Cancer Chemother Pharmacol (2009) 63 (Suppl 1):S1–S13
DOI 10.1007/s00280-009-0955-3

CONSENSUS STATEMENT

Recommendations from the Spanish Oncology Genitourinary Group for the treatment of metastatic renal cancer

Joaquim Bellmunt · Emiliano Calvo · Daniel Castellano · Miguel Ángel Climent · Emilio Esteban · Xavier García del Muro · José Luis González-Larriba · Pablo Maroto · José Manuel Trigo

Published online: 4 March 2009

Abstract For almost the last two decades, interleukin-2 and interferon-α have been the only systemic treatment options available for metastatic renal cell carcinoma. However, in recent years, five new targeted therapies namely sunitinib, sorafenib, temsirolimus, everolimus and bevacizumab have demonstrated clinical activity in these patients. With the availability of new targeted agents that are active in this disease, there is a need to continuously update the treatment algorithm of the disease. Due to the important advances obtained, the Spanish Oncology Genitourinary Group (SOGUG) has considered it would be useful to review the current status of the disease, including the genetic and molecular biology factors involved, the current predicting models for development of metastases as well as the role of surgery, radiotherapy and systemic therapies in the early- or late management of the disease. Based on this previous work, a treatment algorithm was developed.

Introduction

Cancer of the kidney and renal pelvis constitute approximately 2% of all oncological diseases of which most are renal cell carcinomas (RCCs). The incidence of RCC ranges between 12 cases per 100,000 people in some European countries and 1.5 within India. In the United States alone, more than 50,000 people are diagnosed with the disease each year and 12,000 deaths are attributable to it [1]. It is the third leading cause of death amongst genitourinary malignancies and ranks 12th amongst cancer deaths overall [1]. The median age at diagnosis is around 60–65 years and it affects twice as many men as women.

J. Bellmunt (✉)
Medical Oncology Service, Hospital del Mar,
Passeig Maritim 25, 08003 Barcelona, Spain
e-mail: jbellmunt@imas.imim.es

E. Calvo
Medical Oncology Service,
Hospital del Vall d'Hebron, Barcelona, Spain

D. Castellano
Hospital 12 de Octubre, Madrid, Spain

M. Á. Climent
Oncology Medical Service,
Instituto Valenciano de Oncología, Valencia, Spain

E. Esteban
Medical Oncology Service,
Hospital Universitario Central de Asturias, Oviedo, Spain

X. García del Muro
Medical Oncology Service,
Institut Català d'Oncologia, Barcelona, Spain

J. L. González-Larriba
Medical Oncology Service,
Hospital Clínico San Carlos, Madrid, Spain

P. Maroto
Medical Oncology Service,
Hospital de la Santa Creu i San Pau, Barcelona, Spain

J. M. Trigo
Medical Oncology Service,
Hospital Virgen de la Victoria, Malaga, Spain

Risk factors for RCC

Several potential risk factors for RCC have been identified in epidemiological studies. Some of the most solid ones are smoking, obesity, hypertension, occupational exposure and intake of certain antihypertensive drugs [2]. Heavy smokers (more than 20 cigarettes/day) have a risk, i.e. 1.5–2.0 times higher than that observed in people who have never smoked [3]. Also, higher body mass index and elevated blood pressure independently increase the long-term risk of RCC. Obese people usually have increase serum concentrations of free estrogens, which have been linked to RCC in animal studies [4]. Additionally, hypertension may increase a variety of angiogenic and other growth factors that may be involved in renal carcinogenesis [4]. An increased risk of RCC has also been reported in association with occupational exposure to petroleum products or heavy metals such as iron or steel (for exposures longer than 3 years) [5].

Genetics and molecular biology of RCC

It is estimated that RCC is inherited in ~4% of patients and is sporadic in origin in 96% of patients [6]. In spite of that, different genetic anomalies have been identified in most of the patients affected. Hence, RCC is considered to comprise a group of different tumours including clear-cell (75%), papillary (12%), chromophobe (4%), oncocytoma (4%), collecting duct (1%) and other unclassified (3–4%) tumours [6]. Each of them has a distinct phenotypic appearance and molecular characteristics. The pathogenesis of clear-cell RCC is associated with loss of function of the von Hippel–Lindau (VHL) gene and overproduction of the hypoxia-inducible factor (HIF). Under normal oxygen conditions, the VHL gene product binds to a complex of proteins containing the hydroxylated α subunits of HIF (HIF-1α and HIF-2α) for HIF destruction [7]. Under hypoxic conditions, HIF-α is not hydroxylated, and therefore it is not recognised by the protein pVHL. Hence, HIF accumulates and binds to HIF-β in the nucleus, resulting in an increased transcription of different genes, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor beta (TGFβ) and erythropoietin. Even under normoxic conditions, the VHL gene may have mutations that avoid the binding that leads to HIF degradation. To emphasise the key role of the VHL gene in RCC, it is important to know that the VHL gene is mutated in ~70% of patients with RCC; additionally, VHL is silenced in another 20% of patients [8].

Papillary RCC is an inherited RCC characterised by a predisposition to develop multiple, bilateral papillary renal tumours. Type I papillary RCC is associated with multiple mutations of the MET gene on chromosome 7, which may have effects on both the VHL gene and HIF [9]. In contrast, type II papillary RCC is associated with the inhibition of the enzyme fumarate hydratase, which is related to HIF hydroxylation, due to a mutation in chromosome 1. It is thought that this mutation may be responsible for hereditary leiomyomatosis and RCC [7].

One additional familial syndrome named Birt-Hogg-Dubé (BHD) has recently been described and associated with RCC. BHD is an autosomal, dominantly inherited genodermatosis that predisposes to fibrofolliculomas, kidney neoplasms, lung cysts, and spontaneous pneumothorax. Patients with BHD are at risk for multiple renal tumours that are often malignant and which can metastasise [10]. Genetic studies have led to the localisation of the BHD gene, and current studies are trying to explain how a mutation in the BHD gene may lead to chromophobe RCC [7].

In summary, the genetic pathways of RCC are complex and may be interconnected. However, the understanding of the biology and the molecular basis of RCC is of great importance to find out how the disease develops and to optimise the design of new disease-specific therapies for these patients.

Diagnosis and staging of RCC

Symptoms of renal cancer often do not become apparent until the disease has progressed beyond the initial stages. The most defining symptom is haematuria, but there may be other less specific symptoms such as unexplained weight loss, fatigue, swelling of the ankles and the legs, flank mass and/or flank pain. In spite of that, half of RCC cases are discovered to date purely by chance, because imaging techniques such as ultrasound scan or abdominal computed tomography (CT) are becoming more common [5].

When a RCC is suspected, a series of tests and studies need to be performed to confirm the diagnosis of RCC and to evaluate whether the disease has spread outside the kidney. This process includes a complete physical examination of the patient, specifically to detect supraclavicular adenopathies, abdominal masses, lower extremity oedema or subcutaneous nodules. Laboratory analysis should include a complete blood cell count, a liver function assessment, calcium, creatinine, a coagulation profile and urinalysis. In addition, CT of the abdomen and pelvis and chest imaging (either by radiography or a CT scan) should be performed, if not already done. In contrast, bone scans should only be carried out in cases of elevated serum alkaline phosphatase or bone pain. Similarly, CT or magnetic resonance imaging (MRI) of the brain are recommended only in cases where other symptoms suggest brain metastases [11]. However, the definitive diagnosis of RCC is made through biopsy or, in the case of a high risk of bleeding, through surgery.

