DOI: 10.1093/jnci/djr511
Advance Access publication on January 10, 2012.

REVIEW

Targeted Therapies for Renal Cell Carcinoma: Review of Adverse Event Management Strategies

Tim Eisen, Cora N. Sternberg, Caroline Robert, Peter Mulders, Lynda Pyle, Stephan Zbinden, Hassan Izzedine, Bernard Escudier

Manuscript received June 7, 2011; revised November 4, 2011; accepted November 11, 2011.

Correspondence to: Tim Eisen, BSc, MB BChir, PhD, FRCP, Department of Oncology, Cambridge Cancer Trials Center, Box 193 (R4), Addenbrooke's Hospital, Cambridge CB2 0QQ, UK (e-mail: tim.eisen@medschl.cam.ac.uk).

With the advent of targeted agents for the treatment of renal cell carcinoma (RCC), overall survival has improved, and patients are being treated continuously for increasingly long periods of time. This has raised challenges in the management of adverse events (AEs) associated with the six targeted agents approved in RCC—sorafenib, sunitinib, pazopanib, bevacizumab (in combination with interferon alpha), temsirolimus, and everolimus. Suggestions for monitoring and managing AEs have been published, but there are few consensus recommendations. In addition, there is a risk that patients will be subjected to multiple unnecessary investigations. In this review, we aimed to identify the level of supporting evidence for suggested AE management strategies to provide practical guidance on essential monitoring and management that should be undertaken when using targeted agents. Five databases were systematically searched for relevant English language articles (including American Society of Clinical Oncology abstracts) published between January 2007 and March 2011; European Society of Medical Oncology congress abstracts were hand searched. Strategies for AE management were summarized and categorized according to the level of recommendation. A total of 107 articles were identified that describe a large number of different investigations for monitoring AEs and interventions for AE management. We identify and summarize clear recommendations for the management of dermatologic, gastrointestinal, thyroid, cardiovascular, and other AEs, based predominantly on expert opinion. However, because the evidence for the suggested management strategies is largely anecdotal, there is a need for further systematic investigation of management strategies for AEs related to targeted therapies for RCC.

J Natl Cancer Inst 2012;104:93–113

With the expanding use of targeted agents for the treatment of advanced or metastatic renal cell carcinoma (RCC), the prognosis for this condition is shifting toward that of a chronic treatable disease. The treatment of patients for increasingly long periods of time with these agents has raised new challenges related to the management of the associated adverse events (AEs). Six targeted agents for the treatment of advanced RCC are now approved and in clinical use: the tyrosine kinase inhibitors (TKIs) sunitinib and pazopanib, the multikinase inhibitor sorafenib (often also referred to as a TKI and grouped accordingly for the purpose of this review), the anti–vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab, and the mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus (1–6). These agents present a range of AEs for patients and their health-care providers to manage. A growing number of articles are being published offering advice on AE monitoring and management with no clear consensus recommendations. Clearly, the prevention, early detection, and optimal management of AEs are key to maintaining patients on each individual treatment for as long as possible. In addition, minimizing the impact of toxicities on patients' health should increase the likelihood that they will be able to tolerate additional lines of treatment. However, with so many suggested monitoring strategies, the risk is that patients will become subjected to a barrage of assessments that are not always necessary or beneficial.

The objectives of this review were to assess critically the literature on AE monitoring and management during treatment of advanced RCC with targeted agents, to identify where there are adequate supporting data, where supporting data are lacking, and where further study is needed, and to provide physicians with specific practical guidance on essential monitoring and management that should be undertaken when using targeted agents.

