Clinical biomarkers of response in advanced renal cell carcinoma

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There are now a range of effective targeted agents available for the first- and second-line treatment of advanced renal cell carcinoma (RCC). However, patients with advanced RCC have varied responses to therapy; some experience long-term responses while others may not respond, or even progress rapidly. Characteristics or markers that could be used to determine which patients will benefit most from which agent may enable us to select the optimal treatment of each individual patient, thereby improving efficacy and avoiding unnecessary toxic effects. These characteristics may be at the cellular or genetic level. Alternatively, the occurrence of adverse events may act as surrogate markers of a drug’s on treatment activity, enabling prediction of outcomes during treatment. Recently, it has been suggested that during some targeted therapy for advanced RCC, the occurrence of specific adverse events, such as hypertension, hypothyroidism, hand–foot syndrome or fatigue/asthenia, may be associated with improved efficacy. This article reviews the evidence supporting clinical biomarkers in patients with advanced RCC receiving targeted agents. We also consider how these clinical biomarkers may affect the future management of patients with advanced RCC.

Key words: adverse events, clinical biomarkers, RCC, renal cell carcinoma, targeted agents

introduction

The development of biological targeted therapies has dramatically changed the way metastatic renal cell carcinoma (mRCC) is treated, with a number of targeted agents now licenced. Such agents (licensed and under development) include the vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) sunitinib [1], sorafenib [2], pazopanib [3], axitinib [4] and tivozanib [5]. Additionally, the anti-VEGF monoclonal antibody bevacizumab is licenced for the treatment of advanced RCC in combination with interferon-alfa (IFN-α) [6, 7]. The mammalian target of rapamycin (mTOR) inhibitors, temsirolimus [8] and everolimus [9], are also approved for the treatment of advanced RCC. With such an array of agents available, characteristics that would help to define which patients are most likely to respond well to a particular treatment would be beneficial in guiding therapy choice.

Treatment selection is currently dependent on the clinical activity of the different agents, based primarily on progression-free survival (PFS) and overall survival (OS) data reported in clinical trials, and on selection criteria for prognostic risk, such as those developed by the Memorial Sloan-Kettering Cancer Center [10]. However, with the exception of some patients who are excluded from treatment due to a high risk of toxic effect for a given class of drug, there are few data to guide the selection of targeted therapy.

Targeted therapies for mRCC are associated with distinct tolerability profiles, with commonly reported adverse events including gastrointestinal side-effects, hypertension, skin toxic effects and fatigue. The occurrence of these adverse events is related to the agent’s mechanism of action, and is due to the inhibition of target receptors, such as VEGFR, as well as off-target interactions, for example with other tyrosine kinase receptors [11, 12].

The development of some drug-induced adverse events may act as surrogate markers of a drug’s clinical activity and can be used to predict treatment outcomes (see below). These adverse events may be related to the mode of action of the drug and/or could merely be an indication of the exposure of a given drug in an individual patient. Studies have indicated that higher axitinib, sunitinib and pazopanib exposure is associated with higher efficacy; therefore, adverse events may not occur in patients receiving sub-therapeutic exposure [13, 14].

The best way to use clinical biomarkers in guiding cancer therapy, other than to give reassurance that a treatment is likely to be effective, is only just beginning to be established. This review discusses emerging clinical biomarkers in patients with advanced RCC treated with targeted therapy, and what they might mean for the overall management of such patients.
Hypertension is a common adverse event in patients with solid tumours treated with agents that target the VEGF pathway. Meta-analyses of clinical trials in multiple tumour types show that the median incidence of all-grade and grade ≥ 3 hypertension in patients treated with sunitinib is 22% and 6.8%, respectively [15], with corresponding rates of 23% and 5.7% in sorafenib recipients [16], 55% and 17% in patients treated with axitinib [17], 40% and 4% in pazopanib recipients [3, 18] and 25% and 8%–16% in bevacizumab plus IFN-α recipients [19]. In clinical trials in patients with mRCC, the incidence of all-grade and grade 3/4 hypertension varies widely (Table 1) [1–7, 20–30]. This is likely a reflection of the ability of VEGF inhibitors to induce hypertension, the measurement protocols (i.e. methods used to monitor hypertension, timing of assessment and control of hypertension) within different trials, and differences in the study patient populations. For example, in the AXIS trial [4], and the TIVO-1 phase III tivozanib versus sorafenib trial [31], patients appeared to be well balanced, the blood pressure (BP) measurement protocols were the same across the studies, and yet axitinib, tivozanib and sorafenib were associated with different rates of hypertension.

