Metastatic renal cell carcinoma: recent advances and current therapeutic options

Andres Jan Schrader and Rainer Hofmann

For many years immuno(chemo)therapy has been the only therapeutic option for patients with metastatic renal cell carcinoma. Few patients, however, experienced long-term disease control and toxicity was considerable. Recent advances in understanding the biology and genetics of this malignancy have led to novel-targeted therapeutic approaches. Since 2003, a multitude of new drugs have been developed and tested, with small molecule tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors and monoclonal antibodies appearing to be the most promising agents. In the following, we give a concise overview on results of current trials in metastatic renal cell carcinoma published within 2007. Moreover, we will translate these results into therapeutic options and recommendations. *Anti-Cancer Drugs* **19:235–245 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Department of Urology, Philipps University Medical School, Marburg, Germany

Correspondence to Dr Andres Jan Schrader, MD, PhD, Department of Urology, Philipps University Medical School, Baldingerstrasse, 35043 Marburg, Germany
Tel: +49 6421 286 3013; fax: +49 6421 286 5590;
e-mail: ajschrader@gmx.de

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Introduction

The incidence of renal cell carcinoma (RCC) has increased steadily in recent decades, and today it is a common urologic tumor that accounts for about 2–3% of all human malignancies [1–3]. The annual mortality-to-incidence ratio with RCC is significantly higher compared with other urological malignancies. It is estimated that approximately 25–30% of all patients with RCC have metastases at presentation, and even after complete resection of the primary, relapse occurs in about 20% of patients [4].

Surgical resection of the renal tumor for patients with localized disease was and is the only curative therapeutic option for RCC. Conversely, for those patients with distant metastasis the prognosis is poor. During the last few decades, few patients achieved complete cure by receiving immunochemotherapy. A recent Cochrane Analysis reported that the application of interferon (IFN) α led to a median overall chance of partial remission (PR) or complete remission (CR) of 12.9%, only, that the average median improvement in survival was 3.8 months [5].

Recently, several novel therapeutic approaches have raised well-founded hope. By now, two receptor tyrosine kinase inhibitors (TKIs), sunitinib and sorafenib, have become standard of care in meatastatic RCC (mRCC). In addition, monoclonal antibodies targeting vascular endothelial growth factor (VEGF) signaling as well as mammalian target of rapamycin (mTOR) inhibitors appear to become valuable components in single-agent or combination regimens for patients with mRCC [6,7].

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This article reviews the results of current first-line and second-line approaches, their potential efficacy and toxicity, and might help in finding the optimal individual systemic therapy for each patient.

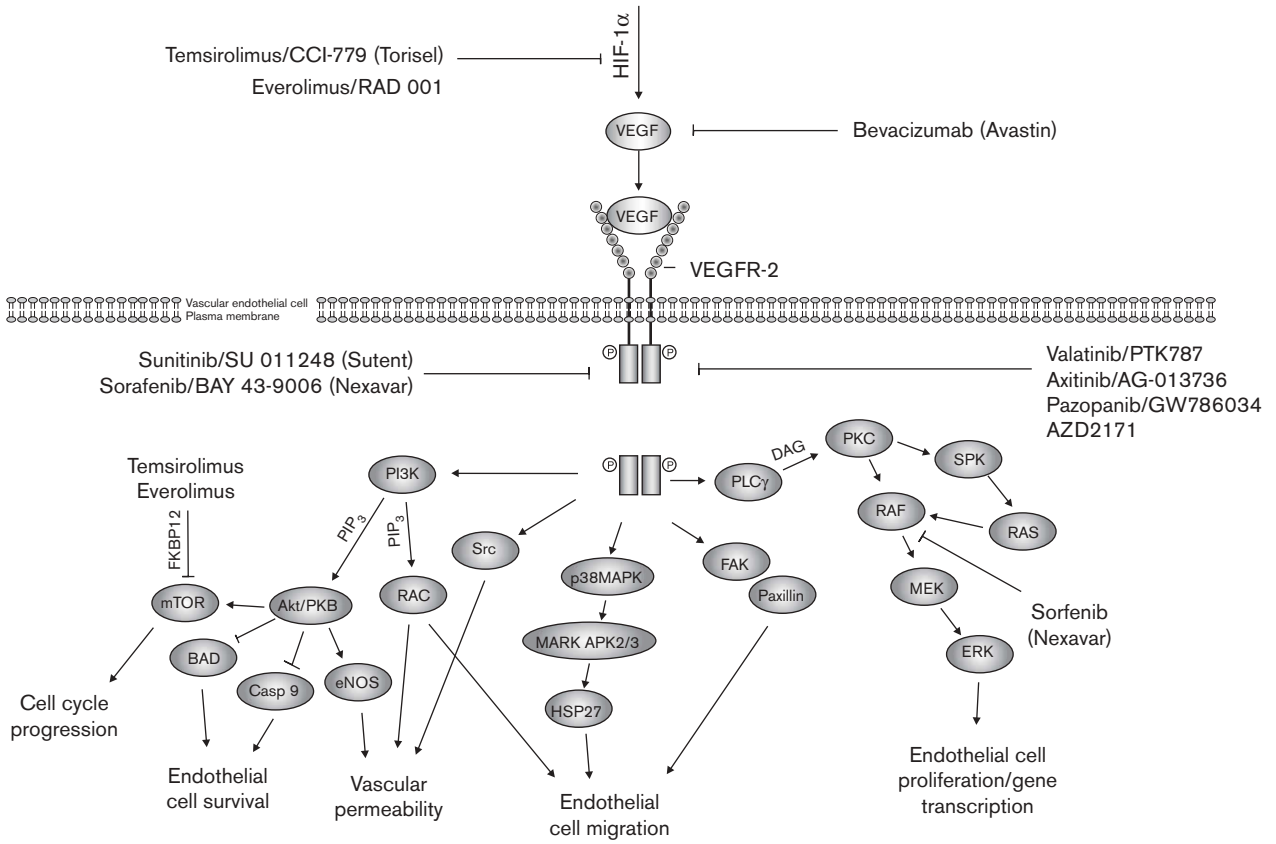
Receptor tyrosin kinase inhibitors

In December 2005 and July 2006, two different orally active multikinase inhibitors (TKIs) were approved by the Food and Drug Administration and the European Medicines Agency, respectively, for the treatment of mRCC: sunitinib (Sutent, SU011248) and sorafenib (Nexavar, BAY 43-9006). They are small molecules which potently inhibit platelet-derived growth factor receptor (PDGFR), VEGF receptor (VEGFR)-1 and VEGFR-2, TKI, and FLT3 (fms-related tyrosine kinase/Flk2/Stk-2), and therefore have both direct antitumor and antiangiogenic properties [7]. Moreover, sorafenib functions as Raf kinase inhibitor. Several additional new TKIs are currently being tested in clinical trials to optimize the treatment of mRCC (Fig. 1).

