Non-clear cell advanced kidney cancer: is there a gold standard?

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Renal cell carcinoma (RCC) accounts for approximately 3% of all new cancer diagnosis every year. RCC arises from the renal epithelium and represents 85% of all kidney tumors. According to histology, these neoplasms are divided into the following types: clear cell, papillary, chromophobe, oncocytoma, collecting duct, and unclassified. Approximately, 75% of RCCs are of the clear cell type and in recent years, there have been substantial advances in the understanding of its molecular biology leading to the development of effective treatments. However, there is still an area of uncertainty with regard to non-clear cell histologies. Scarce studies have been conducted testing different drugs in this patient population. Thus, most of the evidence comes from small phase II trials, retrospective analysis, or expanded access programs. Recent insights in the molecular basis of these tumors have opened a promising research field. Molecules targeting mammalian target of rapamycin, epidermal growth factor receptor, c-MET, vascular endothelial growth factor, and platelet-derived growth factor are among some of the promising drugs tested in this setting. This article reviews the mechanisms of disease on RCC and summarizes treatment options with a particular focus on patients with non-clear cell tumors. ***Anti-Cancer Drugs*** **22 (suppl 1):S9–S14 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Approximately 55 000 patients are diagnosed every year with renal cancer in the United States and approximately 12 000 deaths are caused by this disease. The incidence of this tumor has increased over the last decade and currently kidney cancer represents the seventh most common malignancy in men and the ninth in women [1,2]. Renal cell carcinoma (RCC) arises from the renal epithelium and represents 85% of all kidney cancers. According to histology these tumors are divided into the following types: clear cell, papillary, chromophobe, oncocytoma, collecting duct, and unclassified [3]. Up to 25% of the patients present with locally advanced or metastatic disease at diagnosis. In addition, one third of the patients who undergo resection of localized disease will have a recurrence requiring systemic therapy [2].

The vast majority of RCCs is of the clear cell type and in recent years, there have been substantial advances in the understanding of the molecular biology of this cancer subtype, which has led to the development of more effective treatments. Important progress has also been made in non-clear cell cancers although there is no a well-defined standard care for this patient population.

This article will briefly review the mechanisms of the disease for RCC and will summarize the treatment options with a particular focus on patients with non-clear cell tumors.

Renal cell cancer: mechanisms of disease

Although historically considered as a single entity, we have recently learned that RCC includes a number of different tumor types that occur in the kidney. Each one has a different genetic and molecular basis, a particular histology and clinical course, and responds differently to the available treatments [4]. Increased knowledge of some hereditary syndromes (extensively described in another article of this supplement) has allowed us to better define disease mechanisms and to identify the responsible genes and potential treatment targets.

The von Hippel–Lindau gene and clear cell renal cell carcinoma

The von Hippel–Lindau (*VHL*) gene was identified on the short arm of chromosome 3 in genetic analysis done on families with this syndrome. A mutation in this tumor suppressor gene was found in the germline of approximately 100% individuals with the disease [5]. More recently, when the tumor tissue from patients with sporadic RCC was tested for alteration on this gene, mutations were detected in a higher percentage of cases [6]. In fact, one series reported inactivation of the *VHL* gene by either mutation or methylation in up to 91% of tumors from patients with sporadic clear cell RCC [7]. Interestingly, no mutations of VHL were detected in the tumors from patients with other varieties of RCCs such as chromophobe, papillary, or collecting duct.

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Through the formation of a complex with elongin B and C and Cul2, VHLp (the *VHL* gene product) targets the hypoxia inducible factors, HIF-1-α and HIF-2-α for ubiquitin-mediated degradation. When the VHL gene product is absent by either mutation or methylation of the *VHL* gene, HIF is not degraded and accumulates leading to increased transcription of HIF downstream genes involved in angiogenesis, cell proliferation, glucose uptake, and acid–base balance, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor, transforming growth factor, glucose transporter (GLUT-1), and carbonic anhidrase IX (CAIX) [2]. In addition, the levels of HIF-1-α also increase by the activation of the mammalian target of rapamycin (m-TOR) pathway [8].