The pathophysiological mechanism by which VEGF-pathway inhibition leads to a rise in BP is not fully understood; however, impaired angiogenesis is thought to be central to altered BP control, potentially involving generalised dysfunction of the microcirculation. Activation of the endothelin-1 system, suppression of the renin-angiotensin system, inhibition of endothelial nitric oxide synthase and increased vascular stiffness have also been implicated [32–34].

The development of hypertension during the treatment of mRCC with sunitinib, bevacizumab plus IFN-α, axitinib and tivozanib has been associated with improved outcomes, although until recently, only in retrospective analyses (see below). This hypothesis remains to be further tested and validated in prospective trials.

<table>
<thead>
<tr>
<th>Study phase/type</th>
<th>Hypertension All-grade</th>
<th>Hypertension Grade 3/4</th>
<th>Hypothyroidism All-grade</th>
<th>Hypothyroidism Grade 3/4</th>
<th>Hand-foot syndrome All-grade</th>
<th>Hand-foot syndrome Grade 3/4</th>
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<tbody>
<tr>
<td>Sunitinib</td>
<td>30/0/1</td>
<td>14/2</td>
<td>29/9</td>
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<tr>
<td>Phase III [1]</td>
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<td>NA/NA</td>
<td>15/NA</td>
<td>7/NA</td>
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<tr>
<td>Japanese phase II [22]</td>
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<td>NA</td>
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<tr>
<td>Phase II [23]</td>
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<td>&lt;1/1</td>
<td>24/6</td>
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<td>Vascular access [2]</td>
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<td>Phase II (sorafenib refractory) [28]</td>
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<tr>
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<td>NA</td>
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<tr>
<td>Phase III [3]</td>
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<td>Phase III (CALGB) [7]</td>
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<td>18/1/1</td>
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<td>18/1/1</td>
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BP, blood pressure; HTN, hypertension (systolic BP ≥ 140 mmHg); NA, not available in cited papers; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.
A retrospective single-centre study has shown an independent association between hypertension following sunitinib (as first-, second- or later-line treatment) and PFS in patients with mRCC (hazard ratio [HR] 0.21; 95% confidence interval [CI] 0.076–0.59; P = 0.0030) [35]. In addition, a separate study reported that the development of hypertension in patients receiving second-line sunitinib was associated with both a significant decrease in risk of progression (HR 0.206; 95% CI 0.132–0.32; P < 0.00001) and mortality (HR 0.242; 95% CI 0.154–0.378; P < 0.00001) [36]. A further retrospective review of data from three multinational clinical trials of sunitinib in first- or second-line advanced clear-cell RCC [20, 21, 37] found a significant association between sunitinib-induced hypertension and improved PFS, OS and objective response rate (ORR) [38]. Of the 544 patients included in the efficacy analysis, 81% had a maximum diastolic blood pressure (DBP) ≥140 mmHg and 67% had a maximum diastolic blood pressure (DBP) ≥90 mmHg at some point in the study, despite having well-controlled BP at baseline. Onset was early, with most cases reported before the end of cycle 2 [38]. The development of hypertension was associated with a fourfold improvement in the duration of PFS and OS and a sixfold improvement in ORR with sunitinib (Tables 2 and 3). Effects were independent of the use of anti-hypertensive and/or hypertension-related sunitinib dosage reductions. However, while sunitinib-induced hypertension was associated with statistically improved clinical outcomes across the study, the development of hypertension was not necessary or sufficient for clinical benefit in all patients. An additional retrospective analysis of pooled data from five clinical trials of sunitinib in mRCC (n = 770) has also reported a statistically significant association (by multivariate analysis) between hypertension and survival end points: PFS (HR 0.29; P < 0.0001) and OS (HR 0.30; P < 0.0001) [39].

Similarly, an analysis of the pivotal CALGB 90206 bevacizumab plus IFN-α study found that patients who developed grade ≥2 hypertension had significantly longer PFS than those who did not (median 13.2 versus 8.0 months; P < 0.001), together with significantly longer OS (41.6 versus 16.2 months; P < 0.001) [7]. Multivariate analysis showed that the development of hypertension at 2 months independently predicted improved OS (P = 0.046).