Methods

An English language search of literature published between January 2007 and March 2011 was carried out using therapy-related, disease-related, and AE-related search terms, including the names of approved targeted therapies for renal cancer, all commonly used terms for RCC and a wide variety of terms associated with toxicity such as cardiotoxicity, hepatotoxicity, skin reaction, and nephrotoxicity. Databases searched were PubMed/Medline, Embase, Biosis, Derwent Drug File, and Science Citation Index (search dates were January 2007 to March 2011). In particular, the Science Citation Index database covers abstracts from the American Society of Clinical Oncology (ASCO) annual meeting and genitourinary cancers symposia. ASCO abstracts from January 2010 to March 2011 were hand searched, as were European Society of Medical Oncology congress abstracts. Original articles describing

monitoring and management strategies were included. Additional information was taken from the European summary of product characteristics for each of the agents under consideration. Monitoring and management strategies for groups of AEs were reviewed by at least two co-authors, and any specific recommendations were approved by all co-authors. A total of 107 articles were identified that describe a large number of different investigations for monitoring AEs and interventions for AE management.

Overview of AE Profiles of Targeted Agents

The European summaries of product characteristics (1–6) list commonly reported AEs for six currently licensed targeted agents (sorafenib, sunitinib, pazopanib, bevacizumab + interferon alpha [IFN-α], temsirolimus, and everolimus) (Table 1) as well as potentially serious or life-threatening AEs (Table 2). It should be acknowledged that safety data reported by the European summaries of product characteristics tend to focus on registration trials. Thus, some AEs reported in other data sources may not be included, but focusing on the European summary of product characteristics ensured a consistent, balanced approach. Many of the most common AEs are seen during treatment with all the targeted agents (although they may vary in severity from one agent to another), whereas others are more specific to one class of agent or to individual agents. The risk of hypothyroidism, for example, is high for sunitinib but also associated with the use of other drugs.

Tyrosine Kinase Inhibitors

In general, the TKIs (sorafenib, sunitinib, pazopanib) are most commonly associated with dermatologic and gastrointestinal AEs (Table 1) (1–3). These events are generally of mild to moderate severity and can be relatively easily managed, although the cumulative impact on the patient of multiple, concurrent mild-to-moderate AEs should not be underestimated. There is currently a large body of experience in dealing with the more frequent AEs of sorafenib and sunitinib such as hand–foot skin reaction (HFSR) and rash, for which prevention and management strategies have been established (7). We will examine the utility of these strategies in more detail in this review. Importantly, a follow up to the phase III TARGET trial has demonstrated that no new toxic effects were observed during long-term treatment over approximately 3 years with sorafenib (8). Indeed, most AEs occurred with early cycles of therapy and generally decreased in frequency with each subsequent cycle. For sunitinib, treatment for 6 months or more in an expanded access program was associated with a higher cumulative incidence of any grade and grade 3–4 AEs compared with treatment for less than 6 months, but there was no accumulation of serious toxic effects, no increase in grade 3–4 cardiotoxicity, and no new or unexpected toxic effects with long-term therapy (9,10). Updated safety data from the pazopanib phase III registration study (11) showed no significant changes over time in the type,

Table 1. Most common adverse events reported in European summaries of product characteristics*

Adverse events	Sorafenib	Sunitinib	Pazopanib	Bevacizumab + IFN-α	Temsirolimus	Everolimus
Gastrointestinal disorders						
Constipation	+	++	−	++	++	−
Diarrhea	++	++	++	++	++	++
Dyspepsia	−†	++	+	−	−	+
Dry mouth	−†	++	−	−	−	+
Flatulence	−	++	+	−	−	−
Glossodynia	−	++	−	−	−	−
Nausea	++	++	++	++	++	++
Oral pain	−	++	−	−	+	−
Stomatitis	−†	++	+	++	++	++
Vomiting	++	++	++	++	++	++
Skin and subcutaneous events						
Acne	−†	+	−	−	++	+
Alopecia	++	++	+	−	−	−
Dry skin	++	++	+	++	−	++
Erythema	++	+	+	−	−	+
Hair color changes	−	++	++	−	−	−
HFSR	++	++	+	+	−	+
Nail disorder	−	+	−	−	++	+
Pruritus	++	+	+	−	++	++
Rash	++	++	+	−	++	++
Skin discoloration	−	++	+‡	++	−	−
Infections and infestations						
Bacterial and viral infections	−	−	−	+	++	++
Respiratory, thoracic, and mediastinal disorders						
Cough	−	+	−	−	++	++
Dyspnea	−	+	−	+	++	++
Epistaxis	−	++	+	+	++	++
Pneumonitis	−	−	−	−	+	++

(Table continues)

Table 1 (Continued).