Sunitinib

In 2007, Motzer *et al.* [10] published the final results of a large first-line multicenter phase III trial that randomized 750 patients with clear-cell mRCC to receive sunitinib [50 mg/day orally (p.o.) for 4 weeks followed by 2 weeks without treatment] or IFN-α [9 MU subcutaneously (s.c.), three times per week]. With 11 months the median progression-free survival was significantly longer in the sunitinib group than in the IFN-α group (5 months). Importantly, in all three prognostic risk groups according to Motzer's (MSKCC) prognostic score criteria [11] the median progression-free survival was

Fig. 1



Targeting VEGF receptor signaling – a popular and effective approach to fight mRCC. Binding of VEGF to its receptor leads to dimerization and autophosphorylation of intracellular receptor tyrosine kinases. Subsequently, several downstream protein pathways are activated, leading to biologic effects on endothelial cells (only the major proteins in each pathway are depicted [8,9]). Bevacizumab binds VEGF protein, preventing its interaction with the receptor; sunitinib, sorafenib, valatinib, axitinib, pazopanib, and AZD2171 inhibit phosphorylation of the VEGF receptor (among others). Sorafenib additionally inhibits Raf kinase enzyme. Temsirolimus and everolimus inhibit mTOR and consecutively cell cycle progression, cell proliferation, survival and mobility, and HIF-1α protein translation. Akt/PKB, protein kinase B; DAG, 1,2-diacylglycerol; eNOS, endothelial nitric oxide synthase; Erk, extracellular receptor kinase; FAK, focal adhesion kinase; HIF, hypoxia inducible factor; HSP27, heat-shock protein 27; MAPKAP 2/3, MAPK-activating protein kinase 2 and 3; MEK, mitogen and extracellular kinase; p38 MAPK, p38 mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PLC, phospholipase C; SPK, sphingosine kinase; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

longer for patients receiving sunitinib. Sunitinib was also associated with a higher objective response rate [objective or overall response (OR): 31 vs. 6%]; no CR were achieved. Initial tumor progression was observed in 21 and 45% of all patients who received sunitinib and IFN-α, respectively. Unfortunately, until today the median overall survival data have not been published. Most general adverse events of all grades occurred more frequently in the sunitinib group than in the IFN-α group (e.g. diarrhea, nausea, stomatitis, hypertension, hand–foot syndrome, rash and skin disorders, and decline of ejection fraction). Conversely, pyrexia, chills, and myalgia dominated in patients treated with IFN-α. Both drugs led to pancytopenia including leukopenia, anemia, and thrombocytopenia (only sunitinib) in more than 50% of all patients. Accordingly, dose interruption (38 vs. 32%) and dose reduction (32 vs. 21%) were more frequent in patients in the sunitinib compared with the IFN-α group. The patients in the sunitinib group, however, reported a significantly better quality of life than did patients in the IFN-α group.

A very important subanalysis of this study was reported on the occasion of the American Society of Clinical Oncology (ASCO) meeting 2007 focussing prognostic factors in patients receiving TKI treatment. It was shown that the classic risk factors (MSKCC score including low Karnofsky performance status, high serum lactate dehydrogenase, low hemoglobin, high corrected serum calcium, short time since diagnosis, and probably the absence of prior nephrectomy) which had been elaborated in the era of cytokine therapy, do also apply for the treatment with TKIs [12]. In contrast, the presence of visceral metastases (liver and bone) had no

adverse effect on progression-free survival under sunitinib therapy.

In May 2007, Rosenberg *et al.* [13] updated their pooled data from two similar second-line phase II studies evaluating sunitinib in 169 metastatic clear-cell RCC (ccRCC) patients who showed an objective response rate of 45%. Moreover, 32% achieved stable disease (SD); the median duration of response, progression-free survival, and overall survival were 11.9, 8.4, and 19.9 months, respectively.

Srinivas *et al.* [14] presented a phase II study focussing efficacy and safety of single-agent sunitinib when administered within a continuous 37.5 mg/day regimen. All 107 patients had failed cytokine-based treatment and were randomized to receive sunitinib in the morning (a.m., $n = 54$) or in the evening (p.m., $n = 53$). Twenty-one out of 107 (20%) patients achieved a PR and 43 out of 107 (40%) patients were stable. Forty-six out of 107 (43%) patients had a clinical benefit (PR + SD) for at least 6 months. Patients who received sunitinib in the evening suffered slightly more adverse events which led to dose reductions in 51% compared with 39% in patients who received early morning application; additional 64.5% experienced dose interruptions in both arms.

Results of the sunitinib expanded access trial (EAT) were presented by Gore *et al.* [15]. Two thousand three hundred and forty-one evaluable patients received second-line sunitinib (4 weeks on and 2 weeks off) including 2056 (87.8%) patients with ccRCC. The patients received a median number of four cycles in 5.6 months. The most common grade 1–2/3–4 adverse events were diarrhea (35.8/3.6%), nausea (31.7/1.9%), fatigue (28.5/7.1%), mucositis (24.5/2.5%), stomatitis (23.4/2.1%), hypertension (14.7/5.4%), and hand–foot syndromes (12.9/4.5%). Hematotoxic side effects resulted in grade 1–2/3–4 thrombocytopenia (10.0/6.4%), anemia (7.3/2.6%), and neutropenia (5.2/4.1%); the sunitinib dose was reduced in 37.6% of all patients. Objective responses and SD were found in 217 out of 2341 (9.3%) and 1008 out of 2341 (43.1%) patients, respectively. The median progression-free survival was 8.9 months, independent of prior cytokine-based therapies. Patients with a good prognosis according to the MSKCC score, however, presented a significantly longer progression-free survival compared with those with intermediate or poor prognosis (13.6 vs. 8.2 vs. 4.2 months).