The association between the development of hypertension and improved outcomes has also been observed with the more recently developed TKIs, axitinib and tivozanib, which have an increased specificity for the various kinase domains of VEGF receptors [40]. An analysis of five phase II studies evaluating the safety and efficacy of axitinib in a range of solid tumours, including mRCC, found improved OS in patients who developed DBP ≥90 mmHg (HR 0.55; 95% CI 0.39–0.77; P < 0.0001) [17]. Analysis of the studies that specifically included patients with mRCC [28, 29] found that median OS was significantly longer in axitinib recipients with at least one DBP measurement ≥90 mmHg (P < 0.05; Table 3) [41]. DBP ≥90 mmHg was also associated with an increased likelihood of a partial response and greater decreases in tumour size. Based on these retrospective findings, a prospective randomised double-blind trial of axitinib to investigate the correlation between hypertension and efficacy has completed accrual, and preliminary results were presented recently; data suggest that a change in DBP ≥15 mmHg on day 15 of cycle 1 may be associated with a higher ORR compared with a change in DBP ≤15 mmHg (61% versus 53%, respectively) [42] (NCT00835978). Final data are awaited.

Similarly, retrospective analysis of a phase II trial in patients with RCC of any histology treated with tivozanib showed that development of hypertension at any time during treatment was associated with improved PFS and ORR, which reached statistical significance for PFS in patients with elevated SBP (Tables 2 and 3) [43].

The apparent effect of agents that target the VEGF pathway on hypertension may be influenced by a variety of factors. However, there are data to indicate that when consistently measured using a specific method and schedule, or by one investigator, hypertension on treatment appears to be predictive of clinical benefit regardless of the anti-VEGF agent (sunitinib, sorafenib, bevacizumab, axitinib or tivozanib) and line of treatment [44]. Of note, a recent prospective evaluation of BP measurements from the ongoing randomised double-blind trial of first-line axitinib [42] has reported similar BP values following home, clinic and 24-h ambulatory BP monitoring [45].

Understanding why hypertension may be a surrogate marker of clinical outcome is important. The recently reported prospective phase II trial of first-line axitinib indicated that increased drug exposure following dose titration was associated with elevated DBP (≥90 mmHg) and with increases in DBP ≥10 and ≥15 mmHg, as well as improved outcomes (PFS and OS) [42]. Furthermore, a positive relationship has previously been reported between DBP changes and exposure to sunitinib and its primary metabolite, SU12662 [14]. The use of anti-hypertensives to control BP does not appear to affect the better clinical outcome seen in patients who develop hypertension while on therapy [38]. In fact, one small study has found that patients who received angiotensin inhibitors had improved outcomes with sunitinib compared with patients who did not receive anti-hypertensive therapy [46]. Rini et al. examined the effect of taking anti-hypertensive agents at baseline. Patients receiving anti-hypertensives reported significantly improved OS and PFS compared with those not receiving anti-hypertensives at the start of the study; ORR was similar between the two groups. Furthermore, in a multivariable analysis, anti-hypertensive medication use at baseline remained statistically significantly associated with OS [38]. It has been suggested that some patients with normal blood vessel morphology may be particularly sensitive to VEGF blockade, resulting in hypertension [38]. These patients might also have tumour vessels that are particularly sensitive to VEGF blockade, leading to a stronger anti-angiogenic effect in response to sunitinib treatment.

It is important to ensure that the benefits of developing hypertension are not negated by the harmful effects of rises in BP. A study in animals suggests that sunitinib-induced increases in BP do not have deleterious effects on cardiac structure or function [47]. Rini et al. [38] added a large expanded-access trial including 4371 patients [23] to their retrospective review of sunitinib in first- or second-line advanced clear-cell RCC to evaluate any association between hypertension and hypertension-related complications. A mean SBP of ≥140
mmHg or a mean DBP ≥90 mmHg was associated with an increase in renal adverse events, although the incidence of such events was very low (hypertensive versus normotensive patients, any grade: 5% versus 3%; P = 0.013; grade 3 or higher: 3% versus 2%; P = 0.045) [38]. Few adverse events relating to the brain, eye or heart were reported in the study, and the incidence was similar between patients with and without hypertension [38]. Nevertheless, it is important to ensure that hypertension is properly managed in patients with mRCC to prevent further cardiovascular or renal complications.