The most commonly used staging system for RCC is the TNM (tumour, node, metastases) system of the American Joint Committee of Cancer (AJCC) [12]. Once TNM categories have been assigned, the information obtained is combined to assign an overall stage of I, II, III or IV, in order to group together RCC patients with similar prognosis, and therefore patients that should be treated in a similar way. Thus, stage I includes patients with tumours of less than 7 cm, limited to the kidney, without lymph node involvement and without metastases (T1a–T1b, N0, M0). Stage II includes tumours larger than 7 cm, but still limited to the kidney, without spread to lymph nodes or distant sites (T2N0M0). In stage III, the main tumour is of any size and has reached the adrenal gland, the fatty tissue around the kidney, the renal vein, and/or vena cava; however, it has not spread beyond the fibrous capsule of the kidney (Gerota's fascia), lymph nodes or distant organs (T3a–T3c, N0, M0). Also, stage III includes tumours of any size that have spread to nearby lymph nodes, but not to distant lymph nodes, distant organs or beyond Gerota's fascia (T1a–T3c, N1, M0). Finally, stage IV includes tumours which have spread beyond Gerota's fascia, with or without nearby lymph node involvement and without distant metastases (T4, N0–N1, M0). In addition, stage IV includes tumours of any size that have spread to distant lymph nodes, but not to distant organs (any T, N2, M0) or tumours of any size, with or without nearby or distant lymph node involvement, which have spread to other distant organs (any T, any N, M1).

According to the United States National Cancer Data Base (NCDB), 48% of patients have an early-stage RCC at diagnosis (9% of patients with stage I and 39% of patients with stage II). Additionally, 16 and 25% are stages III and IV, respectively [13].

The role of surgery in localised and metastatic RCC

If RCC is detected in earlier stages, when surgical treatment may be curative, the 5-year survival rate of patients with RCC is around 88–100%. In contrast, when diagnosis is made in more advanced stages, the 5-year survival decreases to 20% or less [14]. These facts point out the importance of surgery in the treatment of RCC. Thus, radical nephrectomy remains the mainstay of the initial treatment for patients with RCC without evidence of metastatic disease [6].

Nephron-sparing surgery (NSS), through open surgical partial nephrectomy or a laparoscopic partial nephrectomy, is also an established approach for certain patients with small, localised RCC, and in these patients similar long-term survival rates have been observed [15]. Although open surgical partial nephrectomy is usually the most common approach for NSS, laparoscopic partial nephrectomy is increasingly used in those patients with relatively small and peripheral RCC. This technique gives a minimally invasive surgical approach with lower postoperative narcotic use, morbidity and hospital stays compared to the open surgical approach [15].

In contrast to the management of other solid tumours in advanced stages such as breast or lung cancer, surgery is also performed in advanced RCC [16]. This approach is justified because cytoreductive nephrectomy not only helps to control the symptoms but also seems to improve patients' survival [17, 18]. Two similar prospective, randomised clinical trials have been performed in Europe and in the United States to demonstrate the benefit of cytoreductive nephrectomy prior to immunotherapy in metastatic RCC. In a study performed by the Southwest Oncology Group (SWOG), 241 metastatic RCC patients were randomised to either interferon-α (IFN-α) alone or nephrectomy followed by IFN-α [17]. Patients who underwent surgery plus immunotherapy obtained a survival advantage of 3.0 months over those who received immunotherapy alone (8.1 vs. 11.1 months, $p = 0.012$). Similarly, in a study performed by the European Organization for Research and Treatment of Cancer (EORTC), 85 patients with metastatic RCC were randomised to either IFN-α alone or nephrectomy followed by IFN-α [18]. The median survival was again significantly higher for patients who underwent surgery plus immunotherapy (17.0 vs. 7.0 months, HR: 0.54, 95% CI: 0.31–0.94). As expected, the strongest benefit was observed in those patients with better performance status. Although the reasons why cytoreductive nephrectomy improves survival of patients with advanced RCC remain unknown, this approach has been widely incorporated into the clinical practice. It is important, however, to select patients properly, i.e. patients with good performance status, without evidence of central nervous system metastases, aggressive extrarenal disease, and/or other important medical comorbidities [19].

Metastasectomy also has an important role in advanced RCC. Thus, resection of solitary metastases after recurrence of RCC has led to long-term survival in 30% of patients [20]. Favourable predictors of survival for these patients included a single site of first recurrence, curative resection disease and a long disease-free interval. Moreover, patients with single or multiple resectable lesions [21], or patients who have achieved a sufficient decrease in tumour load after systemic therapy such as sunitinib [22], may also benefit from metastasectomy. In this regard, two clinical cases of cytokine-refractory metastatic RCC in whom sunitinib was administered have been recently reported. Both patients achieved an important decrease in tumour burden. Subsequently, surgical resection of metastasis allowed them to achieve a long-term complete response [22].

The role of radiotherapy in localised and metastatic RCC

Many patients with large primary cancers have a significant risk of local relapse after surgery. Because of this, several randomised trials have assessed the role of pre- or postoperative radiotherapy in RCC [23–26]. Although all of these trials were small and probably underpowered, none of them showed a significant benefit from radiotherapy. Moreover, in one of these trials [25, 26], postoperative radiotherapy was associated with a high rate of severe complications, and some of them led to patient death. For inoperable RCC only, stereotactic radiotherapy may have a role, but there is only one retrospective study which supports this approach [27].

These studies suggest that the only role that radiotherapy may have in RCC is in the metastatic setting and for palliative purposes, i.e. patients with brain or bone metastases. In patients with RCC with multiple bone metastases, radiotherapy appears to control pain in the short term and prevent fractures [28]. Brain metastases from RCC may cause significant morbidity and mortality and, traditionally, whole-brain radiotherapy has been used in those patients. More recently, advances in radiation oncology, stereotactic radiosurgery and hypofractionated stereotactic radiotherapy, have been utilised for RCC brain metastases, delivering excellent outcomes [29]. Stereotactic radiotherapy may also be considered as a therapeutic option to surgery in patients with a limited number of metastases, as local treatment in RCC with an indolent presentation or as a method of reducing tumour burden prior to medical treatment [30].

On the other hand, targeting tumour vasculature agents such as sunitinib, sorafenib, and bevacizumab, which have recently been approved for renal cancer therapy, have a strong biological rationale in radiation therapy. Thus, preclinical studies have consistently showed an increase in radiosensitization with combined treatment. Nevertheless, the optimal biological doses of antiangiogenic agents with radiotherapy are still unknown, as well as its clinical safety and efficacy. Early clinical trials are needed to minimise the volume of irradiated normal organs and to establish safe dose–volume parameters for phase II–III clinical trials [31].

