Metastatic renal cell carcinoma (mRCC) is largely resistant to conventional chemotherapy, hormonal therapy, and cytokine therapy and is associated with a poor prognosis. The European Association of Urology (EAU) recently published updated guidelines, with specific recommendations for treating mRCC. The EAU recommendations were based on recent clinical study data, which demonstrated the superiority of newer targeted therapies over interferon-\(\alpha\) (IFN-\(\alpha\)). mRCC is a highly vascularised tumour, characterised in the majority of cases by over-production of angiogenic peptides such as vascular endothelial growth factor. The targeted therapies selectively inhibit proteins whose functions include the stimulation of angiogenesis; two of these therapies, sunitinib and sorafenib, are currently approved in the European Union for use in mRCC. Reflecting the improved options now available, the updated EAU guidelines recommend using sunitinib, an orally administered antiangiogenic drug that selectively targets several receptors whose ligands are up-regulated in RCC, as first-line therapy for mRCC in good- and intermediate-risk patients. This recommendation is based on compelling data from a phase 3 trial that demonstrated longer progression-free survival and greater objective response rates for untreated patients with mRCC receiving sunitinib than for those receiving IFN-\(\alpha\). Other recommendations include using sorafenib as second-line therapy for mRCC and considering temsirolimus as first-line therapy for poor-risk patients with mRCC. Clinical studies investigating these agents, both alone and in combination, are ongoing. We review the clinical studies that form the basis of the EAU guidelines to gain an insight into the rationale behind the updated recommendations.
1. Introduction

Until recently, the prognosis for individuals with metastatic renal cell carcinoma (mRCC) was poor: chemotherapy as monotherapy is generally ineffective, and immunotherapy with interferon-α (IFN-α) or interleukin 2 is only recommended for selected patients with a good-risk profile and clear-cell subtype histology [1]. Ongoing research into the molecular biology underlying mRCC has enabled the development and clinical application of new targeted therapies that inhibit angiogenesis, an integral process in tumour development and metastasis, particularly for highly vascularised mRCC. Reflecting the promising results obtained in clinical trials of these targeted agents, the European Association of Urology (EAU) has incorporated recommendations relating to the use of the new therapies into their recently updated guidelines on RCC. These guidelines describe recommended systemic therapy in the treatment of mRCC, based on a comprehensive and independent evaluation of clinical trial data and other resources [1]. As part of the updated guidelines, the EAU now recommends using sunitinib (Sutent®; sunitinib malate; Pfizer), a small molecule tyrosine kinase inhibitor with antitumour and antiangiogenic activity, as first-line treatment for mRCC in patients with good/favourable or intermediate risk [1,2]. Patients with good/favourable-risk profiles have none of the five risk factors associated with short survival (adopted from the Memorial Sloan-Kettering Cancer Center [MSKCC] risk classification), which are low serum haemoglobin levels, elevated corrected serum calcium levels, elevated serum lactate dehydrogenase levels, poor performance status, and intervals <1 yr between diagnosis and treatment [2,3]. This paper provides an overview of the clinical trial data supporting the first-line use of sunitinib in this patient population, along with data on other targeted therapies, including sorafenib (Nexavar®; sorafenib tosylate; Bayer Pharmaceuticals) and temsirolimus (Torisel®; temsirolimus; Wyeth), which also have a place in the current EAU guidelines for systemic therapy of mRCC.

2. Targeted therapies for RCC

RCC over-produces angiogenic peptides such as vascular endothelial growth factor (VEGF) [4]. More than 80% of RCC tumours demonstrate clear-cell histology [5], and functional inactivation of the von Hippel-Lindau (VHL) gene occurs in up to 70% of these clear-cell tumours [6]. The VHL gene product, the VHL protein, is a tumour suppressor protein that binds to hypoxia-inducible factor (HIF), a protein transcription factor, and regulates proteasomal degradation of HIF through its interaction with other cellular proteins [7]. Mutations in VHL that render the VHL protein nonfunctional result in accumulation of HIF [7], which leads to increased transcription of hypoxia-inducible genes, including VEGF and platelet-derived growth factor-β (PDGF-β) [6,8]. A clear correlation has been shown between VEGF mRNA expression and vascularisation in RCC [9]; therefore, it seems likely that these angiogenic growth factors contribute to the hypervascularity of RCC.