**hypothyroidism**

Hypothyroidism (usually of mild or moderate severity) is a known side-effect of treatment with VEGFR TKIs, and has been reported in ~14% of patients treated with these agents in phase III clinical trials (Table 1). Reporting of hypothyroidism in clinical trials has increased since the condition was recognised as a side-effect of treatment and began to be routinely monitored [48, 49].

The direct mechanism by which the VEGFR TKIs cause hypothyroidism is not fully established; it may be associated with development of follicular cell apoptosis that induces a destructive thyroiditis [48] and endothelial dysfunction [50, 51], inhibition of iodine uptake [52, 53], or reduced synthesis of thyroid hormone [50]. Overt hypothyroidism is generally treated with thyroid hormone replacement therapy, primarily when side-effects such as fatigue occur, to allow normalisation of thyroid-stimulating hormone (TSH) levels and resolution of symptoms.

It has been postulated for some time that thyroid dysfunction may actually be beneficial in solid tumours, possibly because of the lack of thyroxine (T4) activity on cancer cell proliferation and angiogenesis. Wolter et al. [54] first showed a possible association between sunitinib outcomes and thyroid dysfunction in 40 patients with advanced RCC. Median PFS was 10.3 and 3.6 months in patients with thyroid dysfunction and normal thyroid function (P = 0.047), respectively; and median OS was 18.2 and 6.6 months in patients with thyroid dysfunction and normal thyroid function (P = 0.13).

More recently, in an exploratory trial in 87 patients with advanced RCC treated with sunitinib or sorafenib, there was a significant association between the development of subclinical hypothyroidism (i.e. elevated TSH levels but normal free T4 levels and often asymptomatic) and improved ORR and OS [55]. In the assessable patient population, ORR was 19.3% in patients with TSH >3.77 μM/ml compared with 3.3% in patients with TSH ≤3.77 μM/ml (P < 0.001). Median PFS was 17.0 months in patients with TSH >3.77 μM/ml at 1 month compared with 10.4 months in patients with TSH ≤3.77 μM/ml at 1 month (not statistically significant). However, a significant improvement was seen in OS, with median OS not reached in patients with TSH >3.77 μM/ml at 1 month compared with 14.1 months in patients with TSH ≤3.77 μM/ml at 1 month (HR 0.39; 95% CI 0.15–1.01; P = 0.044). Furthermore, multivariate analysis showed that the development of subclinical hypothyroidism within the first 2 months of treatment was an independent predictor of survival.

A number of other small studies [35, 56] have also indicated a possible association between the development of hypothyroidism and clinical outcome in RCC, which deserves further investigation.

Larger prospective studies, with routine monitoring of thyroid function, are needed to address the possible association between development of hypothyroidism and clinical outcome in RCC. In particular, the potential confounding effect on outcome of hormone supplementation in patients with subclinical hypothyroidism is an important consideration.

This is illustrated in a prospective study of 111 patients with mRCC treated with sunitinib that did not find any association between abnormal thyroid function and PFS [57]. Patients were evaluated for TSH and T4 levels every 6 weeks during therapy; 53% developed thyroid dysfunction and most (90%) received L-thyroxine replacement. At the 6-month landmark analysis, median PFS did not differ significantly between patients with and without thyroid dysfunction (18.9 versus 15.9 months, respectively; P = 0.94), independent of line of therapy or risk status. The authors noted that all hypothyroidisms (overt and subclinical) were treated with hormone replacement in this

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**Table 3.** Association between elevated diastolic BP and clinical outcomes with different targeted therapies in advanced RCC

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HTN</td>
<td>No HTN</td>
<td>HTN</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Retrospective analysis of three trials [20, 21, 37]</td>
<td>Clear-cell RCC; first- and second-line sunitinib (n = 544)</td>
<td>13.4</td>
<td>5.3</td>
<td>32.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Axitinib</td>
<td>Retrospective analysis of two trials [28, 29]</td>
<td>Sorafenib-/cytokine-refractory RCC (n = 109)</td>
<td>NA</td>
<td>NA</td>
<td>30.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P &lt; 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tivozanib</td>
<td>Retrospective analysis of phase II trial [5]</td>
<td>RCC (any histology) and no prior VEGF targeted therapy (n = 272)</td>
<td>NR</td>
<td>10.6</td>
<td>NA</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>P = 0.0556</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
study, and this may have contributed to a ‘canceling’ of a possible hypothyroidism-induced protective effect on survival.

hand-foot syndrome
In phase III clinical trials, all-grade hand-foot syndrome (HFS) was reported in up to 51% of patients (sorafenib), with grade 3 symptoms presenting in up to 9% (sunitinib; Table 1). The underlying pathogenesis of HFS associated with VEGFR-directed TKIs is not understood, but is possibly related to blockade of VEGFR and platelet-derived growth factor receptor effects on dermal endothelial cells, causing endothelial cell apoptosis. An association with c-KIT inhibition is also suggested due to a high density of c-KIT bearing eccrine glands at sites most affected by HFS [58]. TKIs may also exert a direct toxic effect when secreted into the eccrine glands in the skin [58–60].