Adjuvant systemic therapies for stage I–III RCC

To date, systemic therapy after radical nephrectomy in patients with RCC has not demonstrated an improvement in survival [7]. RCC in the metastatic setting is highly resistant to systemic chemotherapy [32], and therefore it has not even been tested in the adjuvant setting. Immunotherapy with IFN-α or interleukin-2 (IL-2) does not appear to provide significant benefits to patients after complete surgical resection [33–35]. In a previous trial, 283 patients were randomised either to IFN-α or to watchful waiting after radical nephrectomy plus lymphadenectomy [34]. Patients remained on treatment until recurrence or toxicity. After 10 years of follow-up, median survival was 7.4 years in the observation group and 5.1 years in treatment arm ($p = 0.09$). Relapse-free survival was similar in both groups. In a multivariate analysis, only performance status, nodal status and tumour stage were significant prognostic factors for survival. In another prospective trial, 68 patients with resected locally advanced or metastatic RCC were randomised to observation or to one course of high-dose IL-2 after surgery [33]. High-dose IL-2, although feasible, did not result in a significant benefit. Recently, preliminary results of one of the biggest randomised trials have also indicated that adjuvant IFN-α does not seem to add any benefits in the treatment of patients with stage II and III RCC [35]. Other systemic therapies such as vaccines, antibodies or targeted therapies are being evaluated nowadays in the adjuvant setting [36–38].

These results suggest that clinical observation should remain the standard of care in patients with RCC who have undergone surgery. This watchful waiting approach should include several procedures such as physical examinations, chest X-ray and abdominal ultrasound, as well as blood laboratory analyses (including blood urea nitrogen, serum creatinine, calcium levels, lactate dehydrogenase [LDH] and liver function tests), which should be complemented with abdominal and chest CT scans [11]. However, there is no consensus on which tests and studies need to be performed and at what intervals. It is assumed that a strong effort should be made during the first 3–5 years, and subsequently that the frequency of the follow-ups should depend on the specific risk of relapse of each patient [39].

Predicting models for development of metastases in RCC

Between 20 and 30% of patients with localised RCC will experience disease relapse after surgery, most of them within the first 3 years. Thus, prognostic information is essential in the clinical management of RCC. Currently, RCC prognosis is based on standard clinical and pathological parameters such as the performance status of the patients, tumour stage (which evaluates tumour size, nodal status and metastatic lesions), nuclear grade of tumour cells (such as Fuhrman Nuclear Grade) [40] and histological type of the tumour (i.e. clear-cell, papillary, chromophobe, oncocytoma or collecting duct tumours). More recently, the molecular characterisation of tumours has allowed the identification of other more specific prognostic factors, such as carbonic anhydrase IX [41], loss of phosphatase and tensin

homolog (PTEN), or tumour expression of certain molecules such as B7H1 and B7H4, which are known to inactivate local immune cells [7].

All the prognostic factors mentioned may be evaluated separately or together to facilitate the decision-making process. Thus, five prognostic models have been recently reported to predict the outcome of patients with localised RCC after nephrectomy. All of them consider clinical and/or pathologic variables. The Johns Hopkins Hospital has developed a biostatistical prognostic model for postoperative RCC using the records of 296 patients which was based purely on clinical variables, allowing a non-invasive preoperative evaluation of the risk of recurrence [42]. The Memorial Sloan-Kettering Cancer Center (MSKCC) has developed a nomogram using variables of 601 patients such as symptoms, histology, tumour size and pathological stage, which was able to predict the 5-year probability of treatment failure [43]. The nomogram was internally validated. The Mayo Clinic developed a scoring system for patients with only clear-cell RCC which was able to associate TNM stage, tumour size, nuclear grade and histological tumour necrosis with cancer-specific survival (SSIGN score) [44]. A fourth model was developed by the University of California Los Angeles (UCLA) using the medical records of 661 patients, and was called the UCLA Integrated Staging System (UISS). Along with the TNM stage, it takes into account the Fuhrman grade and the Eastern Cooperative Oncology Group (ECOG) performance status to stratify RCC patients into low-, intermediate- or high-risk categories of disease relapse [45]. This model was also validated externally. A prospective large-scale trial with 4,202 patients with localised and metastatic tumours showed that UISS was an accurate predictor of survival for patients with localised RCC, but that it was less accurate in the subset of patients with metastatic RCC due to heterogeneity in the patients and the treatments evaluated [46]. Finally, an Italian group has constructed a recurrence risk formula with two clinical variables such as asymptomatic/symptomatic presentation and tumour size [47].

In a later study, the Italian group compared the discriminating accuracy of their model (Cindolo formula) with three of the four previously mentioned prognostic models [48]. The SSIGN score could not be calculated because, in many patients, the information regarding histological tumour necrosis was not available. Thus, 2,404 medical records of patients from six European sites were retrospectively reviewed. For each patient, four prognostic scores were calculated. The Johns Hopkins Hospital's score and the Cindolo formula used exclusively clinical variables and could be calculated preoperatively. The MSKCC score and the UISS score used clinical and pathologic variables and were calculated postoperatively. All models confirmed their ability to discriminate between categories with different prognoses. The conclusion was that the postoperative scores can discriminate between prognoses substantially better than preoperative ones. Overall, the MSKCC was found to be the most accurate, although the UISS also performed well [48].

Systemic therapies for metastatic RCC

As mentioned before, classical systemic therapies with either chemotherapy or radiotherapy for the advanced stages of the disease have failed to improve patient outcome. Traditionally, metastatic RCC patients have been treated with immunotherapy agents, mainly IFN-α and IL-2, with low clinical benefit and poor safety profile. In the last few years, new targeted therapies against the kinases involved in the pathogenesis of RCC have been developed and rapidly incorporated into the standard clinical practice.

Immunotherapy

For patients with stage IV RCC, different combinations and dosages of IFN-α and IL-2, both as single agent or in combination, have been tested. In a randomised trial, subcutaneous IFN-α, in comparison with oral medroxyprogesterone acetate, demonstrate a small benefit in overall survival (OS) (8.5 vs. 6.0 months, $p = 0.017$). However, patients who received IFN-α had more symptoms of toxicity and a lower quality of life [49]. Additionally, patients treated with IFN-α rarely showed complete or long-lasting responses.

The response to high-dose IL-2 can be achieved in up to 20% of patients, of which 5% of them could be considered long-lasting responses [50]. In spite of that, two large phase III trials in which high-dose IL-2 was compared with low-dose IL-2 or a combination of IFN-α plus low-dose IL-2 were unable to demonstrate any benefit regarding survival [51, 52]. Additionally, higher morbidity was observed in the high-dose arm. In fact, the administration of high-dose IL-2 requires a careful assessment by a physician due to the incidence of capillary leak syndrome and hypotension [53]. Therefore, it is considered that intensive care would be advisable during high-dose IL-2 administration and that 30–50% of patients would require treatment with vasopressor agents to treat hypotension. Additionally, the Programme Etude Rein Cytokines (PERCY) Quattro trial was designed to evaluate the efficacy of both cytokines, IFN-α and IL-2, in metastatic renal cancer patients with intermediate prognosis in comparison with medroxyprogesterone acetate [54]. The results observed in 492 patients included were IFN-α and IL-2 that did not provide any survival benefit. Moreover, they induced a significant increase of toxicity.

