carcinomas Represent a Unique Tumor Entity Based on Genetic Alterations. Black PC, editor. PLoS One. 2013;8: e78137. doi:10.1371/journal.pone.0078137

26. Young AN, Amin MB, Moreno CS, Lim SD, Cohen C, Petros JA, et al. Expression profiling of renal epithelial neoplasms: A method for tumor classification and discovery of diagnostic molecular markers. Am J Pathol. 2001;158: 1639–1651. doi:10.1016/S0002-9440(10)64120-X

27. Takahashi M, Teh BT, Kanayama HO. Elucidation of the molecular signatures of renal cell carcinoma by gene expression profiling. Journal of Medical Investigation. 2006. pp. 9–19. doi:10.2152/jmi.53.9

28. Schuetz AN, Yin-Goen Q, Amin MB, Moreno CS, Cohen C, Hornsby CD, et al. Molecular classification of renal tumors by gene expession profiling. J Mol Diagnostics. 2005;7: 206–218. doi:10.1016/S1525-1578(10)60547-8

29. Carlo MI, Khan N, Chen Y, Hsieh J, Hakimi AA, Lee C-H, et al. The genomic landscape of metastatic non-clear cell renal cell carcinoma. J Clin Oncol. 2017;35: 474–474. doi:10.1200/jco.2017.35.6_suppl.474

30. Osunkoya AO, Yin-Goen Q, Phan JH, Moffitt RA, Stokes TH, Wang MD, et al. Diagnostic biomarkers for renal cell carcinoma: selection using novel bioinformatics systems for microarray data analysis. Hum Pathol. 2009;40: 1671–1678. doi:10.1016/j.humpath.2009.05.006

31. Kroeger N, Xie W, Lee JL, Bjarnason GA, Knox JJ, MacKenzie MJ, 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;119: 2999–3006. doi:10.1002/cncr.28151

32. Ged Y, Chen YB, Knezevic A, Casuscelli J, Redzematovic A, DiNatale RG, et al. Metastatic Chromophobe Renal Cell Carcinoma: Presence or Absence of Sarcomatoid Differentiation Determines Clinical Course and Treatment Outcomes. Clin Genitourin Cancer. 2019;17: e678–e688. doi:10.1016/j.clgc.2019.03.018

33. Armstrong AJ, Halabi S, Eisen T, Broderick S, Stadler WM, Jones RJ, 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: 378–388. doi:10.1016/S1470-2045(15)00515-X

34. Tannir NM, Jonasch E, Albiges L, Altinmakas E, Ng CS, Matin SF, 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: 866–874. doi:10.1016/j.eururo.2015.10.049

35. Kim JK, Kim SH, Song MK, Joo J, Seo S Il, Kwak C, et al. Survival and clinical prognostic factors in metastatic non-clear cell renal cell carcinoma treated with targeted therapy: A multi-institutional, retrospective study using the Korean metastatic renal cell carcinoma registry. Cancer Med. 2019;8: 3401–3410. doi:10.1002/cam4.2222

36. Koshkin VS, Barata PC, Vogelzang NJ, Pal SK, Hsu J, Allman KD, et al. Nivolumab treatment for patients with non-clear cell renal cell carcinoma: A multicenter retrospective analysis. J Clin Oncol. 2017;35: 4586–4586. doi:10.1200/jco.2017.35.15_suppl.4586

37. Chahoud J, Msaouel P, Campbell MT, Bathala T, Xiao L, Gao J, Zurita AJ, Shah AY, Jonasch E, Sharma P TN. Nivolumab for the Treatment of Patients with Metastatic Non-Clear Cell Renal Cell Carcinoma (nccRCC): A Single-Institutional Experience and Literature Meta-Analysis. Oncologist. 2019.

38. Porta C, Szczylik C, Casciano R, Fu S, Amzal B, Lister J, Karcher H, Meng J, Neumann M DJ. Second-line cabozantinib versus nivolumab in advanced renal cell carcinoma: Systematic review and indirect treatment comparison. Crit Rev Oncol Hematol. 2019.

39. Moosavi F, Giovannetti E, Saso L FO. HGF/MET pathway aberrations as diagnostic, prognostic, and predictive biomarkers in human cancers. Crit Rev Clin Lab Sci. 2019.

40. Di Nunno V, Mollica V, Santoni M, Gatto L, Schiavina R, Fiorentino M, et al. New Hormonal Agents in Patients With Nonmetastatic Castration-Resistant Prostate Cancer: Meta-Analysis of Efficacy and Safety Outcomes. Clin Genitourin Cancer. 2019 [cited 1 Oct 2019]. doi:10.1016/j.clgc.2019.07.001

41. Ferrer F, Solas C, Giocanti M, Lacarelle B, Deville JL, Gravis G CJ. A simple and rapid liquid chromatography-mass spectrometry method to assay cabozantinib in plasma: Application to therapeutic drug monitoring in patients with renal cell carcinoma. J Chromatogr B Anal Technol Biomed Life Sci. 2020.