George *et al.* [16] presented a phase II second-line study that evaluated the safety and activity of sunitinib in mRCC patients previously treated with the VEGF neutralizing antibody, bevacizumab. A total of 61 patients were enrolled. The objective partial response rate was 23% (14 out of 61 patients); 36 out of 61 patients (59%) had SD. The median duration of response and progression-free survival was 44 and 30 weeks, respectively. The authors concluded that sunitinib has significant antitumor activity in bevacizumab-refractory mRCC patients, suggesting absence of cross-resistance between bevacizumab and sunitinib.

Unnithan *et al.* [17] reported that receptor TKIs can safely be used in patients with brain metastasis after adequate therapy to the central nervous system (CNS) (surgery and/or radiotherapy). Applying sunitinib ($n = 13$) or sorafenib ($n = 10$), no evidence of CNS intratumoural bleeding or other hemorrhagic complications have been observed.

Sorafenib

The largest phase III, randomized, double-blind, placebo-controlled trial in the history of mRCC evaluated the efficacy and tolerability of sorafenib [400 mg p.o. twice daily (b.i.d.)] in 903 pretreated metastatic conventional RCC patients (TARGET trial) [18]. The median progression-free survival was 5.5 months in the sorafenib group and 2.8 months in the placebo group. This benefit in progression-free survival was independent of age, MSKCC score, previous use or nonuse of cytokines, and presence or absence of visceral metastases. Owing to positive early results, patients on placebo were allowed to cross over into the sorafenib arm early (*de facto* 48% crossover). Therefore, the exact median overall survival was difficult to compare between either group. Looking at the preplanned secondary analysis of the overall survival data with all placebo patients censored, sorafenib-treated patients, however, achieved a significantly longer median overall survival compared with the placebo group (17.8 vs. 14.3 months) [19]. Objective response rates were 10 vs. 2%, disease control (OR + SD for ≥ 3 months) 57 vs. 34%. The median duration of treatment was 23 weeks in the sorafenib group and 12 weeks in the placebo group [18]. The proportion of patients who discontinued the study owing to adverse events was similar in both groups (10 vs. 8%); however, doses were reduced in 13% and interrupted 21% of sorafenib patients but only in 3 and 6% in the placebo group, respectively. Dose interruptions were mostly owing to dermatologic events (hand–foot skin reactions and rash) or gastrointestinal events (diarrhea and nausea). Moreover, 4% of all patients who were treated with sorafenib developed grade 3/4 hypertension or cardiac ischemia.

Knox *et al.* [20] recently summarized and presented the efficacy/toxicity data from the American advanced renal cell carcinoma sorafenib (ARCCS) expended access trial with 1871 evaluable patients (first-line and second-line). Clinical benefit (OR + SD) was reported for 84% of all patients including 68 confirmed responses (318 unconfirmed) as well as 1500 patients with disease stabilization.

Three hundred and three out of 1871 (16%) of all patients immediately progressed under sorafenib, only. Most common grade 1–2/3–4 adverse events were hand–foot skin reactions (15/8%), rash (21.5/5%), fatigue (13/6%), hypertension (11/5%), diarrhea (18/3%), and alopecia (11.5/0%). Clinical benefit did not depend on prior therapy [20,21].

Beck *et al.* [22] presented data of the European ARCCS study which included 1155 patients with metastatic renal cancer. Disease control was observed in 751 out of 1031 (72.8%) evaluable patients for at least 2 months, median progression-free survival and duration of treatment were 6.8 and 6.9 months, respectively. The disease control rate and progression-free survival were independent of age, however, decreasing with rising Eastern Cooperative Oncology Group level and number of metastatic sites. Similar to the American ARCCS data the most common grade 1–2/3–4 adverse events observed were hand–foot skin affection (35/12%), diarrhea (38/5%), fatigue (26/8%), alopecia (28/ < 1%), oral mucositis (23/3%), nausea (16/1%), and hypertension (10/4%). One hundred and nineteen (10.3%) patients stopped treatment owing to intolerable toxicity. No patient experienced significant hypothyroidism; only four out of 1155 (0.3%) and 10 out of 1155 (0.9%) patients, however, presented with an intracranial hemorrhage or myocardial infarction, respectively.

The final results of a randomized first-line phase II trail comparing sorafenib and IFN-α in 189 patients with metastatic ccRCC have recently been demonstrated by Szczylik *et al.* [23]. All patients were randomized to continuous oral sorafenib ($n = 97$, 400 mg b.i.d.) or IFN-α ($n = 92$, 9 MU three times a week, s.c.) (part 1), with an option of dose escalation to sorafenib 600 mg b.i.d. or crossover from IFN-α to sorafenib 400 mg b.i.d. upon disease progression (part 2). In part 1, disease control rate (OR + SD) was 79 vs. 64%, and median progression-free survival was 5.7 vs. 5.6 months for sorafenib vs. IFN-α, respectively. Tumor shrinkage was seen in 68% after sorafenib and 39% after IFN-α application. Overall, the incidence of adverse events was similar between both treatment arms. Although skin toxicity (rash and hand–foot skin reaction) and diarrhea occurred more frequently in the sorafenib group, flu-like symptoms were found more frequently in the IFN-α group. In part 2 (after initial tumor progression), median progression-free survival was 5.7 months in patients ($n = 50$) who crossed from IFN-α to sorafenib. The median progression-free survival for patients ($n = 44$) with dose escalation to 600 mg b.i.d. was 4.1 months. The disease control rate in part 2 was 76 and 46%, respectively, and tumor shrinkage was seen in 75 and 44% of the patients who crossed from IFN-α to sorafenib and patients with dose-escalated sorafenib, respectively. Szczylik *et al.* reported that the 600 mg b.i.d. dose was well tolerated. Interestingly, in this trial the second-line sorafenib application (part 2) was as successful as the first-line application, that is, sorafenib after IFN-α or sorafenib 600 mg b.i.d. after standard dose led to doubled progression-free survival and produced significant responses and disease stabilization after failure to initial treatment.