Adverse events	Sorafenib	Sunitinib	Pazopanib	Bevacizumab + IFN-α	Temsirolimus	Everolimus
Cardiac and vascular disorders						
Ejection fraction decreased	−	++	−	−	−	−
Hemorrhage (including GI, rectal)	−§	−	−	+	+	+/−‖
Hypertension	++	++	++	++	+	+
Others						
Allergic/hypersensitivity reactions	−	−	−	−	+	++
Asthenia/Fatigue	++	++	++¶	++	++	++
Dysgeusia	−	++	++#	++	++	++
Headache	++	++	+	++	−	+
Hypothyroidism	−	++	+	−	−	−
Insomnia	−	+	−	−	++	+
Mucosal inflammation	−	++	+	++	++	++
Edema	−	++	+	−	++	++
Proteinurea	−	−	+	−	−	++
Metabolism and nutrition						
Anorexia	+	++**	++††	++	++	++
Hypokalemia	−	−	−	+	++	++
Hyperglycemia/diabetes mellitus	−	−	−	+	++	++
Hypercholesterolemia	−	−	−	−	++	++
Hyperlipidemia	−	−	−	−	++	++
Blood and lymphatic system						
Neutropenia	−†	++	+	++	+	++
Thrombocytopenia	−	++	+	++	++	++
Anemia	−†	++	−	+	++	++
Leucopenia	−†	+	+	++	+	−
Lymphopenia	−§	+	−	−	+	++
Laboratory abnormalities						
Blood creatinine increased	−	+	+	−	++	++
Increased aspartate aminotransferase	−†	+	++	−	++	++
Increased alanine aminotransferase	−†	+	++	−	+	++
Bilirubin increased	−	−‡‡	+‡‡,§§	−	−	++

* Events reported in ≥10% of patients with RCC treated with any agent (or in patients with different tumor types for bevacizumab). GI = gastointestinal; HFSR = hand–foot skin reaction; IFN-α = interferon alpha; ++ = reported at a frequency of ≥10%; + = reported at a frequency of ≥1 to <10%; − = not reported or reported at a frequency of <1%.

† Reported at a frequency of ≥1 to <10% in studies in multiple tumor types.

‡ Hypopigmentation and depigmentation are listed separately—both reported at a frequency of ≥1 to <10%.

§ Reported at a frequency of ≥10% in studies in multiple tumor types.

‖ Incidence listed as "not known."

¶ Fatigue reported at a frequency of >10%; asthenia reported at a frequency of ≥1 to <10%.

Dysgeusia, ageusia, and hypogeusia.

** Anorexia and decreased appetite.

†† Decreased appetite.

‡‡ The US Food and Drug Administration has added a black box warning for hepatotoxicity in the US labels for sunitinib and pazopanib.

§§ Hyperbilirubinemia.

frequency, or severity of AEs; median duration of exposure was 7.4 months (11).

The range of frequently observed but not necessarily serious or life-threatening AEs with the newly licensed TKI pazopanib appears to be lower compared with sorafenib and sunitinib (Table 1) (12). However, experience with this agent is clearly less extensive, and it is possible that different AEs or increased frequency of known AEs may emerge with time. For example, with sunitinib, the incidence of hypothyroidism was initially reported at 14% (grades 3–4, 2%) in a phase III clinical trial (3); however, an analysis of retrospective and prospective studies suggested that the incidence may be greater than 50% (13). It is also important to note that a lower frequency of common AEs does not necessarily translate into a lower risk of serious or life-threatening AEs (Table 2).

Hypertension is a frequent AE associated with all the TKIs and one that can have serious consequences if not properly managed (14–16). The optimal monitoring and management of hypertension is key to successful treatment with these agents and is currently an area of intense debate (14–16). Cardiovascular events such as decline in left ventricular ejection fraction (LVEF), heart failure, and QT interval (the time from start of the Q wave to the end of the T wave of the cardiac electrical cycle) prolongation have also been reported in patients receiving TKIs, although the degree of severity differs among agents (Table 1) (2,3).