Targeted therapies act against components of the angiogenic VHL–HIF–VEGF/PDGF-β pathway, with the aim of counteracting, at least in part, the consequences of losing VHL function, thus blocking angiogenesis and inhibiting tumour growth. Sunitinib and sorafenib, both of which are approved in the European Union for the treatment of mRCC, target the receptors to the HIF-responsive gene products, VEGF and PDGF-β [10], whereas temsirolimus, a specific inhibitor of the mammalian target of rapamycin (mTOR) kinase, indirectly inhibits HIF. Temsirolimus is not yet approved for the treatment of mRCC in the European Union.

3. Sunitinib as first-line therapy for advanced/mRCC: support from clinical studies

3.1. Sunitinib: an orally administered small-molecule VEGF and PDGF receptor tyrosine kinase inhibitor

Sunitinib is an orally administered small molecule that simultaneously inhibits multiple receptor tyrosine kinases implicated in tumour angiogenesis, tumour growth, and metastatic progression [4,11,12]. Receptors inhibited include PDGFR receptor (PDGFR) and VEGF receptor (VEGFR) [13]. In preclinical studies, sunitinib exhibited direct antitumour activity against tumour cells that are dependent on signalling through VEGFR or PDGFR for proliferation/survival, as well as antiangiogenic activity through its inhibition of VEGFR and PDGFR signalling [13].

Sunitinib is indicated for the treatment of advanced RCC and/or mRCC [14]. It can be administered either as first-line or as second-line therapy in disease that is refractory to cytokine therapy. Several studies have demonstrated clinical benefits for sunitinib in the treatment of mRCC [5,15–17]. As a result of these studies, the EAU now recommends using sunitinib as first-line therapy in
good/favourable- or intermediate-risk patients [1]. Table 1 summarises the treatment recommendations by the EAU for the different mRCC settings.

### 3.2. Phase 2 trials of sunitinib as second-line therapy for mRCC

Results from phase 2 trials of sunitinib as second-line therapy for mRCC demonstrated the efficacy and manageable adverse event (AE) profile of the agent [5,15]. Two independent, single-arm, multicentre, phase 2 trials were conducted in a total of 169 patients with mRCC who had progressed despite previous cytokine therapy. The two trials had similar eligibility criteria (age ≥18 yr, histologic confirmation of RCC, measurable disease with evidence of metastases, failure of one cytokine therapy because of disease progression, Eastern Cooperative Oncology Group (ECOG) performance status of ≤1, and adequate organ function) and treatment plans, allowing an analysis of pooled data from both studies. Sunitinib was administered orally at a dose of 50 mg/d in repeated 6-wk cycles of daily therapy for 4 wk, followed by 2 wk off therapy. Dose reduction due to toxicity was allowed to 37.5 mg/d and then to 25 mg/d. Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent. The primary end point was objective response rate (ORR); secondary end points included response duration, progression-free survival (PFS), overall survival (OS), and safety.

As shown in Table 2, investigator-assessed partial response (PR) rates of ≥40% were reported in both studies, and >20% of patients in both studies had stable disease (SD) for ≥3 mo [15]. Median PFS (pooled data) was 8.2 mo (Fig. 1), and median PFS in patients who achieved a complete response (CR) or PR was 14.8 mo. An updated analysis (pooled data) demonstrated an ORR of 45%, median PFS of 8.4 mo, and median OS of 22.3 mo [18]. At the time of the updated analysis, 48% of patients remained alive at 2 yr. These results compare favourably with previous second-line therapies for mRCC; Escudier et al [19] reported that only 4 patients (3.5%) achieved PR in their study of 113 mRCC patients with progressive disease (PD) after first-line cytokine therapy. Similar findings were reported by Motzer et al [20] in their retrospective analysis of 251 patients with mRCC previously treated with various systemic therapies for metastases. In this analysis, only 10 patients (4%) had achieved a PR, with a median survival for all 251 patients of 10.2 mo (95% confidence interval [CI], 8–12).