Another study supporting the use of escalating doses of sorafenib was presented by Amato *et al.* [24] at the ASCO meeting 2007. Forty-four evaluable patients received an initial dose of 400 mg b.i.d. In 41 out of 44 patients the sorafenib doses could be escalated at least to 1200 mg/day 32 out of 41 patients received up to 1600 mg/day, 25 out of 32 patients of those enduringly. Limiting adverse events for the dose escalation in the other 19 patients were hand–foot syndrome, skin rash, diarrhea, alopecia, fatigue, hypertension, hypophosphatemia, and elevated amylase/lipase. Amato *et al.* demonstrated an overall response rate of 55% [seven out of 44 (16%) patients achieved CR and 17 out of 44 (39%) patients achieved PR]. An additional nine (20%) patients achieved SD for at least 6 months. In May 2007, the median time to disease progression had not been reached (8.4 + months).

Within the ARCCS expended access trial 197 evaluable patients were included who had failed bevacizumab. One hundred and fifty-four out of 197 (78%) patients showed at least SD including 27 patients with unconfirmed PR. The authors concluded that sorafenib is highly efficient after prior bevacizumab application, no additional toxicity was reported [25]. The same results were observed in the EU-ARCCS trial [22].

Pazopanib

Pazopanib (GW786034) is another new selective multitargeted receptor TKI of VEGFR1–3, PDGFR, and c-kit. Interim results of a current phase II randomized discontinuation trial have recently been demonstrated [26]. Two hundred and twenty-five patients ($n = 154$ first-line, $n = 71$ second-line after bevacizumab and/or IFN) with clear-cell mRCC received 800 mg pazopanib orally once daily for 12 weeks. Total disease control at that point was 73% [61 out of 225 (27%) PR and 104 out of 225 (46%) SD]. Overall survival was not yet reached. Most common adverse events were diarrhea (56%), hair color changes (40%), hypertension (37%), nausea (36%), fatigue (32%), and alanine aminotransferase/aspartate aminotransferase elevations (50%). Moreover, several patients presented with hand–foot syndromes (10%), rash (12%), dysgeusia (22%), and leukopenia (32%).

AZD2171

Likewise, AZD2171 is a TKI that inhibits VEGFR signaling as well as c-kit, PDGFR, and FLT-4. In small

first-line and second-line phase I/II trails, as single agent or in combination with gefintinib, it has proven high disease control rates of up to 75% [27,28]. A randomized placebo-controlled phase II investigation of AZD2171 monotherapy (45 mg/day p.o.) in patients with advance RCC is ongoing.

Sequential application of receptor tyrosine kinase inhibitors

Sunitinib and sorafenib are two small-molecule TKIs that have been shown to have antitumor activity in advanced renal cell carcinoma (*vide supra*). The optimal sequence of first-line and second-line therapies with sunitinib and sorafenib, however, is still unclear. Sablin *et al.* [29] retrospectively evaluated clinical outcome of 90 patients with mRCC who sequentially received sorafenib–sunitinib ($n = 68$) or sunitinib–sorafenib ($n = 22$). Median progression-free survival, partial response, and SD rates for sorafenib–sunibinib vs. sunitinib–sorafenib were 26 + 25 weeks vs. 22 + 17 weeks, 16 + 15 vs. 23 + 9%, and 66 + 51 vs. 54 + 55%, respectively. Only six patients had progressive disease under both drugs, all of them were in intermediate or poor MSKCC risk groups. These results suggest the lack of cross-resistance between both agents and support their sequential use. In this retrospective study, the fairly longer median progression-free survival (51 vs. 39 weeks) and median time on treatment (61 vs. 49 weeks) might argue for the sorafenib–sunitinib sequence.

Similar results were published by Dham and Dudek [30] who found that the median duration of disease control using the sorafenib–sunitinib sequence (42 weeks, $n = 23$) was longer compared with the sunitinib–sorafenib sequence (30.5 weeks, $n = 14$).

Axitinib (AG-013736) is a TKI of the VEGF (Fig. 1) and PDGF receptors and has shown substantial efficacy in a previous phase II study in patients with cytokine-refractory mRCC [31]. Rini *et al.* [32] presented data of a second-line phase II trial with 62 patients refractory to prior sorafenib ($n = 48$) or sorafenib and sunitinib ($n = 14$) therapy. All patients received a starting dose of 5 mg p.o., b.i.d., titrated according to tolerance up to 10 mg b.i.d. 13 out of 62 (21%) and 21 out of 62 (34%) patients achieved partial responses and SD, respectively. Interestingly, nine out of 14 patients who had failed prior sorafenib and sunitinib therapy showed at least some degree of tumor regression on computed tomography scans. Median progression-free survival for all patients was 7.4 months. Median overall survival was not reached after a median follow-up time of 8.1 months. Toxicity was typical of TKI therapy and included grade 1–2/3–4 hypertension (23/16%), hand–foot syndrome (18/11%), diarrhea (50/6%), fatigue (50/18%), and anorexia. Nine out of 62 (15%) patients withdrew owing to adverse events.

Mammalian target of rapamycin inhibitors

The so-called mTOR inhibitos such as temsirolimus (CCI-779) or everolimus (RAD001) block the mTOR kinase, a component of intracellular signaling pathways involved in the growth and proliferation of cells and the response of those to hypoxic stress. Briefly, they bind to an abundant intracellular protein, FKBP-12, and by this form a complex that inhibits mTOR signaling. The disruption of mTOR signaling suppresses the production of proteins that regulate progression through the cell cycle (at late G_1) as well as angiogenesis (via HIF-1α suppression).