In terms of life-threatening AEs (Table 2), serious hemorrhage is identified as a risk with all three licensed TKIs, and fatal events have been recorded during the post-marketing phase for sunitinib and during clinical studies with pazopanib (2,3). In addition, a new

Table 2. Potentially serious or life-threatening adverse events reported in European summaries of product characteristics*

Adverse events	Sorafenib	Sunitinib	Pazopanib	Bevacizumab + IFN-α	Temsirolimus	Everolimus
Hematological events	–	U†	–	+	–	–
Infections	–	–	–	–	–	++†
Pneumonitis	–	–	–	–	+†	++†
Inflammation of the lungs	–	–	–	–	+	–
Pleural effusion	–	–	–	–	+	–
Pericardial effusion	–	–	–	–	U	–
Hepatotoxicity	–	–	+†	–	–	–
Hepatobiliary events	–	U†	–	–	–	–
Pancreatic events	–	U†	–	–	–	–
Renal failure	–	–	–	–	+†	–
GI perforation	U	U†	U†	+	U	–
Hemorrhage	++	++	U†	+	–	–
Intracerebral bleeding	–	–	U	–	U†	–
Problems with wound healing	–	–	–	++	+	U
VTE events	–	U†	–	–	+†	–
ATE events	–	–	U†	+	–	–
Cardiac ischemia/infarction	U†	–	U	–	–	–
CV events	–	U†	U	+	–	–
Hypertensive crisis	U	–	–	–	–	–
Hypertensive encephalopathy	–	–	–	U†	–	–
Reversible posterior leukoencephalopathy	U	–	–	U	–	–

* Events included under special warnings and precautions or associated with fatal outcomes in the European summary of product characteristics. ATE = arterial thromboembolism; CV = cardiovascular; GI = gastrointestinal; IFN-α = interferon alpha; LVEF = left ventricular ejection fraction; VTE = venous thromboembolism; ++ = reported at a frequency of ≥10%; + = reported at a frequency of ≥1 to <10%; – = not included under special warnings and precautions or associated with fatal outcomes; U = uncommon, reported at a frequency of <1%.

† Fatal outcomes have been reported.

concern—liver toxicity—has emerged (11). For pazopanib, increases in serum alanine transaminase (ALT) occurred in 14% of patients and hyperbilirubinemia occurred in 3% of patients; fatal hepatotoxicity has also been recorded (2). The US Food and Drug Administration (FDA) approved pazopanib with a black box warning (a boxed warning regarding the risk of a serious AE that may be added to the package insert of a prescription drug) for hepatotoxicity (17). The FDA has also added a black box warning for hepatotoxicity in the US label for sunitinib (18). With sorafenib, transient increases in transaminases and bilirubin were also seen in pivotal studies. In post-marketing experience, isolated reports have been received consistent with drug-induced hepatitis (a potentially life-threatening or fatal condition).

Anti-VEGF Monoclonal Antibody

Although the TKIs and multikinase inhibitors have activity at the VEGF receptor, the humanized monoclonal antibody bevacizumab is the only currently available agent that directly targets only VEGF. Because bevacizumab is licensed for the treatment of a number of different tumors, its safety profile is very well described (5). In the treatment of RCC, it is used in combination with IFN-α, adding an additional range of AEs to its toxicity profile. As with the TKIs, bevacizumab + IFN-α treatment is commonly associated with gastrointestinal disorders and general AEs such as fatigue and headache. Proteinuria appears to be a more "class-specific" AE of bevacizumab + IFN-α treatment, occurring at an overall incidence of between 0.7% and 38% across clinical trials (5). Some of the most important AEs of bevacizumab + IFN-α therapy are gastrointestinal perforation, hemorrhage, and cardiovascular events (5). Although these AEs are less common than constipation and diarrhea, for example, they can be potentially life threatening and should therefore be monitored and managed promptly.

mTOR Inhibitors

Everolimus is one of the newer targeted therapies approved for the treatment of advanced RCC (6). As a consequence, clinical experience with this agent is more limited, and its AE profile is less well established compared with sorafenib, sunitinib, and bevacizumab. However, data from the everolimus expanded access program are now becoming available (19). Although temsirolimus is a more well-established mTOR inhibitor, there are relatively few real-life clinical data on the tolerability of this agent (20).