### Table 1 – Treatment recommendations according to EAU guidelines for the various mRCC settings [15]

<table>
<thead>
<tr>
<th>mRCC setting</th>
<th>Sunitinib</th>
<th>Sorafenib</th>
<th>Temsirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
<td>&lt;</td>
<td>&lt;</td>
<td>&lt;</td>
</tr>
<tr>
<td>Risk profile*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good/favourable</td>
<td>&lt;</td>
<td></td>
<td>&lt;</td>
</tr>
<tr>
<td>(no risk factors)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>&lt;</td>
<td></td>
<td>&lt;</td>
</tr>
<tr>
<td>(1–2 risk factors)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor risk</td>
<td>&lt;</td>
<td></td>
<td>&lt;</td>
</tr>
<tr>
<td>(≥3 risk factors)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second line</strong></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

EAU = European Association of Urology; mRCC = metastatic renal cell carcinoma.

* Risk factors associated with short survival, according to the Memorial Sloan-Kettering Cancer Center risk classification, are low serum haemoglobin levels, elevated corrected serum calcium levels, elevated serum lactate dehydrogenase levels, poor performance status, and intervals <1 yr between diagnosis and treatment [2,3].

### Table 2 – Treatment outcomes for patients included in the phase 2 studies of sunitinib as second-line therapy [15]

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>Trial 1 (n = 63)</th>
<th>Trial 2 (n = 105)</th>
<th>Pooled analysis (n = 168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best response*, no. of patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>1 (&lt; 1)</td>
</tr>
<tr>
<td>PR</td>
<td>25 (40)</td>
<td>45 (43)</td>
<td>70 (42)</td>
</tr>
<tr>
<td>SD ≥3 mo</td>
<td>17 (27)</td>
<td>23 (22)</td>
<td>40 (24)</td>
</tr>
<tr>
<td>PD, SD &lt;3 mo, or not evaluable</td>
<td>21 (33)</td>
<td>36 (34)</td>
<td>57 (34)</td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>8.7</td>
<td>8.1</td>
<td>8.2</td>
</tr>
</tbody>
</table>

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; PFS = progression-free survival.

*Assessed by the investigator.

Sunitinib was generally well tolerated in the two phase 2 trials, with manageable toxicities [5,15]. The most common AEs in the two trials were fatigue and diarrhoea. Grade 3 fatigue or diarrhoea were reported by 11% and 3% of patients from each study, respectively.

3.3. Phase 3 study comparing sunitinib with IFN-α as first-line therapy for mRCC

Building on the promising findings from the phase 2 studies [5,15], Motzer et al demonstrated the clinical superiority of sunitinib over IFN-α as first-line therapy for mRCC [16,17]; this study forms the basis for the EAU’s recommendation of sunitinib as first-line therapy for mRCC [1]. In this international, multicentre, phase 3 study, 750 patients were randomised in a 1:1 ratio to receive either sunitinib or IFN-α until disease progression, unacceptable AEs, or withdrawal of consent. Sunitinib (50 mg) was administered orally once daily in 6-wk cycles consisting of 4 wk of treatment followed by 2 wk without treatment. Patients received IFN-α by subcutaneous injection three times per week on nonconsecutive days at 3 million units (MU)/dose during the first week, 6 MU/dose the second week, and 9 MU/dose thereafter. Randomisation was stratified according to baseline levels of lactate dehydrogenase (>1.5 vs. ≤1.5 times the upper limit of the normal range), ECOG performance status (0 vs. 1), and previous nephrectomy (yes vs. no). The primary end point was PFS; secondary end points included ORR, OS, patient-reported outcomes, and safety. The two treatment groups were well balanced with respect to baseline demographic and disease characteristics.