A retrospective analysis of prospective clinical trials including 770 patients with advanced RCC treated with sunitinib found that patients who developed HFS had significantly better clinical outcomes (OS, PFS and ORR) than those who did not [61]. Median OS was 38.2 months in patients with HFS compared with 18.9 months in patients without HFS (P < 0.001). Similarly, median PFS was significantly prolonged in patients with HFS versus those without (14.3 versus 8.3 months, respectively; P < 0.001). ORR was also significantly improved in patients who experienced HFS (66.5%) compared with those who did not (31.8%; P < 0.001) [61].

In landmark analyses of HFS onset by the end of 6 or 12 weeks, sunitinib-associated HFS was a significant predictor of OS (P < 0.001) but not PFS in mRCC. After multivariate analysis, HFS remained a significant independent predictor of PFS (HR 0.75; 95% CI 0.60–0.94; P = 0.0148) and OS (HR 0.58; 95% CI 0.44–0.77; P = 0.0001) [39], thus the development of HFS identified a group of patients who had particularly favourable outcomes with this treatment.

While a relationship appears to exist between the development of HFS and clinical benefit from sunitinib, HFS as a clinical biomarker of response should be regarded with caution as it may be confounded by adequate prophylactic treatment.

fatigue
Fatigue is commonly reported in patients receiving targeted therapy. It may be related to the disease itself or other potential factors, such as co-medications, anaemia or hypothyroidism that may also cause or exacerbate fatigue. In a review of clinical trials, all-grade fatigue was reported in 19%–54% of patients with mRCC receiving targeted therapy in phase III studies [62].

In the retrospective analysis of clinical trials including 770 patients with advanced RCC treated with sunitinib discussed above, patients who developed fatigue or asthenia had statistically significantly better clinical outcomes (PFS and OS) than those who did not [39, 63]. After multivariate analysis, fatigue or asthenia remained significant independent predictors for all outcomes. However, time-dependent covariate analysis suggested that development of asthenia/fatigue may be related to longer drug exposure. It is important to note that this is the first reported link between drug-associated asthenia or fatigue and efficacy, and prospective validation of these results is required. Fatigue may also be the result of VEGFR TKI-associated hypogonadism [64]. As such, the association between gonadal status and clinical outcome may warrant study.

pneumonitis
Drug-related pneumonitis is a class effect of mTOR inhibitors, and is possibly a hypersensitivity response [65, 66]. It has been reported as a clinical adverse effect in 2%–29% of patients with mRCC treated with temsirolimus [67–69]. This range reflects the varying incidence as diagnosed by investigators in clinical trials according to symptoms (2%–5%) [67, 68] compared with that observed in retrospective radiographic analyses (29%) [69]. Similar findings have been reported with everolimus, where the incidence of pneumonitis ranges from 6% to 13% in clinical trials [9, 70], to 54% in a retrospective radiographic review [71]. Initial data suggest that the incidence of pneumonitis with mTOR inhibitors may also be higher in patients of Asian ethnicity than those of other ethnic origin [72].

Pneumonitis may be a marker of therapeutic benefit in patients treated with mTOR inhibitors. Review of clinical data from a series of 46 patients with advanced RCC treated with temsirolimus or everolimus at two US-based clinics found radiographic pneumonitis in 30% of patients [73]. Of the patients with pneumonitis, 86% achieved stable disease and 14% had progressive disease. Of those without pneumonitis, 44% had stable disease and 56% had progressive disease. A statistically significant difference in the mean change in tumour (long axis) size for target lesions by RECIST was also noted; −2.9% change in the pneumonitis group compared with +4.3% in the non-pneumonitis group (P = 0.002).

other potential biomarkers
A number of clinical trials with mTOR inhibitors have reported increases in serum cholesterol, triglyceride and glucose [74]. A retrospective analysis of a phase III study explored the value of their change in serum as predictors of temsirolimus efficacy. An increase in cholesterol, and not glucose or triglycerides, was associated with longer OS and PFS and predicted efficacy. A second, smaller, retrospective French review which included 75 patients, reported no significant relationship between cholesteroalaemia and efficacy outcomes (OR and TTP). In contrast, hyperglycaemia and hypertriglyceridaemia showed significant correlation [75].

discussion: implications for therapy
While several promising clinical biomarkers of a drug’s on treatment activity are now emerging, the optimal use of these biomarkers to facilitate treatment decisions remains to be established.