In a retrospective analysis of six clinical trials in which 463 patients received IFN-α as first-line systemic therapy

[55], it was concluded that the efficacy outcomes achieved by IFN-α could be used as a baseline for the assessment of new therapies. It is possible that patients treated with high-dose IL-2 achieve durable responses, but the severe treatment-related toxicity may prevent its use in the control arms of randomised phase II/III trials. Also, the need to select patients before high-dose IL-2 administration may bias the results obtained with new investigational drugs against metastatic RCC. In contrast, IFN-α may be administered to a broader set of patients in an outpatient basis. Also, in this retrospective analysis, three risk categories based on five pre-treatment clinical features were defined to predict survival (Table 1). Those features were (1) low-risk Karnofsky status; (2) high lactate dehydrogenase; (3) low serum haemoglobin; (4) high corrected serum calcium; and (5) less than 1 year from diagnosis to IFN-α administration. Thus, patients had a favourable risk if they had none of these clinical features; intermediate risk was assigned to those patients with one or two risk factors; and poor risk category was assigned to those patients with three or more risk factors. When this classification named Motzer's prognostic factor criteria was applied, median survival time was 30 months for the favourable-risk group, 14 months for the intermediate-risk group, and 5 months for the poor-risk group [56]. These results were externally validated by the Cleveland Clinic prognostic scoring [57].

Multikinase inhibitors

Multikinase inhibitors are small molecules that inhibit tyrosine kinase receptors at more than one target [16].

Sunitinib is a multitargeted inhibitor of several tyrosine kinases, including VEGF receptor, PDGFR, c-kit and Flt-3 tyrosine kinase [58], which play a key role in the pathogenesis of RCC. The activity of sunitinib was evidenced for the first time in two phase II trials in patients with cytokine-refractory metastatic RCC in which sunitinib achieved clinical responses in more than 30% of patients, and median progression free-survivals (PFS) of 8.3 and 8.7 months [59, 60] (Table 2). Later on, sunitinib was evaluated as first-line therapy in a large phase III trial of 750 patients with clear-cell RCC [61]. Patients were randomised to sunitinib (50 mg orally once daily for 4 weeks followed by 2-week rest) or IFN-α (9 million international units [MIU] subcutaneously three times a week). The primary endpoint of the study was PFS. Secondary endpoints included overall response rate (ORR), OS, patient-reported outcomes and safety.

According to investigators' criteria, sunitinib produced higher ORR in comparison with IFN-α (37 vs. 9%, respectively; $p < 0.001$). Stable disease was observed in 47% of patients treated with sunitinib and 57% of patients treated with IFN-α. These results were confirmed by a blinded central review panel for whom ORR was 31% [95% CI: 26–36] versus 6% [95% CI: 4–9], respectively ($p < 0.001$); and stable disease was 48 and 49%, respectively. PFS was also statistically longer in the sunitinib arm in comparison with the IFN-α arm, independently it was assessed by investigators (11 months [95% CI: 8–14] vs. 4 months [95% CI: 4–5], respectively; HR: 0.42 [95% CI: 0.33–0.52]; $p < 0.001$) or by a central panel (11.0 months [95% CI: 10–12] vs. 5.0 months [95% CI: 4–6]; HR: 0.42 [95% CI: 0.32–0.54]; $p < 0.001$) (Table 2). Benefits from sunitinib extended across all patients in the favourable- and intermediate-risk groups as defined by the MSKCC score [55]. In the poor-risk group, the respective median values for 23 patients in the sunitinib group and 25 patients in the IFN-α group were 4 months and 1 month (HR: 0.53 [95% CI: 0.23–1.23]), respectively. At the time the trial was reported, 13% of patients treated with sunitinib and 17% of patients treated with IFN-α had died (HR: 0.65 [95% CI: 0.45–0.94]; $p = 0.02$). However, the results did not meet the pre-specified level of significance for the interim analysis [61]. Recently, these results were updated [62] (Table 2). Thus, ORR was 47% (95% CI: 42–52) versus 12% (95% CI: 9–16] for sunitinib and IFN-α, respectively ($p < 0.000001$). Regarding OS, the final analysis was reported and a non-significant strong trend was observed in favour of sunitinib arm (26.4 months [95% CI: 23.0–32.9] vs. 21.8 months [95% CI: 17.9–26.9], respectively; HR: 0.821 [95% CI: 0.673–1.001]; $p = 0.051$). However, when patients allowed to crossover between both treatment arms were censored, a significant improvement in OS was observed in favour of sunitinib (26.4 months [95% CI: 23.0–32.9] vs. 20.0 months [95% CI: 17.8–26.9], respectively; HR: 0.808 [95% CI: 0.661–0.987]; $p = 0.036$).

Regarding the safety profile, the incidence of severe adverse events in both treatment groups was relatively low [61] (Table 3). Patients in the sunitinib arm, as compared with those in the IFN-α arm, had higher rates of severe diarrhoea (5 vs. 0%), vomiting (4 vs. 1%), hypertension (8 vs. 1%), hand-foot syndrome (5 vs. 0%), leukopenia (5 vs. 2%), neutropenia (12 vs. 7%) and thrombocytopenia

Table 1 Risk factors to define prognostic groups for patients with RCC

Low-risk Karnofsky status (<80%)
High lactate dehydrogenase (>1.5 × ULN)
Low serum haemoglobin (<LLN)
High corrected serum calcium (>10 mg/dL)
<1 year from diagnosis to IFN-α administration

Favourable risk, if patient had none of these clinical features; intermediate risk, if patient had one or two risk factors; poor risk, if patient had three or more risk factors

LLN lower limit of normal, *ULN* upper limit of normal

Table 2 Main efficacy data of targeted therapies for RCC

Author	Phase	Treatment	Patients	Setting	ORR (%)	PFS (months)	OS (months)
Sunitinib							
Motzer et al. [60]	II	Sunitinib	106	Second line	34	8.3	NR
Motzer et al. [59]	II	Sunitinib	63	Second line	40	8.7	NR
Motzer et al. [61, 62]	III	Sunitinib	750	First line	47	11.0	26.4
		IFN-α			12; $p < 0.000001$	5.0; $p < 0.001$	21.8; $p = 0.051$
Sorafenib							
Akaza et al. [64]	II	Sorafenib	129	Second line	15	7.4	NR
Escudier et al. [65, 66]	III	Sorafenib	903	Second line	10	5.5	17.8
		Placebo			2; $p < 0.001$	2.8; $p < 0.01$	15.2; $p = 0.146$
Szczylik et al. [67]	IIb	Sorafenib	189	First line	5	5.7	NR
		IFN-α			9; NS	5.6; NS	
Bevacizumab							
Yang et al. [73]	IIb	Bevacizumab HD/LD	116	Second line	NR	HD > P; $p < 0.001$	NS
		Placebo				LD ~ P; $p = 0.053$	
Bukowski et al. [70]	IIb	Bevacizumab + erlotinib	104	First line	14	9.9	20.0
		Bevacizumab			13; NS	8.5; NS	Not reached; NS
Escudier et al. [71]	III	Bevacizumab + IFN-α	649	First line	31	10.2	Not reached
		IFN-α			13; $p = 0.0001$	5.4; $p = 0.0001$	19.8; NS
Rini et al. [72]	III	Bevacizumab + IFN-α	732	First line	26	8.5	NR
		IFN-α			13; $p < 0.0001$	5.2; $p < 0.0001$	
Temsirolimus							
Atkins et al. [77]	IIb	Temsirolimus	111	Second line	7	5.8	15.0
Hudes et al. [78]	III	IFN-α	626	First line	5	3.1	7.3
		Temsirolimus		Poor prognosis	9; NS	5.5; $p < 0.001$	10.9; $p = 0.008$
		Temsirolimus + IFN-α			8; NS	4.7; NS	8.4; $p = 0.70$
Everolimus							
Jac et al. [79]		Everolimus	22	Second/third line	16	5.5	8.0
Motzer et al. [80]		Everolimus	362	Second/third line	3	4.0	Not reached
		Placebo			0	1.9; $p < 0.001$	8.8; $p = 0.233$