The *MET* gene and type 1 papillary kidney cancer

The study of families with hereditary papillary renal carcinoma (HPRC) syndrome shows that the affected individuals have a higher risk of presenting bilateral multifocal type I papillary RCC. Genetic analysis showed that the *MET* gene located on chromosome 7 was the gene responsible for HPRC [9]. Mutations in the tyrosine kinase domain of MET are found in the germ line of patients suffering from this syndrome and in patients with sporadic forms of this tumor variety. As a consequence, an abnormal c-MET protein (also known as hepatocyte growth factor receptor) is synthesized originating a ligand-independent activation of the hepatocyte growth factor receptor and its downstream pathways, which lead to uncontrolled cell proliferation [2,4].

Chromophobe kidney cancer and the Birt–Hogg–Dubé syndrome

Another inherited RCC characterized by benign cutaneous lesions (fibrofoliculomas), pulmonary cysts, spontaneous pneumothorax, and renal tumors, is the Birt–Hogg–Dubé (BHD) syndrome. The affected individuals are at a higher risk of developing bilateral multifocal renal tumors with chromophobe, oncocytic, clear cell, or mixed histologies involved. The BHD gene has been identified on chromosome 17 and more than 90% of patients with the syndrome present germ line mutations of this tumor suppressor gene [10]. The gene product is the folliculin that, in normal conditions, forms a complex with two other proteins that bind AMP-activated protein kinase (AMPK) to negatively regulate mTOR activity [11].

Type II papillary kidney cancer and hereditary leiomyomatosis renal cell carcinoma

The hereditary leiomyomatosis RCC syndrome is another genodermatosis in which the affected individuals have a higher risk of developing leiomyomas in the uterus or the skin and RCC. The predominant RCC variety is the type II papillary type, which is abnormally aggressive and has a high propensity to metastasize even with small primary tumors. Genetic analysis has shown that the fumarate hydratase (*FH*) gene involved in Krebs cycle control, is the responsible gene for this syndrome and is mutated in more than 90% of the families with hereditary leiomyomatosis RCC syndrome [12]. The mutations of FH lead to the accumulation of fumarate that inhibits, in a competitive manner, the HIF prolyl hydroxylase activity. This prevents HIF hydroxylation and leads to the accumulation of this transcription factor and increased proangiogenic and cell proliferation activity. Moreover, there is accumulation of the reactive oxygen species that also contribute to the stabilization of HIF and increase its transcriptional activity [13,14].

Treatment of non-clear cell advanced renal cell cancer

There has been impressive progress in the treatment of clear cell RCC parallel to the improvement in the knowledge of its molecular/genetic basis. Thus, there are at least six different drugs (tyrosine kinase inhibitors, monoclonal antibodies, and m-TOR inhibitors) that have been approved by the Food and Drug Administration or European Medicines Agency for the treatment of this disease including sunitinib, sorafenib, pazopanib, bevacizumab (in combination with interferon-α), temsirolimus, and everolimus [15].

However, there is still an area of uncertainty for the clinician as little evidence is currently available to decide about treatment of patients with non-clear cell histologies. Most of the pivotal studies that led to the approval of the currently available drugs for advanced RCC excluded patients with the non-clear cell varieties (except for the randomized trial of temsirolimus) [16].

Different analyses testing the efficacy of tyrosine kinase inhibitors and mTOR inhibitors in patients with non-clear cell tumors have shown quite variable response rates ranging from 0 to 46% [16–26]. A number of prospective trials are ongoing in this patient population and promising targets, such as c-MET in papillary tumors, have been identified, opening new treatment options that are being currently tested.

There is a great need to better define how to treat this group of patients that represent approximately one out of four patients with advanced RCC seen in the clinic.

In the following paragraphs the evidence regarding currently available treatment options for the different subtypes of non-clear cell RCC will be presented and summarized in Table 1.