After a median treatment duration of 6 mo (range: 1–15 mo) in the sunitinib group and 4 mo (range: 1–13 mo) in the IFN-α group, median OS had not been reached in either group; death occurred in 13% of patients in the sunitinib group and 17% of patients in the IFN-α group [16]. There was a trend towards increased survival for sunitinib (hazard ratio [HR] for death = 0.65); however, the comparison did not meet the prespecified level of significance [16]. Reasons for discontinuing treatment to this point were PD (in 25% of patients in the sunitinib group and 45% in the IFN-α group; p < 0.001), AEs (8% and 13%, respectively; p = 0.05), withdrawal of consent (1% and 8%, respectively; p < 0.001), and protocol violation (<1% in each group) [16].

After a median treatment duration of 11 mo (range: <1–25 mo) for sunitinib and 4 mo (range: <1–22 mo) for IFN-α, patients treated with sunitinib had a longer PFS than patients treated with IFN-α (11 mo [95%CI, 10–11] vs. 4 mo [95%CI, 4–5]) [17]. Investigator-assessed ORRs were significantly higher in the sunitinib group than in the IFN-α group (44% vs. 11%; p < 0.000001). Four patients were considered by investigators to have had a CR with sunitinib and two patients with IFN-α. The median duration of response in the sunitinib group (n = 165) was 12 mo compared with 10 mo in the IFN-α group (n = 43) [17]. When the influence of baseline clinical features and previously identified prognostic factors on treatment effect were analysed using a Cox proportional hazards model, a clear benefit for sunitinib was observed across all subgroups of patients analysed (Fig. 2) [16]. This benefit was shown to extend across all MSKCC prognostic risk factor groups [2] (HR = 0.488; Table 3) [17]. Sunitinib conferred the greatest advantage in the groups with fewer risk factors, hence the EAU recommendation for sunitinib as first-line therapy in patients with good and intermediate risk [1]. Confirmation of results is awaited in the final analysis, which is yet to be completed.

Table 3 – Median progression-free survival for subgroups of patients according to the number of risk factors present [17]

<table>
<thead>
<tr>
<th>No. of risk factors</th>
<th>Median PFS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sunitinib</td>
</tr>
<tr>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>1-2</td>
<td>9</td>
</tr>
<tr>
<td>≥3</td>
<td>4</td>
</tr>
</tbody>
</table>

PFS = progression-free survival.
The range and severity of treatment-related AEs indicated an acceptable safety profile for sunitinib [16]. The proportion of patients with grade 3 or 4 AEs was relatively low in both groups, although most general AEs of all grades occurred more frequently in the sunitinib group than in the IFN-α group. Patients in the sunitinib group had significantly (\(p < 0.05\) for all comparisons) higher rates of grade 3 diarrhoea (5% vs. 0%), vomiting (4% vs. 1%), hypertension (8% vs. 1%), and hand-foot syndrome (5% vs. 0%) compared with the IFN-α group. Grade 3 or 4 leukopenia, neutropenia, and thrombocytopenia also occurred more frequently in the sunitinib group than in the IFN-α group (\(p < 0.05\) for all comparisons). Treatment-related grade 3 or 4 fatigue was significantly higher in patients receiving IFN-α than in patients receiving sunitinib (12% vs. 7%; \(p < 0.05\)).

Grade 3 decline in left ventricular ejection fraction occurred with similar frequencies in both treatment groups (2% vs. 1% for sunitinib and IFN-α, respectively). Most sunitinib-related AEs were ameliorated by interruption or modification of the dose, and treatment was discontinued in <10% of patients as a result of AEs.