The use of adverse events as predictive on treatment biomarkers of a drug’s efficacy will have important implications for the future use of targeted therapies in mRCC. For example a specific adverse event may provide the clinician with an early insight into a patient’s likelihood of response to a targeted agent. BP elevation is an effect common to all VEGF signalling pathway inhibitors, and at present, hypertension is one of the
most promising and well-studied clinical biomarkers in mRCC as a marker of VEGF inhibition and improved clinical outcome. Given that hypertension in this context is relatively easy and cost-effective to monitor, occurs early in treatment and is manageable with standard anti-hypertensive medication (without affecting, or even improving, overall clinical outcome [46]), it has the potential to make a good biomarker of response. The retrospective data showing a correlation between the induction of hypertension by VEGF-targeted agents and improved clinical outcome require validation in prospective trials; preliminary results of the prospective phase II axitinib first-line study suggest that a change in DBP ≥15 mmHg (day 15, cycle 1) correlates with increased drug exposure and may be associated with an increased ORR; unblinding of the randomised placebo cohort will provide further insight [42]. BP may thus provide an indication of the level of exposure to a targeted agent, which in turn appears to be related to efficacy [14]. If the retrospective data are further validated (to date this targeted agent, which in turn appears to be related to efficacy [42]. BP may thus provide an indication of the level of exposure to a targeted agent, which in turn appears to be related to efficacy [14]. If the retrospective data are further validated (to date this relationship has been reported prospectively only with axitinib), BP could potentially act as a surrogate for drug exposure and thus be used by the clinician as a marker to guide dose adjustment for individual patients.

HFS and thyroid dysfunction also have the potential to be useful biomarkers; however, further investigation is required to determine the reliability of the association between the development of symptoms and clinical outcome, and the possible confounding effects of therapy management. Ease of measurement is an important consideration when considering potential biomarkers and raises questions about the viability of a marker such as pneumonitis, given the difference in rates reported in clinical trials (based on symptoms) and radiographic rates reported retrospectively.

In addition to the clinical biomarkers reviewed above, expression of some genes and the presence or absence of single nucleotide polymorphisms (SNPs) have been associated with a differential response to targeted agents, such as sunitinib and pazopanib in patients with mRCC. For example exploratory studies suggest that tSNPs in VEGFR3, CYP3A5*1, IL8, FGFR2, NR112 and ABCB1 may enable prediction of efficacy and tolerability [76–78]. While there are currently insufficient prospective data to support the use of any molecular biomarker in the clinic, once validated in appropriate trials, these molecular predictors are likely to play a key role in guiding personalised therapy options in combination with clinical biomarkers of response.

There is therefore an urgent need for prospective trials to validate the most promising biomarkers (both molecular and clinical) so that these surrogate markers of a drug’s activity can be used practically in the clinic. Part of this process will be the generation of guidelines to ensure that such biomarkers are useful in clinical practice; for example a biomarker that can be identified early in the course of treatment could help clinicians to quickly identify non-responding patients (so that therapy can be discontinued and thus prevent unnecessary toxic effect), or help to ensure that a specific adverse event (that may be indicative of future response) is appropriately managed to help keep the patient on treatment and reach the optimal therapeutic dose. Biomarkers of both efficacy and toxic effect should be considered, and their likely predictive value for response in each individual patient, when making decisions regarding dose escalation, dose reduction and discontinuation of treatment. It will be interesting to establish whether multiple clinical biomarkers are present in patients who are responding well to therapy: for example does a patient who develops hypertension on sunitinib have an increased likelihood of developing hypothyroidism and HFS, and are specific molecular biomarkers also present? Furthermore, much of the current evidence centres around sunitinib, and more evidence will need to be generated on other drugs used for mRCC in order to differentiate between agents on an individual patient basis.

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disclosure
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