Papillary renal cell carcinoma

Papillary RCC (PRCC) accounts for approximately 10–15% of RCC, being the most common subtype after clear cell tumors. The overall prognosis of these patients is similar, stage by stage, to clear cell subtypes [18,27,28]. PRCC is resistant to conventional chemotherapy and immunotherapy treatments [28,29]. There are two histological subtypes of PRCC: type I tumors that are formed by small cells with pale cytoplasm and type II PRCC

Table 1 Treatment options for non-clear cell renal cell carcinoma subtypes

Subtypes of non-clear cell RCC	Percentage of total cases of RCC	Treatment options	References	Trials ongoing
Papillary	15%	Temsirolimus	[16]	Everolimus
		Erlotinib	[22]	Bevacizumab + erlotinib
		Sorafenib	[17,19, 23,24,27]	Sunitinib
		Sunitinib	[17,20,21]	Temsirolimus vs. sunitinib
		C-MET inhibitors (GSK1363089)	[27,32]	
Chromophobe	4–8%	Temsirolimus	[16]	Sunitinib
		Sorafenib	[17,19,23,24]	Temsirolimus vs. sunitinib
		Sunitinib	[17,21]	
		C-KIT inhibitors	[37]	
Collecting duct	3%	Cisplatin–gemcitabine	[39]	Sunitinib
		Sorafenib	[41]	Temsirolimus vs. sunitinib
		Topoisomerase inhibition (AQ4)	[43]	
Sarcomatoid	1%	Doxorubicin combinations	[25,26]	Sunitinib
		Temsirolimus	[16]	
		Sorafenib	[18]	Gemcitabine + sunitinib
		Sunitinib	[18]	
		Bevacizumab	[18]	Capecitabine + gemcitabine + bevacizumab

RCC, renal cell carcinoma.

tumors that are characterized by large eosinophilic cells. Type I tumors have been associated with alterations in the cMET pathway whereas type II hereditary tumors have been linked to mutations in the *FH* gene. By gene expression profiling, PRCC tumors have been classified into two groups: those that have a good prognosis and includes type I tumors, low-grade type II, and mixed tumors and those that have poor prognosis, which correspond to high-grade type II tumors [30].

Tyrosine kinase inhibitors

Sorafenib: There are very few studies testing new agents in PRCC. In the initial randomized discontinuation trial of sorafenib in patients with RCC, 15 patients with PRCC were included and two achieved a partial response.

Sorafenib has been administered to patients with PRCC as part of the expanded access programs available both in the United States and in Europe. In a total of 170 patients treated with the drug in the United States, 27 patients have achieved a partial response (confirmed only in four patients). In 104 patients treated in Europe, the disease control rate was 66% and median progression-free survival (PFS) was 5.8 months [19,24,27].

Sunitinib: Sunitinib has also been tested in patients with non-clear cell histologies as part of an expansion access program. However, the results of this study have not been reported separately for the different subtypes included [21]. Moreover, a retrospective analysis conducted on 41 patients with histologically confirmed PRCC, who received either sunitinib (13 patients) or sorafenib (28 patients) suggests that sunitinib may be more effective. In this trial, sunitinib resulted in 15% partial responses and a PFS of 11.9 months compared with no objective responses and PFS of 5.1 months for patients treated with sorafenib [17]. Nevertheless, these results were not replicated in a prospective manner. Thus, in a recently reported prospective phase II study of sunitinib in patients with RCC and non-clear cell histology, the agent did not result in any objective response in 23 patients with the PRCC subtype. The PFS and overall survival (OS) were, respectively, 1.6 and 10.8 months [20].

Mammalian target of rapamycin inhibitors

Unlike the registration studies with tyrosine kinase inhibitors, which were restricted to patients with clear cell histology, the pivotal trial of temsirolimus in RCC included a significant percentage of patients with non-clear cell histology [16]. In a subset analysis of this group, temsirolimus showed a higher OS (11.6 versus 4.6 months) and PFS (7 versus 1.8 months) compared with interferon. These tumors were not, however, centrally reviewed. On the basis of these data, new studies are currently ongoing to test the efficacy of mTOR inhibitors in patients with PRCC, such as the RAPTOR trial (NCT00688753) that will test the efficacy of everolimus in patients with PRCC.