IFN-α interferon-α, *HD* high dose, *LD* low dose, *NA* not applicable, *NR* not reported, *NS* non-significant, *P* placebo, *RCC* renal cell carcinoma

(8 vs. 0%), with a p value of less than 0.05 for all symptoms (Table 3). In contrast, severe fatigue (7 vs. 12%) and lymphopenia (12 vs. 22%) occurred with greater frequency in patients treated with IFN-α ($p < 0.05$). The incidence of a grade 3 decrease in the left ventricular ejection fraction was 2% in the sunitinib and 1% in the IFN-α arm. In the sunitinib group, this decrease did not have any clinical sequelae and was reversible after dose modification or treatment discontinuation. As a consequence, 38% of patients with sunitinib and 32% of patients with IFN-α had a dose interruption due to an adverse event, and 32 and 21%, respectively, had a dose reduction. Sunitinib may be reduced from 50 mg once daily to a minimum of 25 mg/day at intervals of 12.5 mg each.

Sorafenib was originally developed as an inhibitor of Raf-1, a member of the Raf/MEK/ERK signalling pathway [63]. Soon after, it also proved to be active against B-Raf, VEGFR-2 and PDGFR [63]. Its activity was evaluated throughout several phase II trials as well as through the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) [64–67] (Table 2). In this randomised, double-blind, phase III trial, 903 patients with previously cytokine-treated metastatic clear-cell RCC of low- or intermediate risk were randomised to sorafenib (400 mg orally twice a day) or placebo [65, 66]. The primary endpoint of the study was OS and secondary endpoints were PFS, ORR and safety.

Treatment with sorafenib prolonged PFS in comparison with placebo (5.5 vs. 2.8 months, HR: 0.44; 95% CI: 0.35–0.55; $p < 0.01$). The difference of survival in favour of sorafenib was not statistically significant in the intention to treat analysis but was positive when censoring placebo

Table 3 Severe adverse events of targeted therapies for RCC

	Sunitinib [61]	Sorafenib [66]	Bevacizumab + IFN-α [71]	Temsorolimus [78]	Everolimus [80]
Grade 3–4 toxicities					
Anorexia			3	3	
Asthenia	4		10	11	3
Bleeding			3		
Decline in ejection fraction	2				
Depression			3		
Diarrhoea	5	2	2		
Dyspnoea		4		9	
Fatigue	7	5	12		3
Hand-foot syndrome	5	6			
Headache			2		
Hypertension	8	4	3		
Infection				5	3
Influenza-like illness			3		
Mucosal inflammation	2				
Nausea	3			2	
Pain		7		12	
Peripheral oedema				2	
Pneumonitis					3
Proteinuria			7		
Pyrexia			2		
Rash	2			4	
Stomatitis					3
Vomiting	4			2	
Venous thromboembolic event			3		
Laboratory abnormalities					
Anaemia	4	3	3	20	10
Hypercholesterolemia					3
Hyperglycaemia				11	12
Hyperlipidemia				3	
Hypophosphatemia	5				4
Increased acid uric	12				
Increased ALAT	3				
Increased alkaline phosphatase	2				
Increased amylase	5				
Increased ASAT	2				
Increased creatinine				3	
Increased lipase	16				
Leukopenia	5				
Lymphopenia	12				15
Neutropenia	12		4	3	
Thrombocytopenia	8		2		
Other					
Dose interruption due to AEs	38	21	NR	NR	
Dose reduction due to AEs	32	13	NR	23	
Study discontinuation due to AEs	8	10	28	7	10

>2% of patients

AE adverse event, *ALAT* alanine aminotransferase, *ASAT* aspartate aminotransferase, *NR* not reported, *RCC* renal cell carcinoma

patients that crossed over to receive sorafenib. Partial responses were reported in 10% of patients treated with sorafenib and 2% of patients treated with placebo ($p < 0.001$).

The most common severe adverse events associated with sorafenib were hand-foot skin reactions (6% of patients), fatigue (5%), dyspnoea (4%), hypertension (4%) and anaemia (3%) (Table 3). Cardiac ischaemia or infarction (3% of patients) was rare. Lastly, serious adverse events leading to patient hospitalisation were reported in 34% of patients receiving sorafenib and 24% of patients receiving placebo ($p < 0.01$) [66]. As a consequence, 13% of patients treated with sorafenib reduced the dosage compared with 3% of patients in the placebo arm ($p < 0.001$). Additionally, 21% of patients in the sorafenib arm interrupted doses opposed to 6% in the placebo arm ($p < 0.001$), with a median duration of dose interruption of 7 and 6 days, respectively. Sorafenib may be reduced from 400 to 200 mg twice a day, or even to 200 mg once a day. Also, it is possible to alternate sorafenib's dosage between 400 and 200 mg/day.

Sorafenib was also compared with IFN-α in a randomised phase II trial of untreated RCC patients. In this trial, sorafenib did not show any advantage over IFN-α in terms of PFS (5.7 vs. 5.6 months, respectively; $p = 0.504$) [67].

Anti-VEGF antibodies

Anti-VEGF antibodies are used in the treatment of RCC because it has been demonstrated that more than 50% of these tumours are up-regulated by HIF-1α, HIF-2α and HIF target genes such as VEGF [68].

Bevacizumab is a humanised recombinant anti-VEGF antibody that binds VEGF-A isoform and neutralises its activity [69]. Bevacizumab in combination with IFN-α has demonstrated its activity in metastatic RCC in several randomised trials [70–73] (Table 2). In a double-blind phase III trial of 649 patients with previously untreated metastatic RCC, 10 mg/kg of intravenous bevacizumab every 2 weeks, plus 9 MIU of IFN-α three times per week by subcutaneous injection, were compared with placebo plus the same dose of IFN-α [71]. The primary endpoint of the trial was OS. Secondary endpoints included PFS, ORR and safety. According to the investigator's criteria, the ORR was significantly higher with bevacizumab plus IFN-α than with placebo plus IFN-α (31 vs. 13%, $p = 0.0001$). Also, a longer PFS was observed in favour of the bevacizumab plus IFN-α arm (10.2 vs. 5.4 months, HR: 0.63; 95% CI: 0.52–0.75; $p = 0.0001$), regardless of the patient's risk group (stratified according to MSKCC criteria) [71]. However, at the time of data cut-off, median OS was not reached. Serious adverse events were reported in 29% of patients treated with bevacizumab plus IFN-α and in 16% of patients treated with placebo plus IFN-α. Twenty-eight percent of patients treated with bevacizumab plus IFN-α interrupted the study drug due to an adverse event compared with 12% in the control arm (Table 3). The most frequent severe adverse events observed in patients treated with bevacizumab plus IFN-α were fatigue (12% of patients), asthenia (10%), proteinuria (7%) and neutropenia (4%) [71]. Importantly, thromboembolic events (3%) and severe gastrointestinal perforations (2%) were also described. In a retrospective subgroup analysis, it was observed that the dose of IFN-α may be reduced to manage side effects whilst maintaining efficacy of the combination [74].