Temsirolimus

In May 2007, Hudes *et al.* [33] published the final results of a multicenter phase III trial in which 626 patients with previously untreated, poor prognosis (≥ 3/6 risk factors, i.e. MSKCC risk factors plus > 1 site of metastasis) mRCC were randomized to receive temsirolimus [25 mg intravenous (i.v.), once weekly], IFN-α (up to 18 MU s.c., three times per week) or a combination therapy (temsirolimus 15 mg i.v. plus IFN-α 6 MU s.c., three times per week). Patients who received temsirolimus alone had a longer overall survival and progression-free survival than did patients who received IFN-α alone. Median overall survival times in the IFN-α group, the temsirolimus group, and the combination-therapy group were 7.3, 10.9, and 8.4 months, respectively. The median progression-free survival times for the IFN-α, temsirolimus, and combination-therapy groups were 3.1, 5.5, and 4.7 months. The objective response rates of 4.8, 8.6, and 8.1% did not differ significantly; however, the proportion of patients who showed disease control (SD ≥ 6 months or an objective response) was significantly greater in the temsirolimus group (32.1%) and the combination-therapy group (28.1%) than in the IFN-α control arm (15.5%). The beneficial effect of temsirolimus on overall survival was most pronounced in patients with high serum lactate dehydrogenase levels, poor MSKCC prognosis, and those with nonclear-cell cancer. In contrast to IFN-α, temsirolimus was less active in patients older than 65 years [34].

The most common grade 1–2/3–4 adverse effects of temsirolimus were asthenia (40/11%), rash (43/4%), anemia (25/20%), nausea (35/2%), dyspnea (19/9%), diarrhea (26/1%), and peripheral edema (25/2%). Hyperglycemia, hypercholesterolemia, and hyperlipidemia reflected the inhibition of mTOR-regulated glucose and lipid metabolism. Grade 3–4 adverse events occurred in 67% of patients in the temsirolimus group, as compared with 78% in the IFN-α and 87% in the combination-therapy group. Dose reductions and dose delays were also less common in the temsirolimus group: here the patients

actually received 92% of the planned dose. In contrast, in the IFN-α and the combination-therapy arm the actual average doses had to be reduced to 56 and 73% of the maximum planned doses, respectively. Consequently, the quality of life was significantly higher in the temsirolimus-mono group compared with those receiving IFN-α or both [35].

Temsirolimus has been approved for the treatment of poor prognosis mRCC by the Food and Drug Administration in May 2007. Moreover, with respect to its antiproliferative capacity a phase III study has been initiated in the USA to evaluate the efficacy of temsirolimus second-line after sunitinib and versus sorafenib [36].

Everolimus

Everolimus (RAD001) is an oral mTOR inhibitor (Fig. 1). Jac *et al.* [37] treated 37 patients with everolimus 10 mg daily (first-line and second-line). Twelve (32%) patients had partial responses, 19 (51%) patients were stable for more than 3 months. Median overall survival had not yet been reached (11.5 + months). The treatment-related adverse events were similar to those observed with temsirolimus and included mucositis, skin rash, pneumonitis, hypophosphatemia, hyperglycemia, hypertriglyceridemia, hypercholesterolemia, thrombocytopenia, and anemia. Facing these encouraging results combined with rather mild toxicity the authors planned to expand the study.

Monoclonal antibodies

Volociximab

A critical survival step for proliferating endothelial cells is the ligation of fibronectin in the extracellular matrix to integrin $\alpha_5\beta_1$. Voloximab (M200), a chimeric monoclonal antibody, blocks fibronectin binding to $\alpha_5\beta_1$ and induces apoptosis of proliferating endothelial cells. Voloximab activity is independent of growth factor stimulus, suggesting that $\alpha_5\beta_1$ signaling occurs downstream of growth factor signaling, and is possibly a final common pathway for the development of neovasculature. Yazji *et al.* [38] presented first results of their multicenter, open label, phase II study in metastatic ccRCC. All patients ($n = 40$) had been pretreated with cytokines and/or antiangiogenic therapy and received 10 mg/kg volociximab i.v. every 2 weeks. Thirty-eight patients had had prior tumor nephrectomy. Under volociximab SD was observed in 32 out of 40 (80%) patients including one confirmed PR (2.6%). Median progression-free survival was 113 days. Median overall survival was not yet reached (25.9 + months). Most frequent side effects were fatigue (68%), nausea (35%), dyspnea (25%), and arthralgia (18%); grade 3/4 toxicity was seldom: anemia (2.5%) and hypertension (2.5%). The authors concluded that volociximab is a well-tolerated active drug in mRCC, a randomized-controlled trial is being planned.

Combination therapy

Bevacizumab plus interferon-alpha

In 2003, Yang *et al.* [39] published a highly interesting randomized double-blind placebo-controlled phase II study evaluating bevacizumab, a neutralizing monoclonal antibody against VEGF (Fig. 1), in 116 patients with pretreated metastatic RCC. Toxic effects were mild, with reversible hypertension and asymptomatic proteinuria predominating. Median time to progression in the group receiving 10 mg of bevacizumab per kilogram was 4.8 months and thus significantly longer than that in the placebo group (median, 2.5 months). Ten percent of the patients receiving bevacizumab achieved partial responses, there was no significant difference in overall survival between either group, however, cross-over treatment in case of disease progression was permitted in this study. Encouraged by these results, a first-line phase III trial (AVERON) was initiated comparing bevacizumab plus IFN-α with IFN-α plus placebo in 649 patients with clear-cell mRCC. Results were presented at the ASCO meeting 2007 [40]. The objective response rate for those patients treated with both drugs was 31% (CR: 1% and PR: 30%) and significantly higher than that for patients receiving IFN-α alone (13%; CR: 2% and PR: 11%). Median duration of response was comparable with 13 and 11 months; SD rates were not given. Tumor shrinkage was observed in 70 and 39% of patients receiving the combination and mono-therapy, respectively. The median progression-free survival time was doubled by the addition of bevacizumab (10.2 vs. 5.4 months). A subgroup analysis, however, revealed that only patients with good and intermediate prognosis profited from the bevacizumab/IFN-α combination; among poor prognosis patients there was no difference in progression-free survival (2.2 vs. 2.1 months). The median overall survival in the combination arm had not been reached yet and was notably longer than in the IFN-α/placebo arm. Bevacizumab-related side effects were generally mild and consistent with previous observations, however, grade 3/4 adverse events were more common in the combination-therapy group: fatigue/asthenia (23 vs. 15%), proteinuria (6.5 vs. 0%), hypertension (3.9 vs. 0.7%), hemorrhage (3.3 vs. 0.3%), venous thromboembolism (1.8 vs. 0.7%), gastrointestinal perforation (1.5 vs. 0%), and arterial ischemia (1.2 vs. 0.3%).