Epidermal growth factor receptor inhibitors

In preclinical studies, the blockage of the epidermal growth factor receptor by a monoclonal antibody against the receptor resulted in significant tumor growth inhibition in PRCC cell lines [31]. These data prompted a phase II study in patients with PRCC: Patients with advanced PRCC were treated with erlotinib (150 mg orally, once daily). The overall response rate was 11% (five of 45 patients), and the disease control rate was 64% being the median OS of 27 months. The single-agent erlotinib, yielded disease control and survival outcomes of interest with an expected toxicity profile [22].

c-MET inhibitors

As mentioned above, hereditary PRCC harbors mutations in the *c-MET* gene. In addition, sporadic PRCC often has

amplification or overexpression of the *c-MET* oncogene. In a phase I study of the MET inhibitor, GSK1363089, three patients with PRCC, of the four patients treated, achieved a partial response [27,32]. These data led to a phase II study of this agent in patients with histologically proven PRCC stratified into two groups based on c-MET activation. In a preliminary analysis of this group, of 25 evaluable patients there have been two confirmed partial responses.

New directions: lactate dehydrogenase-A

Inhibition of FH in type II PRCC results in a significant decrease in oxidative phosphorylation necessitating glycolysis followed by fermentation of pyruvate to lactate to provide adequate ATP and to regenerate nicotinamide adenine dinucleotide (NAD^+). Moreover, FH deficiency is known to upregulate the expression of HIF-1-α by enhancing the stability of the HIF transcript. Lactate dehydrogenase-A, also a HIF-1-α target, promotes fermentative glycolysis (conversion of pyruvate to lactate), a step essential for regenerating NAD^+. It has been shown that RCC tumors indeed overexpress lactate dehydrogenase-A and that lactate dehydrogenase-A inhibition results in increased apoptosis in cells with FH deficiency, suggesting that this could be another therapeutic opportunity for these tumor types [33].

Ongoing studies

There is currently a phase II study at MD Anderson Cancer Center (Houston, USA) testing the efficacy of sunitinib in patients with non-clear cell histologies including papillary tumors (NCT00465179). Another randomized phase II study is testing the efficacy of sunitinib versus temsirolimus in non-clear cell RCC patients (NCT00979966).

Chromophobe renal cell carcinoma

Chromophobe RCC (ChRCC) accounts for approximately 4–8% of all RCCs and has an overall more favorable prognosis compared with clear cell RCC and PRCC although this 'advantage' seems to be lost in the advanced setting in some patients [34]. Given the relative rarity of ChrRCC, there is no current standard of care for patients with advanced disease pending results from ongoing trials.

Mammalian target of rapamycin inhibitors: temsirolimus

From the analysis of the BHD syndrome patients and recent genomic studies focused on this population, there are new data that have allowed shedding of light on the underlying genetic abnormalities that drive the tumorigenesis of this tumor type. Two major pathways, the c-erbB2/HER2 and the mTOR signaling pathway, have been shown to be deregulated in ChRCC on exploratory analysis of mRNA expression [35]. It has also been reported that these tumors have phosphorylation and overexpression of energy pathway genes [36].

Therefore, the mTOR inhibitors seem a reasonable option for the treatment of this tumor type. The pivotal study of temsirolimus included approximately 20% of non-clear cell tumors (how many of each subtype is not specified) and is the only prospective data in this regard [16].

c-KIT inhibitors

One of the characteristics of ChrRCC is the expression of CD117 (KIT), a membrane receptor that plays an important role in the signal transduction. Different from other tumor types such as gastrointestinal stromal tumors, KIT mutations have not been detected in ChrRCC. These data support the hypothesis that KIT inhibitors such as imatinib, dasatinib, or nilotinib could be effective in this type of RCC but no hard data are yet available [37].

Tyrosine kinase inhibitors

Sorafenib and sunitinib have been studied in patients with ChrRCC [23]. The expanded access program of sorafenib in North America included 20 patients with ChrRCC and reported one partial response (5%) [24]. In another report, among the 12 patients with ChRCC included, seven were treated with sunitinib and five were treated with sorafenib. Two patients treated with sorafenib and one patient treated with sunitinib achieved a partial response, corresponding to a response rate of 25% (three of 12 patients). PFS for patients with ChRCC was 10.6 months. Patients treated with sorafenib tended to have a prolonged median PFS (27.5 months) [17].