In another multicenter phase III trial, previously untreated metastatic RCC patients were randomised to bevacizumab (10 mg/kg every 2 weeks) plus IFN-α (9 MIU three times per week) or IFN-α monotherapy [72] (Table 2). The median PFS was 8.5 months (95% CI: 7.5–9.7) and 5.2 months (95% CI: 3.1–5.6) in the study and the control arms, respectively ($p < 0.0001$). Bevacizumab plus IFN-α also had a higher ORR (26% [95% CI: 21–31] vs. 13% [95% CI: 10–17]; $p < 0.0001$, respectively). On the other hand, severe toxicity was greater in the bevacizumab arm, including severe hypertension (9 vs. 0%), anorexia (17 vs. 8%), fatigue (35 vs. 28%) and proteinuria (13 vs. 0%) [72].

mTOR inhibitors

mTOR inhibitors are directed towards the inhibition of the mammalian target of rapamycin (mTOR) kinase, a component of the intracellular signalling pathways involved in cellular growth, proliferation and hypoxic stress response [75].

Specifically, temsirolimus binds to the intracellular protein FKBP-12, forming a complex that inhibits mTOR signalling. This inhibition affects cell cycle regulation and angiogenesis [76]. Temsirolimus has shown its activity in metastatic RCC in previous phase II and III trials [77, 78] (Table 2). In a large, multicentre, phase III trial, 626 previously untreated RCC patients with poor prognosis were included [78]. Poor prognosis was defined slightly different than previously [55]. Thus, poor-risk patients were those with at least three of the following six predictors of short survival: (1) a serum lactate dehydrogenase level >1.5 × upper normal limit (UNL); (2) a haemoglobin level below the lower normal limit (LNL); (3) a corrected serum calcium level >2.5 mmol/L; (4) a time from initial diagnosis to randomisation <1 year; (5) a Karnofsky performance score <60–70; and (6) a new criteria based on the existence of metastases in multiple organs. Patients received treatment with IFN-α (escalated from 3 to 18 MIU three times per week if tolerated), temsirolimus (25 mg as a weekly intravenous infusion), or a combination of both (15 mg of temsirolimus and 3–6 MIU). The primary endpoint of the

study was OS. Secondary endpoints included PFS, ORR, clinical benefit rate and safety. Temsirolimus as single agent was superior to IFN-α in terms of OS (10.9 vs. 7.3 months, $p = 0.008$), which was the main endpoint of the study, and PFS (5.5 vs. 3.1 months, $p < 0.001$). In contrast, administration of both temsirolimus and IFN-α did not improve the results obtained with IFN-α alone [78], probably due to dose reduction applied to the combination (Table 2).

Additionally, temsirolimus as single agent had a good safety profile (Table 3). Thus, the highest incidence of severe adverse events was observed in the combination arm (87% of patients) followed by the IFN-α arm (78%) and the temsirolimus arm (67%; $p = 0.02$) [78]. Asthenia was the most frequent adverse event in those patients that received IFN-α alone or in combination (Table 3). Severe asthenia was reported in 11% of patients treated with temsirolimus, 26% of patients treated with IFN-α and in 28% of patients treated with the combination of both. Dyspnoea, diarrhoea, nausea, or vomiting were reported similarly in the three treatment arms. In contrast, the incidence of rash, peripheral oedema, stomatitis, anaemia, neutropenia and thrombocytopenia at any grade was higher in patients who received temsirolimus, either alone or in combination, than in patients treated with IFN-α alone ($p < 0.05$) [78]. Importantly, hyperglycaemia, hypercholesterolemia and hyperlipidemia were more common in patients treated with temsirolimus, reflecting the effect of this drug on glucose and lipid metabolisms (Table 3). As a consequence, 23% of patients treated with temsirolimus as single agent had to reduce the treatment dosage. In the case of severe neutropenia or thrombocytopenia, temsirolimus was interrupted and restarted with a 5 mg reduction from the recommended dosage of 25 mg a week.

Everolimus is another mTOR oral inhibitor that affects tumour growth by blocking growth factor stimulation, arresting cell cycle progression and inhibiting angiogenesis. In a recent phase II trial, everolimus demonstrated to be an active drug in previously treated RCC patients [79] (Table 2). In another randomised phase III trial [80], everolimus (10 mg/day orally) or placebo was administered to 362 patients with metastatic RCC who had progressed with previous multikinase inhibitors or anti-VEGF therapies (Table 2). The primary endpoint of the study was PFS and secondary endpoints included OS, ORR, patient-reported outcomes and safety. Patients were previously stratified into three risk groups (favourable, intermediate and poor) according to MSKCC prognostic criteria [81]. According to the central panel review, PFS was significantly prolonged in the everolimus arm (4.0 months) in comparison with the placebo arm (1.9 months, HR: 0.30 [95% CI: 0.22–0.40]; $p < 0.001$). These results were confirmed by investigators' assessment and were observed across all risk groups. Regarding OS, mature results have not yet been reached.

Regarding safety profile, 10% of patients treated with everolimus discontinued treatment due to an adverse event in comparison with 1% of patients in the placebo arm. Most common severe adverse events in the study arm were lymphopenia (15%), hyperglycaemia (12%) and anaemia (10%) (Table 3).

Recommendations from the Spanish Oncology Genitourinary Group (SOGUG) for the treatment of metastatic RCC

For the last 15 years, IL-2 and IFN-α have been the only systemic treatment options available for metastatic RCC. However, in recent years, five new targeted therapies (sunitinib, sorafenib, temsirolimus, everolimus and bevacizumab) have provided benefits to patients with advanced RCC. Consequently, these new drugs are now being used as first-, second- or third-line treatment of metastatic RCC.

The Spanish Oncology Genitourinary Group (SOGUG, www.sogug.es) is a non-profit health association dedicated to develop high-quality research programmes and to improve the management of patients with urological tumours. Due to important advances obtained in the treatment of RCC, it seemed pertinent that SOGUG made a public statement of its own position in this field. All recommendations issued by SOGUG on the treatment of metastatic RCC with systemic therapies are based on the data obtained from previously performed phase III trials (Table 2).

Based on these data, we concluded that patients with metastatic RCC need to be primarily stratified according to the risk factors they may have (Table 1). Patients with favourable or intermediate prognosis should receive sunitinib as first-line treatment (Table 4). In this setting, bevacizumab plus IFN-α is another option for these patients.

Table 4 Treatment algorithm based on phase III derived data

Prognostic risk groups[a]	Treatment options		
	First line	Second line	
		After cytokines	After TKIs
Favourable risk	Sunitinib Bevacizumab–IFN-α	Sorafenib	Everolimus
Intermediate risk	Sunitinib Bevacizumab–IFN-α		
Poor risk	Temsirolimus		

[a] Prognostic risks are defined according to the criteria defined in Table 1

IFN-α interferon-α, *TKIs* tyrosine kinases

According to our criteria, patients with poor prognosis should receive temsirolimus as first-line treatment. After clinical progression, all patients previously treated with cytokines should be treated with sorafenib as second-line treatment. In contrast, all patients previously treated with tyrosine kinases should receive everolimus.

Acknowledgments The authors acknowledge the support of Pfizer Spain, which has facilitated the necessary meetings to evaluate and discuss all the data presented in this review, and Dr. Beatriz Gil-Alberdi from HealthCo SL (Madrid, Spain) for her assistance in the preparation of this manuscript.

Conflict of interest statement M. Climent is a consultant and advisor for Pfizer and Novartis. All other authors have no disclosures to be made.