Sunitinib plus gefitinib

Patel *et al.* [41] presented results of a phase I/II trial, which was conducted to test the safety and efficacy of sunitinib (37.5–50 mg/day, days 1–28, q42) in combination with gefitinib (250 mg/day), an epidermal growth factor receptor inhibitor, in metastatic ccRCC. Fifteen out of 42 (36%) patients achieved a partial response and 20 out of 42 (48%) patients SD. Median duration of

response was 9.2 months. Most common grade 1–2/3–4 treatment-related adverse events observed were diarrhea (36/12%), rash (21/5%), nausea (nine/5%), hand–foot syndrome (14/0%), fatigue (10/2%), and hypertension (seven/2%). Grade 1–2/3–4 laboratory abnormalities were neutropenia (19/17%), hyperlipasemia (15/21%), thrombocytopenia (19/12%), anemia (24/2%), and hyperamylasemia (nine/12%).

Sunitinib plus interferon-alpha

First-line sunitinib (37.5–50 mg/day p.o., days 1–28, q42) was tested in combination with IFN-α (3 up to 9 MU s.c., three times per week) by Kondagunta *et al.* [42] in patients with metastatic ccRCC. They observed partial responses and SD in three out of 25 (12%) and 20 out of 25 (80%) patients. Toxicity, however, was substantial, including fatigue (100%), diarrhea (76%), nausea (56%), stomatitis (52%), and neutropenia (48%). Grade 3/4 toxicity included neutropenia (36%), fatigue (28%), thrombocytopenia (20%), hypertension (16%), hand–foot syndrome (12%), and diarrhea and stomatitis (4% each). The maximum tolerable dose (MTD) was determined to be sunitinib 37.5 mg plus IFN-α at 3 MU s.c., three times per week.

Sorafenib plus interferon-alpha

In 2007, three studies were published evaluating activity and toxicity of sorafenib in combination with IFN-α:

Ryan *et al.* [43] treated ccRCC patients, who had received no prior systemic therapy with sorafenib (800 mg/day) plus IFN-α (10 MU, three times per week). Twelve out of 62 (19%) assessable patients achieved an objective confirmed response (one CR and 11 PR). An additional 31 out of 62 (50%) patients had an unconfirmed PR or SD as best response. The median progression-free survival was 7 months. The current Kaplan–Meier estimate of median overall survival was 17 months. The most common adverse events were fatigue (90%), anorexia (71%), anemia (66%), diarrhea (63%), nausea (63%), rigors/chills (63%), leucopenia (58%), fever (56%), and rash (39%). Moreover, 77% of all patients experienced a grade 3 or worse adverse event including fatigue (29%), diarrhea (16%), leukopenia (13%), and anorexia (10%). The authors concluded that the confirmed response rate for the combination of sorafenib and IFN-α in advanced renal carcinoma was greater than expected with either IFN-α or sorafenib alone, but that the increased response rate did not justify the relatively high toxicity profile of this combination.

A similar but first-line and second-line study, which included 40 mRCC patients, was presented by Gollob *et al.* [44]. The response rate was 33% (two out of 40 CR and 11 out of 40 PR); the median duration of response was 12 months. Moreover, 18 out of 40 patients had SD. The median progression-free survival time was 10 months; the median overall survival had not yet been reached. The toxicity, however, described by Gollob *et al.* was not insignificant, either. Again, fatigue (90%), anorexia (78%), anemia (75%), diarrhea (75%), hypophosphatemia (73%), rash (70%), nausea (65%), alopecia (60%), leucopenia (60%), and chills (55%) were the most common toxicities. Grade 3 toxicities were less common but included hypophosphatemia (37%), neutropenia (25%), rash (13%), fatigue (13%), and anemia (8%). Dose reductions were required in 65% of all patients. Like Ryan *et al.* [43], Gollob *et al.* [44] stated that the combination of sorafenib and IFN-α had substantial activity in mRCC. Nevertheless, the incidence of several toxicities such as fatigue, anorexia, anemia, diarrhea, rash, and hypophasphatemia with the combination was higher than expected for either agent alone leading to an unacceptable high number of necessary dose reductions or treatment interruptions.

The third trial was presented by Bracarda *et al.* [45] who prospectively randomized 63 patients to receive sorafenib (800 mg/day) in combination with IFN-α 9 MU three times per week (arm A) or 3 MU five times per week (arm B). Sixteen out of 63 (25.4%) patients achieved a partial response (29% in arm A and 22% in arm B), 26 out of 63 (41.3%) patients had an SD (29% in arm A and 53% in arm B) and 21 out of 63 patients progressed (33.3%: 42% in arm A and 25% in arm B). Owing to a short follow-up period progression-free survival data had not yet been available. The most common grade 3–4 toxicities affecting more than 5% of all patients were equally distributed between the treatment arms except for fatigue and skin rash (19 and 8%, respectively, only arm A): hypophosphatemia (43%), hand–foot syndrome (22%), anorexia, stomatitis, hyperamylasemia (11% each), diarrhea (8%), and hyperlipasemia (5%).

Facing the high toxicity of sorafenib plus conventional dose IFN-α, Jonasch *et al.* [46] initiated a phase II study to compare sorafenib with or without low dose IFN-α (0.5 MU b.i.d.). An interim analysis after the randomization of 50 patients did not show any difference concerning disease control or progression-free survival time.