Ongoing studies

Two studies using sunitinib are ongoing in patients with chRCC: a single-arm phase II study (NCT00465179) and a randomized phase II trial testing sunitinib versus temsirolimus (NCT00979966).

Collecting duct renal cell carcinoma

Collecting duct RCC, also known as 'Bellini duct tumor', is a rare entity that represents less than 3% of all renal cell cancers. Compared with other histologies, collecting duct RCC are usually diagnosed at higher stages and have worse disease-specific survival [38–43].

Cisplatin–gemcitabine

As with other non-clear cell RCCs, cytokines have shown little efficacy in the treatment of these tumors while some chemosensitivity has been observed. Thus, studies combining platinum and gemcitabine showed response rates of 26% and PFS and OS of 7.1 and 10.5 months, respectively [39]. Certain common features of urothelial tumors could explain this unusual response to cytotoxics not common in a clear cell RCC [40].

Sorafenib

A case report in the literature reported a significant response to sorafenib but there are very few additional data to support its use [41].

New directions: topoisomerase inhibitors

Recent studies on cell lines have identified some genetic alterations and chemosensitivity profiles for collecting duct RCC. Topoisomerase I was identified as a valid molecular target in this tumor type in a genomic analysis [42]. In fact AQ4N, a novel prodrug, which is selectively bioreduced to AQ4 (a topoisomerase II inhibitor) in hypoxic tumor, showed remarkable activity in a patient participating in the phase I study [43].

Ongoing studies

Two phase II studies are testing the efficacy of sunitinib in this population: the NCT00465179 as a single-agent, one-arm trial and the NCT00979966 with a randomized phase II design testing the efficacy of sunitinib versus temsirolimus.

Sarcomatoid differentiation

Sarcomatoid differentiation is not a distinct histological entity itself but rather a growth pattern characterized by malignant spindle-shaped cell histology that can be observed across all RCC subtypes, including clear cell, papillary, chromophobe, and collecting ducts [18,44]. In fact, the sarcomatoid differentiation is thought to represent transformation of a RCC to a much-undifferentiated form being by definition a Fuhrman grade 4. These tumors have a high incidence of metastases to the bone and lung at presentation and very dismal prognosis overall. Median overall survival for stage IV patients varies from 3 to 10 months and for those patients with localized disease the 5-year survival rate is approximately 19% [45,46].

Historically, patients with RCC and sarcomatoid features have shown limited response to the treatment. A few prospective studies that were carried out, most of them with doxorubicin-based chemotherapy involved relatively small numbers of patients and had disappointing results [25,26].

Vascular endothelial growth factor/vascular endothelial growth factor receptor inhibitors

The major trials conducted with VEGF/VEGF receptor inhibitors, such as sunitinib, sorafenib, and bevacizumab, in metastatic RCC did not report the percentage of patients who had sarcomatoid elements making it difficult to reach any conclusion regarding the activity of these compounds. Golshayan *et al.* [18] reported data from a retrospective analysis of 43 patients with metastatic sarcomatoid RCC treated with either sunitinib ($n = 21$), sorafenib ($n = 12$), bevacizumab ($n = 8$), or the combination of bevacizumab and sunitinib ($n = 2$). They confirmed that the VEGF-targeted therapy had clinical activity in patients with metastatic RCC with sarcomatoid features, most notably in patients with clear cell histology and a low percentage of sarcomatoid elements. However, the retrospective nature of the study limits its conclusions.

Mammalian target of rapamycin inhibitors

With regard to mTOR inhibitors, of the 626 patients randomized in the pivotal phase III study of temsirolimus, 63 patients had sarcomatoid RCC. However, no subanalysis was carried out on this particular subset of patients [16].