References

1. Jemal A, Siegel R, Ward E et al (2008) Cancer statistics, 2008. CA Cancer J Clin 58:71–96
2. Dhote R, Thiounn N, Debre B et al (2004) Risk factors for adult renal cell carcinoma. Urol Clin N Am 31:237–247
3. Vineis P, Alavanja M, Buffler P et al (2004) Tobacco and cancer: recent epidemiological evidence. J Natl Cancer Inst 96:99–106
4. Chow WH, Gridley G, Fraumeni JF Jr et al (2000) Obesity, hypertension, and the risk of kidney cancer in men. N Engl J Med 343:1305–1311
5. Dhote R, Pellicer-Coeuret M, Thiounn N et al (2000) Risk factors for adult renal cell carcinoma: a systematic review and implications for prevention. BJU Int 86:20–27
6. Wagstaff J (2006) New horizons in the treatment of renal cell cancer. Ann Oncol 17(Suppl 10):x19–x22
7. Atkins MB, Ernstoff MS, Figlin RA et al (2007) Innovations and challenges in renal cell carcinoma: summary statement from the Second Cambridge Conference. Clin Cancer Res 13:667s–670s
8. Banks RE, Tirukonda P, Taylor C et al (2006) Genetic and epigenetic analysis of von Hippel–Lindau (VHL) gene alterations and relationship with clinical variables in sporadic renal cancer. Cancer Res 66:2000–2011
9. Schmidt L, Duh FM, Chen F et al (1997) Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat Genet 16:68–73
10. Schmidt LS, Nickerson ML, Warren MB et al (2005) Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dube syndrome. Am J Hum Genet 76:1023–1033
11. Motzer RJ, Bolger GB, Boston B et al (2006) Kidney cancer. Clinical practice guidelines in oncology. J Natl Compr Cancer Netw 4:1072–1081
12. Greene FL, Page DL, Fleming ID et al (2002) AJCC cancer staging handbook: TNM classification of malignant tumors. Springer, New York
13. Drucker BJ (2005) Renal cell carcinoma: current status and future prospects. Cancer Treat Rev 31:536–545
14. Guinan PD, Vogelzang NJ, Fremgen AM et al (1995) Renal cell carcinoma: tumor size, stage and survival. Members of the Cancer Incidence and End Results Committee. J Urol 153:901–903
15. Novick AC (2004) Laparoscopic and partial nephrectomy. Clin Cancer Res 10:6322S–6327S
16. Costa LJ, Drabkin HA (2007) Renal cell carcinoma: new developments in molecular biology and potential for targeted therapies. Oncologist 12:1404–1415
17. Flanigan RC, Salmon SE, Blumenstein BA et al (2001) Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med 345:1655–1659
18. Mickisch GH, Garin A, van Poppel H et al (2001) Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet 358:966–970
19. Garcia JA, Rini BI (2007) Recent progress in the management of advanced renal cell carcinoma. CA Cancer J Clin 57:112–125
20. Kavolius JP, Mastorakos DP, Pavlovich C et al (1998) Resection of metastatic renal cell carcinoma. J Clin Oncol 16:2261–2266
21. Russo P (2004) Surgical intervention in patients with metastatic renal cancer: current status of metastasectomy and cytoreductive nephrectomy. Nat Clin Pract Urol 1:26–30
22. Rini BI, Shaw V, Rosenberg JE et al (2006) Patients with metastatic renal cell carcinoma with long-term disease-free survival after treatment with sunitinib and resection of residual metastases. Clin Genitourin Cancer 5:232–234
23. Finney R (1973) The value of radiotherapy in the treatment of hypernephroma—a clinical trial. Br J Urol 45:258–269
24. Juusela H, Malmio K, Alfthan O et al (1977) Preoperative irradiation in the treatment of renal adenocarcinoma. Scand J Urol Nephrol 11:277–281
25. Kjaer M, Frederiksen PL, Engelholm SA (1987) Postoperative radiotherapy in stage II and III renal adenocarcinoma. A randomized trial by the Copenhagen Renal Cancer Study Group. Int J Radiat Oncol Biol Phys 13:665–672
26. Kjaer M, Iversen P, Hvidt V et al (1987) A randomized trial of postoperative radiotherapy versus observation in stage II and III renal adenocarcinoma. A study by the Copenhagen Renal Cancer Study Group. Scand J Urol Nephrol 21:285–289
27. Wersall PJ, Blomgren H, Lax I et al (2005) Extracranial stereotactic radiotherapy for primary and metastatic renal cell carcinoma. Radiother Oncol 77:88–95
28. Reichel LM, Pohar S, Heiner J et al (2007) Radiotherapy to bone has utility in multifocal metastatic renal carcinoma. Clin Orthop Relat Res 459:133–138
29. Doh LS, Amato RJ, Paulino AC et al (2006) Radiation therapy in the management of brain metastases from renal cell carcinoma. Oncology (Williston Park) 20:603–613 discussion 613, 616, 619–620 passsim
30. Svedman C, Sandstrom P, Pisa P et al (2006) A prospective phase II trial of using extracranial stereotactic radiotherapy in primary and metastatic renal cell carcinoma. Acta Oncol 45:870–875
31. Senan S, Smit EF (2007) Design of clinical trials of radiation combined with antiangiogenic therapy. Oncologist 12:465–477
32. Amato RJ (2000) Chemotherapy for renal cell carcinoma. Semin Oncol 27:177–186
33. Clark JI, Atkins MB, Urba WJ et al (2003) Adjuvant high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: a cytokine working group randomized trial. J Clin Oncol 21:3133–3140
34. Messing EM, Manola J, Wilding G et al (2003) Phase III study of interferon alfa-NL as adjuvant treatment for resectable renal cell carcinoma: an Eastern Cooperative Oncology Group/Intergroup trial. J Clin Oncol 21:1214–1222
35. Pizzocaro G, Piva L, Costa A, Silvestrini R (1997) Adjuvant interferon (IFN) to radical nephrectomy in Robson's stages II and III renal cell cancer (RCC), a multicenter randomized study with some biological evaluations, 1997 ASCO annual meeting, abstract 1132
36. Jocham D, Richter A, Hoffmann L et al (2004) Adjuvant autologous renal tumour cell vaccine and risk of tumour progression in patients with renal-cell carcinoma after radical nephrectomy: phase III, randomised controlled trial. Lancet 363:594–599