Valatinib plus everolimus

Valatinib (PTK/ZK, PTK787/ZK222584) is an orally active TKI that blocks all known VEGF receptors (Fig. 1) [6]. Everolimus (RAD001) is an orally active macrolide which selectively inhibits mTOR. Combination therapy with VEGFR and mTOR inhibition was supposed to have additive efficacy in RCC. Therefore, Speca *et al.* [47] conducted a phase I/II trial including 14 patients with mRCC. MTDs of valatinib 1 g and everolimus 5 mg daily were determined; 13 evaluable patients demonstrated two (15%) PR and eight (62%) SD for

more than 3 months. Dose-limiting toxicity included grade 3 diarrhea, hypertriglyceridemia, asthenia, fatigue, and mucositis. The authors recommended the planning of a phase II/III trial applying the MTD.

Meloxicam plus interferon-α

Shinohara *et al.* [48] conducted a first-line phase II trial combining meloxicam, a selective cyclooxygenase-2 inhibitor, and IFN-α in mRCC to confirm their hypothesis that meloxicam enhances the response to the immunotherapy. Twenty-one patients received IFN-α at 3–5 MU three times per week and meloxicam 10 mg/day.

Toxicities were mostly grade 1 or 2 (fever, fatigue, anorexia, and depression), except one patient with grade 3 liver dysfunction. Among 20 patients evaluable for response, complete response was observed in three patients (14%) and partial response in five (24%), yielding an overall response rate of 38%. An additional five patients (24%) had SD. Five of six patients classified as poor risk by MSKCC prognostic classification obtained an objective remission, as did three of 14 patients at good or intermediate risk. Median time to progression for all 20 patients was 6 months (1–29+ months). The authors conclude that that meloxicam can enhance the response to immunotherapy and suggest conducting further investigations with this combination.

Nonclear-cell renal cell carcinoma

Clear-cell carcinoma is the most common histopathologic subtype of kidney tumors (around 70%). Consequently, clinical trials for advanced-stage kidney cancer have focused on patients with this RCC subtype (ccRCC) and not on the less common tumors such as papillary, chromophobe, collecting-duct carcinoma, and sarcomatoid-variant tumors. Genetic and clinical studies during the past two decades, however, have shown that kidney cancer is not a single disease; it is made up of a number of different types of cancer that occur in the same organ [49]. Each may have a distinct histologic type, a different clinical course, caused by alteration of different genes, and, after all, respond differently to systemic therapy. Therefore, it is not surprising that immuno(chemo)therapy, which has successfully been used for some patients with ccRCC, does not appear to have any significant activity in other RCC subtypes [50,51]. Novel-targeted therapies are currently under investigation in the treatment of nonclear-cell kidney cancer (n-ccRCC).

Sorafenib

The American ARCCS EAT included 209 patients with n-ccRCC; 141 patients with papillary ($n = 118$), chromophobe ($n = 18$), or collecting duct ($n = 5$) were evaluable for response [52]. In papillary tumors disease control (OR + SD) was 80% including 3 and 19% confirmed and unconfirmed PR, respectively. The disease control rate for chromophobe mRCC was even higher (95%); in contrast, three out of five patients with collecting duct tumors achieved SD only.

On the occasion of the ECCO meeting 2007, Beck *et al.* [22] presented results of the European ARCCS trial, an open-label, noncomparative phase III study, that included 104 evaluable patients with metastatic papillary RCC. Even though sorafenib showed significant activity in this subgroup of patients, the results were less striking than in clear-cell patients (disease control rate of 66.4 vs. 75.7%, median progression-free survival 5.8 vs. 7.5 months).

Plantade *et al.* [53], on the contrary, did not see objective responses in patients with papillary mRCC ($n = 28$) treated with sorafenib; the median progression-free survival in this study was 5.7 months only. Yet, median overall survival was 19.6 months.

Staehler *et al.* [54] used sorafenib to treat 11 patients with metastatic progressive sarcomatoid RCC who had been pretreated with and failed to respond to a gemcitabine/doxorubicin combination. They observed one partial response (9%), four patients (36%) achieved SD, and six were progressive. Median time to progression was 5 months.

Forty-six patients with sarcomatoid tumors received sorafenib within the EU-ARCCS trial [22]: with 67.4% and 4.3 months, respectively, the disease control rate and median progression-free survival were considerable but significantly lower than in patients with conventional RCC (75% and 7.5 months).

Temsirolimus

At the ASCO meeting 2007, Dutcher *et al.* [34] presented a subgroup analysis of the temsirolimus vs. IFN-α trial ([33], *vide supra*), comparing the activity of temsirolimus and IFN-α in metastatic n-ccRCC as well as the efficacy of temsirolimus in ccRCC and n-ccRCC. This study included poor prognosis patients without pretreatment, 75% of the n-ccRCC patients suffered from papillary tumors. The median progression-free and overall survival in 36 n-ccRCC patients who were treated with IFN-α was significantly shorter than in 37 n-ccRCC patients who received temsirolimus, respectively (1.8 vs. 7.0 months and 4.3 vs. 11.6 months). Moreover, there was a trend toward an even higher efficacy of temsirolimus in n-ccRCC than in ccRCC (median overall survival, 11.6 vs. 10.6 months). The authors concluded that temsirolimus might be the agent of choice for n-ccRCC, regardless to age and MSKCC risk group (in contrast to ccRCC, where it is particularly recommended for poor prognosis and age < 65 years).

Sunitinib

Within the sunitinib EAT, 276 evaluable n-ccRCC patients received second-line sunitinib (4 weeks on and 2 weeks off); most of them had failed prior cytokine-based therapy [15]. Even though the results were less remarkable than in ccRCC, sunitinib showed significant activity in n-ccRCC, too. Overall response and disease control rates for n-ccRCC vs. ccRCC were 5.4 vs. 9.3%, 47.0 vs. 52.4%, respectively. Unfortunately, the authors did not differentiate between n-ccRCC subtypes.