Ongoing studies

There are three ongoing phase II trials that use VEGF-targeted agents in sarcomatoid RCC. One is testing the combination of gemcitabine and sunitinib in sarcomatoid and/or poor-risk patients with metastatic RCC (NCT 0556049). The other two trials are designed specifically for sarcomatoid tumors. One evaluates the activity of the combination of capecitabine, gemcitabine, and bevacizumab (NCT00496587) and in the other trial sunitinib as a single agent (NCT00465179).

Conclusion

The progress in the understanding of the genetics and molecular basis of RCC has provided the foundation for the recent development of targeted drugs in this disease. Regarding the non-clear cell tumors most of the current data come from retrospective analysis or some prospective series with scarce number of patients, which, in general terms show the trends of activity for the available targeted drugs in these tumor subtypes. Overall, these methodological limitations need to be taken into account when analyzing the data and making treatment decisions. There is a real need of including more patients with non-clear cell histologies in randomized studies. Several studies are currently ongoing to test different compounds alone or within combinations. The results of these trials are highly awaited and will contribute to defining a standard. Pharmacodynamic and biomarker endpoints are also critical in these trials to aid in responding to some of the multiple unanswered questions in this field of medical oncology.

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References

1 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; **59**:225–249.

2 Cohen HT, McGovern FJ. Renal cell carcinoma. *N Engl J Med* 2005; **353**:2477–2490.
3 Kovacs G, Akhtar M, Beckwith BJ, Bugert P, Cooper CS, Delahunt B, *et al.* The Heidelberg classification of renal cell tumours. *J Pathol* 1997; **183**:131–133.
4 Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. *J Urol* 2003; **170**:2163–2172.
5 Pack SD, Zbar B, Pak E, Ault DO, Humphrey JS, Pham T, *et al.* Constitutional von Hippel–Lindau (*VHL*) gene deletions detected in VHL families by fluorescence in-situ hybridization. *Cancer Res* 1999; **59**:5560–5564.
6 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.
7 Nickerson ML, Jaeger E, Shi Y, Durocher JA, Mahurkar S, Zaridze D, *et al.* Improved identification of von Hippel–Lindau gene alterations in clear cell renal tumors. *Clin Cancer Res* 2008; **14**:4726–4734.
8 Guertin DA, Sabatini DM. The pharmacology of mTOR inhibition. *Sci Signal* 2009; **2**:pe24.
9 Schmidt L, Junker K, Weirich G, Glenn G, Choyke P, Lubensky I, *et al.* Two North American families with hereditary papillary renal carcinoma and identical novel mutations in the MET proto-oncogene. *Cancer Res* 1998; **58**:1719–1722.
10 Schmidt LS, Nickerson ML, Warren MB, Glenn GM, Toro JR, Merino MJ, *et al.* Germ line BHD mutation spectrum and phenotype analysis of a large cohort of families with Birt–Hogg–Dube syndrome. *Am J Hum Genet* 2005; **76**:1023–1033.
11 Baba M, Hong SB, Sharma N, Warren MB, Nickerson ML, Iwamatsu A, *et al.* Folliculin encoded by the *BHD* gene interacts with a binding protein, FNIP1, and AMPK, and is involved in AMPK and mTOR signaling. *Proc Natl Acad Sci U S A* 2006; **103**:15552–15557.
12 Tomlinson IP, Alam NA, Rowan AJ, Barclay E, Jaeger EE, Kelsell D, *et al.* Germ line mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. *Nat Genet* 2002; **30**:406–410.