### 4. Other targeted therapies for advanced/mRCC

#### 4.1. Sorafenib as second-line therapy for mRCC

Sorafenib is an oral multikinase inhibitor that decreases tumour-cell proliferation and tumour angiogenesis [21]. This action is mediated by its effects on multiple targets, such as Raf kinase, VEGFR, and PDGFR [21]. The drug is indicated in the European Union for the treatment of patients with advanced RCC in which prior cytokine-based...
therapy has failed or who are unsuitable for such therapy [22]; in the United States, sorafenib is indicated for the treatment of patients with advanced RCC [23]. In the updated guidelines, the EAU advocates using sorafenib as second-line treatment for mRCC [1]. This recommendation is based on results from an international, multicentre, phase 3 trial that compared sorafenib with placebo as second-line therapy after failure of a prior systemic therapy in patients with advanced metastatic clear-cell RCC [24]. Eligibility criteria included age $\geq$ 18 yr, histologically confirmed metastatic clear-cell RCC, an ECOG performance status of 0 or 1, an intermediate- or low-risk status according to MSKCC prognostic score [20], a life expectancy of at least 12 wk, and adequate organ function. Patients were stratified according to country and MSKCC prognostic score and randomised in a double-blind fashion to receive either continuous treatment with oral sorafenib (400 mg twice daily, $n = 451$) or placebo ($n = 452$). The primary end point was OS; secondary end points included OS and PFS. Baseline characteristics were well balanced between the study groups.

Results clearly showed the clinical benefits of sorafenib compared with placebo; PFS was longer in patients receiving sorafenib than in placebo recipients (5.5 mo vs. 2.8 mo; $p < 0.001$), and the HR for PD in the sorafenib group was 0.44 ($p < 0.01$) [24]. The first interim analysis of OS showed that sorafenib reduced the risk of death compared with placebo (HR = 0.72; $p = 0.02$; Fig. 3), although this benefit was not considered to be statistically significant according to the threshold set in the protocol. In the sorafenib group, one patient (<1%) had a CR, 43 patients (10%) had a PR, 333 patients (74%) had SD, and 56 patients (12%) had PD (18 patients [4%] were not evaluated). In comparison, no patients in the placebo group had a CR, 8 patients (2%) had a PR, 239 patients (53%) had SD, and 167 patients (37%) had PD (38 patients [8%] were not evaluated). AEs were predominantly grade 1 or 2. The most common AEs were diarrhea, rash, fatigue, hand-foot skin reactions, alopecia, and nausea. Significantly more patients receiving sorafenib experienced grade 3 or 4 hypertension than did placebo patients (4% vs. <1%; $p = 0.001$). The incidence of grade 2 diarrhea was also significantly higher in patients receiving sorafenib than placebo (12% vs. 3%; $p < 0.001$), as was grade 2 rash (13% vs. 2%), grade 3 or 4 hand-foot skin reaction (6% vs. 0%), grade 2 alopecia (4% vs. <1%), and grade 2 pruritus (5% vs. <1%; $p < 0.001$ for all comparisons). The proportion of patients discontinuing treatment as a result of AEs was similar between the two groups at 10% of sorafenib versus 8% of placebo patients.

4.2. Temsirolimus as first-line therapy for poor-risk mRCC

Temsirolimus is an intravenously administered specific inhibitor of mTOR kinase [25], a positive regulator of HIF-dependent gene transcription in response to hypoxia [26]. The drug is indicated in the United States for the treatment of advanced RCC and, although approval has not yet been granted for use in the European Union, the EAU recommends considering temsirolimus for first-line treatment of poor-risk patients with mRCC, that is, those with three or more risk factors for short survival [1], as defined by the modified MSKCC poor-risk criteria. In a multicentre, phase 3 study, 626 patients with
previously untreated, poor-prognosis mRCC were randomised to receive either 25 mg intravenous temsirolimus weekly (n = 209), 3 MU IFN-α (with an increase to 18 MU) subcutaneously three times a week (n = 207), or combination therapy with 15 mg temsirolimus weekly plus 6 MU IFN-α three times a week (n = 210) [27]. Eligible patients had stage 4 or recurrent histologically confirmed RCC, a Karnofsky score of ≥60, no prior systemic therapy, and at least three of six specified predictors of short survival. Patients were stratified according to geographic region and whether they had undergone nephrectomy. The primary end point was OS; PFS and ORR were also assessed. The three treatment groups were well balanced with respect to age, sex, and performance status score.