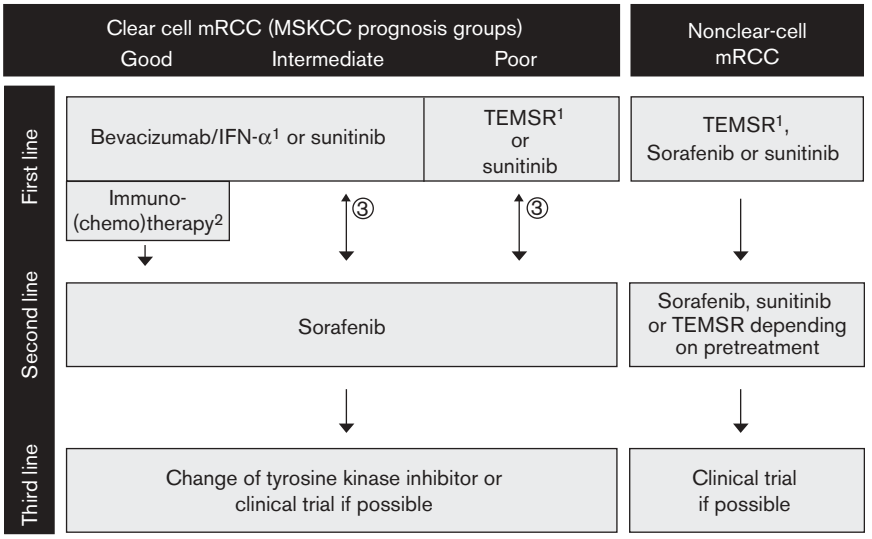
Conclusions and recommendations

In recent years, numerous innovative approaches to fight mRCC have been tested, partly with promising results. In 2007, several phase II and III trials have been published which could confirm, objectify, qualify, or disprove early results.

The introduction and approval of receptor TKIs have changed the face of first-line and second-line treatment of patients with metastatic RCC. In addition, the application of monoclonal antibodies targeting VEGF signaling (e.g. bevacizumab) in combination with IFN-α seems to have the potential to become one standard first-line option for metastatic good/intermediate prognosis ccRCC [40]. Cytokine-based immunotherapy as applied during the last two decades may still be considered as first-line therapy for those (few) patients who are young, in good physical condition, and present with nonvisceral metastasis of a ccRCC only. In contrast, TKIs (e.g. sorafenib and sunitinib) are about equally effective used in first-line and second-line settings [15,16,23,25]. As there is no significant cross-resistance between either agent we recommend a sequential use [22,29,30,32] is observed. Yet, the application of sorafenib and sunitinib in patients with severe arterial hypertension should be considered carefully as an increase of hypertension [10,18], a decline in ejection fraction [10], as well as rare cases of cardiac ischemia or infarction have been reported [18]. However, for the majority of these patients no alternative is available; therefore, the treatment with TKI should at least be closely monitored. Sunitinib induces biochemical hypothyroidism in about 85% of mRCC patients, the majority of whom can have signs or symptoms of hypothyroidism [55]. Therefore, routine monitoring is warranted. Thyroid hormone replacement should be undertaken if necessary.

Sunitinib and sorafenib can be safely administered to mRCC patients with previously treated CNS metastases (surgery and/or radiotherapy) [17,22] and, in contrast to

Fig. 2



Current therapeutic options. [1]Multikinase inhibitors (TKIs) are highly effective second-line agents with no/little cross-resistance among each other. Their application, however, can lead to overexpression of respective growth factors such as VEGF [16,19,23] which could lead to a rebound effect, that is, accelerated tumor growth after TKI withdrawal. Therefore, it might be advantageous to use other agents (cytokines, monoclonal antibodies, mTOR inhibitors) first-line wherever reasonable/practicable and multikinase inhibitors thereafter in a sequential manner. The use of mTOR inhibitors after TKI failure is currently under investigation [36]. [2]Immunotherapy may still be beneficial and chosen as first-line treatment in good-risk patients with clear-cell mRCC without visceral nonpulmonary metastases. [3]In spite of two retrospective studies which have recently shown advantages for the sorafenib–sunitinib sequence ([29,30], compare text), according to the EAU guidelines 2007 [58] sunitinib is currently advised as first-line therapy in good-risk and intermediate-risk patients. Sorafenib is advised as second-line treatment. Both agents, however, are active in first-line and second-line settings and can be used sequentially. The application of all recommended agents should always be conform to the official approval in the respective country or approved in the context of compassionate use programs. IFN, interferon; mRCC, metastatic renal cell carcinoma; TEMSR, temsirolimus; TKI, tyrosine kinase inhibitor.

cytokines, seem to be efficient in nonclear-cell mRCC, too [15,22,52,54].

Recent data suggest that the use of TKIs (particularly sorafenib and sunitinib) in escalating doses can increase their therapeutic potential [23,24,56]. Future studies will have to determine efficacy and toxicity of high-dose TKI administration.

mTOR inhibitors comprise a promising novel group of agents in cancer treatment. Regarding RCC, they have shown significant efficacy particularly in poor prognosis clear-cell mRCC [33,37] as well as in nonclear-cell mRCC [34]. Combinations with other drugs are still under investigation [47].

In general, any clinical benefit achieved with combination therapy should be balanced with the potential increase in toxicity. Combinations of drugs with different targets (e.g. antibodies, TKIs, cytokines, mTOR inhibitors) have not yet shown improved long-term clinical benefit in metastatic RCC, however, often side effects increased dramatically and MTDs had to be reduced in the majority of studies [42–45,57]. An exception might be bevacizumab/IFN-α, follow-up data and SD rates are awaited. An additional disadvantage of combination therapy is that the chance for long-term sequential treatment with different consecutive drugs in this still incurable disease might be missed.

Taken together, currently numerous established and experimental novel agents are focused in phase II and III trials, either as mono and/or combination therapy. Up to now, the exact place of the new drugs is still open for discussion. Currently, none of the data available shows that they will cure any patient but rather seem to stabilize metastatic RCC for a prolonged period. Today with the advent of numerous new drugs and trials, however, it is our chance and duty to individualize the treatment for each patient (Fig. 2).

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