13 Isaacs JS, Jung YJ, Mole DR, Lee S, Torres-Cabala C, Chung YL, *et al.* HIF overexpression correlates with biallelic loss of fumarate hydratase in renal cancer: novel role of fumarate in regulation of HIF stability. *Cancer Cell* 2005; **8**:143–153.
14 Sudarshan S, Sourbier C, Kong HS, Block K, Valera Romero VA, Yang Y, *et al.* Fumarate hydratase deficiency in renal cancer induces glycolytic addiction and hypoxia-inducible transcription factor–1-α stabilization by glucose-dependent generation of reactive oxygen species. *Mol Cell Biol* 2009; **29**:4080–4090.
15 Motzer RJ, Agarwal N, Beard C, Bolger GB, Boston B, Carducci MA, *et al.* NCCN clinical practice guidelines in oncology: kidney cancer. *J Natl Compr Canc Netw* 2009; **7**:618–630.
16 Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, *et al.* Temsirolimus, interferon-α, or both for advanced renal cell carcinoma. *N Engl J Med* 2007; **356**:2271–2281.
17 Choueiri TK, Plantade A, Elson P, Negrier S, Ravaud A, Oudard S, *et al.* Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. *J Clin Oncol* 2008; **26**:127–131.
18 Golshayan AR, George S, Heng DY, Elson P, Wood LS, Mekhail TM, *et al.* Metastatic sarcomatoid renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. *J Clin Oncol* 2009; **27**:235–241.
19 Stadler WM, Ernstoff MS, Curti B, Figlin A, Pendergrass K, Srinivas S, *et al.* The Advanced Renal Cell Carcinoma Sorafenib (ARCCS) expanded access trial: safety and efficacy in patients (pts) with non-clear cell (NCC) renal cell carcinoma (RCC). *Journal of Clinical Oncology* 2007; **25**:5036.
20 Plimack E, Jonasch E, Bekele B, Qiao W, Ng CS, Tannir NM. Sunitinib in non-clear cell renal cell carcinoma (NCC-RCC): a phase II study. *J Clin Oncol* 2010; **28**:4604.
21 Gore ME, Oudard S, Bjarnason G, Porta C, Castellano D, Szczylik C, *et al.* Sunitinib in metastatic renal cell carcinoma (mRCC): Preliminary assessment of toxicity in an expanded access trial with subpopulation analysis. *J Clin Oncol* 2007; **20**:5010.
22 Pan C, Lara N, Mack PC, Hussey M, Nagle R, Dutcher JP, *et al.* Encouraging survival with erlotinib in advanced papillary renal cell carcinoma (PRCC): Final results from Southwest Oncology Group study 0317. *J Clin Oncol* 2008; **20**:5051.
23 Procopio G, Verzoni E, Gevorgyan A, Mancin M, Pusceddu S, Catena L, *et al.* Safety and activity of sorafenib in different histotypes of advanced renal cell carcinoma. *Oncology* 2007; **73**:204–209.
24 Stadler WM, Figlin RA, McDermott DF, Dutcher JP, Knox JJ, Miller WH Jr, *et al.* Safety and efficacy results of the advanced renal cell carcinoma sorafenib expanded access program in North America. *Cancer* 2010; **116**:1272–1280.
25 Escudier B, Droz JP, Rolland F, Terrier-Lacombe MJ, Gravis G, Beuzeboc P, *et al.* Doxorubicin and ifosfamide in patients with metastatic sarcomatoid renal cell carcinoma: a phase II study of the Genitourinary Group of the French Federation of Cancer Centers. *J Urol* 2002; **168**:959–961.
26 Nanus DM, Garino A, Milowsky MI, Larkin M, Dutcher JP. Active chemotherapy for sarcomatoid and rapidly progressing renal cell carcinoma. *Cancer* 2004; **101**:1545–1551.
27 Chowdhury S, Choueiri TK. Recent advances in the systemic treatment of metastatic papillary renal cancer. *Expert Rev Anticancer Ther* 2009; **9**:373–379.
28 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* 2002; **20**:2376–2381.
29 Ronnen EA, Kondagunta GV, Ishill N, Spodek L, Russo P, Reuter V, *et al.* Treatment outcome for metastatic papillary renal cell carcinoma patients. *Cancer* 2006; **107**:2617–2621.