Results from the second interim analysis showed that patients receiving temsirolimus had longer OS (HR for death = 0.73; p = 0.008) than patients receiving IFN-α alone [27]. OS in the group receiving temsirolimus plus IFN-α was not significantly different from that in the group receiving IFN-α alone (HR = 0.96; p = 0.70; Fig. 4). Median survival was 7.3 mo in the IFN-α group, 10.9 mo in the temsirolimus group, and 8.4 mo in the temsirolimus plus IFN-α group. Investigator-assessed PFS duration in the IFN-α, temsirolimus, and temsirolimus plus IFN-α groups was 1.9 mo, 3.8 mo, and 3.7 mo, respectively (Fig. 4). The ORRs of 4.8%, 8.6%, and 8.1% in patients receiving IFN-α, temsirolimus, or temsirolimus plus IFN-α were not significantly different; however, the proportion of patients with SD for at least 6 mo or an objective response was greater in the temsirolimus and combination therapy groups than in the IFN-α only group.

The most common AEs experienced with temsirolimus were asthenia, rash, anaemia, nausea, dyspnoea, diarrhoea, peripheral oedema, hyperlipidaemia, and hyperglycaemia, which were usually manageable with supportive care or a dose reduction. Sixty-seven percent of patients in the temsirolimus group experienced grade 3 or 4 AEs compared with 78% of patients in the IFN-α group (p = 0.02) and 87% of patients in the combination therapy group (p = 0.02). Grade 3 or 4 asthenia was reported in 11% of patients in the temsirolimus group, in 26% of the IFN-α group (p < 0.001), and in 28% of combination therapy patients (p < 0.001). The proportions of patients reporting dyspnoea, diarrhoea, nausea, or vomiting were similar among the three groups. Patients in the temsirolimus or combination therapy groups experienced higher incidences of rash (all grades: 47%, 21%, and 6%, for temsirolimus, temsirolimus plus IFN-α, and IFN-α, respectively), peripheral oedema (all grades: 27%, 16%, and 8%, respectively), and stomatitis (all grades: 20%, 21%, and 4%, respectively) than did patients in the IFN-α alone group. Anaemia, neutropenia, and thrombocytopenia also occurred more often in patients receiving temsirolimus (either alone or in combination with IFN-α; p ≤ 0.002), as did hyperglycaemia, hypercholesterolaemia, and hyperlipidaemia.

5. Conclusions
As research into the molecular basis of cancer continues, the options available to the clinician for the treatment of mRCC will continue to expand. With the introduction of targeted antiangiogenic therapies, such as sunitinib and sorafenib for mRCC, survival has improved dramatically for patients who previously would have had few treatment options.
once their disease had become advanced. Clinical trial data showing improved survival and higher ORRs relative to IFN-α have led to the EAU recommendation of sunitinib as first-line therapy in good- or intermediate-risk mRCC. Likewise, evidence from clinical studies of sorafenib and temsirolimus has also formed the basis for recommended use of these agents as second-line therapy and first-line therapy in poor-risk patients, respectively. Incorporation of these agents into guidelines, such as those from the EAU, highlights the current and future role of such targeted therapies and brings hope that greater future improvements in survival can be achieved. Future clinical trials involving newer agents such as axitinib, or combinations of targeted agents, possibly with other targeted therapies, conventional cytotoxic chemotherapy, or cytokine therapy, may lead to even greater gains in survival for patients with advanced cancer than are currently being achieved.

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Conflicts of interest

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