37. Jonasch E, Wood C, Tamboli P et al (2008) Vaccination of metastatic renal cell carcinoma patients with autologous tumour-derived vitespen vaccine: clinical findings. Br J Cancer 98:1336–1341
38. Wood C, Srivastava P, Bukowski R et al (2008) An adjuvant autologous therapeutic vaccine (HSPPC-96; vitespen) versus observation alone for patients at high risk of recurrence after nephrectomy for renal cell carcinoma: a multicentre, open-label, randomised phase III trial. Lancet 372:145–154
39. Skolarikos A, Alivizatos G, Laguna P et al (2007) A review on follow-up strategies for renal cell carcinoma after nephrectomy. Eur Urol 51:1490–1500 discussion 1501
40. Fuhrman SA, Lasky LC, Limas C (1982) Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol 6:655–663
41. Sandlund J, Oosterwijk E, Grankvist K et al (2007) Prognostic impact of carbonic anhydrase IX expression in human renal cell carcinoma. BJU Int 100:556–560
42. Yaycioglu O, Roberts WW, Chan T et al (2001) Prognostic assessment of nonmetastatic renal cell carcinoma: a clinically based model. Urology 58:141–145
43. Kattan MW, Reuter V, Motzer RJ et al (2001) A postoperative prognostic nomogram for renal cell carcinoma. J Urol 166:63–67
44. Frank I, Blute ML, Cheville JC et al (2002) An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. J Urol 168:2395–2400
45. Zisman A, Pantuck AJ, Dorey F et al (2001) Improved prognostication of renal cell carcinoma using an integrated staging system. J Clin Oncol 19:1649–1657
46. Patard JJ, Kim HL, Lam JS et al (2004) Use of the University of California Los Angeles integrated staging system to predict survival in renal cell carcinoma: an international multicenter study. J Clin Oncol 22:3316–3322
47. Cindolo L, de la Taille A, Messina G et al (2003) A preoperative clinical prognostic model for non-metastatic renal cell carcinoma. BJU Int 92:901–905
48. Cindolo L, Patard JJ, Chiodini P et al (2005) Comparison of predictive accuracy of four prognostic models for nonmetastatic renal cell carcinoma after nephrectomy: a multicenter European study. Cancer 104:1362–1371
49. Ritchie A, Griffiths G, Parmar M, for the MRC Renal Cancer Collaborators (1999) Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomised controlled trial. Medical Research Council Renal Cancer Collaborators. Lancet 353:14–17
50. Fyfe G, Fisher RI, Rosenberg SA et al (1995) Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. J Clin Oncol 13:688–696
51. McDermott DF, Regan MM, Clark JI et al (2005) Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. J Clin Oncol 23:133–141
52. Yang JC, Sherry RM, Steinberg SM et al (2003) Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. J Clin Oncol 21:3127–3132
53. Margolin KA, Rayner AA, Hawkins MJ et al (1989) Interleukin-2 and lymphokine-activated killer cell therapy of solid tumors: analysis of toxicity and management guidelines. J Clin Oncol 7:486–498
54. Negrier S, Perol D, Ravaud A et al (2007) Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results of a randomized controlled trial. Cancer 110:2468–2477
55. Motzer RJ, Bacik J, Murphy BA et al (2002) Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol 20:289–296
56. Motzer RJ, Mazumdar M, Bacik J et al (1999) Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 17:2530–2540
57. Bukowski RM, Negrier S, Elson P (2004) Prognostic factors in patients with advanced renal cell carcinoma: development of an international kidney cancer working group. Clin Cancer Res 10:6310S–6314S
58. Mendel DB, Laird AD, Xin X et al (2003) In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res 9:327–337
59. Motzer RJ, Michaelson MD, Redman BG et al (2006) Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. J Clin Oncol 24:16–24
60. Motzer RJ, Rini BI, Bukowski RM et al (2006) Sunitinib in patients with metastatic renal cell carcinoma. JAMA 295:2516–2524
61. Motzer RJ, Hutson TE, Tomczak P et al (2007) Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 356:115–124
62. Figlin RA, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Négrier S, Huang X, Kim ST, Chen I, Motzer RJ (2008) Overall survival with sunitinib versus interferon (IFN)-alfa as first-line treatment of metastatic renal cell carcinoma (mRCC). J Clin Oncol, vol 26 (May 20 suppl), abstr 5024
63. Hilger RA, Scheulen ME, Strumberg D (2002) The Ras-Raf-MEK-ERK pathway in the treatment of cancer. Onkologie 25:511–518
64. Akaza H, Tsukamoto T, Murai M et al (2007) Phase II study to investigate the efficacy, safety, and pharmacokinetics of sorafenib in Japanese patients with advanced renal cell carcinoma. Jpn J Clin Oncol 37:755–762
65. Bukowski RM, Eisen T, Szczylik C, Stadler WM, Simantov R, Shan M, Elting J, Pena C, Escudier B (2007) Final results of the randomized phase III trial of sorafenib in advanced renal cell carcinoma: survival and biomarker analysis. In: 2007 ASCO annual meeting proceedings, part I. J Clin Oncol, vol 25, no. 18S (June 20 supplement), abstr 5023
66. Escudier B, Eisen T, Stadler WM et al (2007) Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 356:125–134
67. Szczylik C, Demkow T, Staehler M, Rolland F, Negrier S, Hutson TE, Bukowski RM, Scheuring UJ, Burk K, Escudier B (2007) Randomized phase II trial of first-line treatment with sorafenib versus interferon in patients with advanced renal cell carcinoma: final results. In: 2007 ASCO annual meeting proceedings, part I. J Clin Oncol, vol 25, no. 18S (June 20 supplement), abstr 5025
68. Rini BI, Small EJ (2005) Biology and clinical development of vascular endothelial growth factor-targeted therapy in renal cell carcinoma. J Clin Oncol 23:1028–1043
69. Presta LG, Chen H, O'Connor SJ et al (1997) Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res 57:4593–4599
70. Bukowski RM, Kabbinavar FF, Figlin RA et al (2007) Randomized phase II study of erlotinib combined with bevacizumab compared with bevacizumab alone in metastatic renal cell cancer. J Clin Oncol 25:4536–4541
71. Escudier B, Pluzanska A, Koralewski P et al (2007) Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell

carcinoma: a randomised, double-blind phase III trial. Lancet 370:2103–2111
72. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena D, Ou S, Taylor J, Tanguay S, Dutcher J, Small EJ (2008) CALGB 90206: a phase III trial of bevacizumab plus interferon-alpha versus interferon-alpha monotherapy in metastatic renal cell carcinoma, 2008 genitourinary cancers symposium, abstract no. 350
73. Yang JC, Haworth L, Sherry RM et al (2003) A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 349:427–434
74. Melichar B, Koralewski P, Ravaud A et al (2008) First-line bevacizumab combined with reduced dose interferon-alpha2a is active in patients with metastatic renal cell carcinoma. Ann Oncol 19:1470–1476
75. Hudson CC, Liu M, Chiang GG et al (2002) Regulation of hypoxia-inducible factor 1alpha expression and function by the mammalian target of rapamycin. Mol Cell Biol 22:7004–7014
76. Del Bufalo D, Ciuffreda L, Trisciuoglio D et al (2006) Antiangiogenic potential of the Mammalian target of rapamycin inhibitor temsirolimus. Cancer Res 66:5549–5554
77. Atkins MB, Hidalgo M, Stadler WM et al (2004) Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. J Clin Oncol 22:909–918
78. Hudes G, Carducci M, Tomczak P et al (2007) Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 356:2271–2281
79. Jac J, Amato RJ, Giessinger S, Saxena S, Willis JP (2008) A phase II study with a daily regimen of the oral mTOR inhibitor RAD001 (everolimus) in patients with metastatic renal cell carcinoma which has progressed on tyrosine kinase inhibition therapy. J Clin Oncol 26(May 20 suppl):abstr 5113
80. Motzer RJ, Escudier B, Oudard S, Porta C, Hutson TE, Bracarda S, Hollaender N, Urbanowitz G, Kay A, Ravaud A (2008) RAD001 vs placebo in patients with metastatic renal cell carcinoma (RCC) after progression on VEGFr-TKI therapy: results from a randomized, double-blind, multicenter phase-III study. J Clin Oncol 26(May 20 suppl):abstr LBA5026
81. Motzer RJ, Bacik J, Schwartz LH et al (2004) Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol 22:454–463