30 Yang XJ, Tan MH, Kim HL, Ditlev JA, Betten MW, Png CE, *et al.* A molecular classification of papillary renal cell carcinoma. *Cancer Res* 2005; **65**:5628–5637.
31 Perera AD, Kleymenova EV, Walker CL. Requirement for the von Hippel–Lindau tumor suppressor gene for functional epidermal growth factor receptor blockade by monoclonal antibody C225 in renal cell carcinoma. *Clin Cancer Res* 2000; **6**:1518–1523.
32 Qian F, Engst S, Yamaguchi K, Yu P, Won KA, Mock L, *et al.* Inhibition of tumor cell growth, invasion, and metastasis by EXEL-2880 (XL880, GSK1363089), a novel inhibitor of HGF and VEGF receptor tyrosine kinases. *Cancer Res* 2009; **69**:8009–8016.
33 Xie H, Valera VA, Merino MJ, Amato AM, Signoretti S, Linehan WM, *et al.* LDH-A inhibition, a therapeutic strategy for treatment of hereditary leiomyomatosis and renal cell cancer. *Mol Cancer Ther* 2009; **8**:626–635.
34 Amin MB, Paner GP, Alvarado-Cabrero I, Young AN, Stricker HJ, Lyles RH, Moch H. Chromophobe renal cell carcinoma: histomorphologic characteristics and evaluation of conventional pathologic prognostic parameters in 145 cases. *Am J Surg Pathol* 2008; **32**:1822–1834.
35 Tan MH, Wong CF, Tan HL, Yang XJ, Ditlev J, Matsuda D, *et al.* Genomic expression and single nucleotide polymorphism profiling discriminates chromophobe renal cell carcinoma and oncocytoma. *BMC Cancer* 2010; **10**:196.
36 Schuetz AN, Yin-Goen Q, Amin MB, Moreno CS, Cohen C, Hornsby CD, *et al.* Molecular classification of renal tumors by gene expression profiling. *J Mol Diagn* 2005; **7**:206–218.
37 Stec R, Grala B, Maczewski M, Bodnar L, Szczylik C. Chromophobe renal cell cancer: review of the literature and potential methods of treating metastatic disease. *J Exp Clin Cancer Res* 2009; **28**:134.
38 Wright JL, Risk MC, Hotaling J, Lin DW. Effect of collecting duct histology on renal cell cancer outcome. *J Urol* 2009; **182**:2595–2599.
39 Oudard S, Banu E, Vieillefond A, Fournier L, Priou F, Medioni J, *et al.* Prospective multicenter phase II study of gemcitabine plus platinum salt for metastatic collecting duct carcinoma: results of a GETUG (Groupe d'Etudes des Tumeurs Uro-Genitales) study. *J Urol* 2007; **177**:1698–1702.
40 Orsola A, Trias I, Raventos CX, Español I, Cecchini L, Orsola I. Renal collecting (Bellini) duct carcinoma displays similar characteristics to upper tract urothelial cell carcinoma. *Urology* 2005; **65**:49–54.
41 Ansari J, Fatima A, Chaudhri S, Bhatt RI, Wallace M, James ND. Sorafenib induces therapeutic response in a patient with metastatic collecting duct carcinoma of kidney. *Onkologie* 2009; **32**:44–46.
42 Wu ZS, Lee JH, Kwon JA, Kim SH, Han SH, An JS, *et al.* Genetic alterations and chemosensitivity profile in newly established human renal collecting duct carcinoma cell lines. *BJU Int* 2009; **103**:1721–1728.
43 Papadopoulos KP, Goel S, Beeram M, Wong A, Desai K, Haigentz M, *et al.* A phase 1 open-label, accelerated dose-escalation study of the hypoxia-activated prodrug AQ4N in patients with advanced malignancies. *Clin Cancer Res* 2008; **14**:7110–7115.
44 Lopez-Beltran A, Scarpelli M, Montironi R, Kirkali Z. 2004 WHO classification of the renal tumors of the adults. *Eur Urol* 2006; **49**:798–805.
45 Margulis V, McDonald M, Tamboli P, Swanson DA, Wood CG. Predictors of oncological outcome after resection of locally recurrent renal cell carcinoma. *J Urol* 2009; **181**:2044–2051.
46 de Peralta-Venturina M, Moch H, Amin M, Tamboli P, Hailemariam S, Mihatsch M, *et al.* Sarcomatoid differentiation in renal cell carcinoma: a study of 101 cases. *Am J Surg Pathol* 2001; **25**:275–284.