Because of their immunosuppressive properties, the mTOR inhibitors temsirolimus and everolimus are associated with treatment-related infections. In addition to general bacterial and viral infections, the European summary of product characteristics for temsirolimus specifically lists temsirolimus-related pharyngitis, rhinitis, urinary tract infections, folliculitis, upper respiratory tract infections, and pneumonia (4). In everolimus-treated patients, there have also been reports of aspergillosis, candidiasis, and reactivation of hepatitis B (6). Noninfectious pneumonitis is a class effect of the mTOR inhibitors. The incidence of pneumonitis in patients treated with everolimus or temsirolimus may be higher than originally reported in phase II and phase III studies (21–23). Retrospective examinations of computed tomography scans collected during clinical studies suggest that more than one-quarter of RCC patients treated with mTOR inhibitors have evidence of pneumonitis (24,25).

The mTOR inhibitors are also the targeted agents most commonly associated with disorders of metabolism and nutrition. Awareness of these AEs is important because the insidious nature

of disorders such as hypercholesterolemia and hyperglycemia means that symptoms are generally lacking until the condition becomes so severe that organ damage occurs. mTOR inhibitors also cause fatigue, asthenia, rash, and anemia (26). Because these AEs are common among targeted agents, management and coping strategies applicable to one agent should be applicable to another.

Review of Management Strategies

Most articles reporting AE management strategies in RCC were specific to sorafenib and sunitinib, and there were substantially fewer articles related to pazopanib, bevacizumab, temsirolimus, and everolimus in this indication. This is to be expected, given that sorafenib and sunitinib have been licensed for considerably longer than the other targeted therapies, thereby allowing time for their AE profiles and subsequent management strategies to become established. The specific management strategies identified are discussed in the following sections.

Skin and Subcutaneous Adverse Events

A wide range of dermatologic AEs occur with targeted anticancer therapies with the frequency of these events varying according to the individual targeted agent (overview in Table 1). Rash and HFSR are generally held to be the most troublesome side effects with sorafenib. However, these side effects are also seen with other agents in this class (2,3). Data from the pivotal trial of sorafenib in RCC show rash (all grades) occurring in 28% of patients (grade 3–4 in <1%) (1). HFSR occurred in 19% of patients treated with sorafenib and was grade 3–4 in 4%. HFSR is also frequently seen in RCC patients treated with sunitinib; the European summary of product characteristics gives frequencies of 26% for HFSR (listed as palmar–plantar erythrodysesthesia) of any grade and 8% for grade 3–4 events (3). The frequency of rash with sunitinib (any grade, 15%; grade 3–4, <1%) is comparable with that seen during treatment with sorafenib (1,3). With pazopanib, HFSR is relatively infrequent (any grade, 7%; grade 3–4, 1%), as is rash (any grade, 9%; grade 3–4, <1%) (2). HFSR is not listed among the undesirable effects seen with temsirolimus, although rash and pruritus are the most common dermatologic AEs associated with this agent (4). In the pivotal phase III trial of temsirolimus, rash (any grade) occurred in 42% of patients and was of grade 3–4 severity in 5%, whereas pruritus (any grade) occurred in 40% of patients and was of grade 3–4 severity in 1% (4). Pruritus is less common with sorafenib (all grades, 17%; grade 3–4, 1%), sunitinib (all grades, 7.4%; grade 3–4, 0.2%), and pazopanib (all grades, 2%) than with temsirolimus.

The severity of HFSR can range from minimal skin changes (grade 1) to painful ulcerative dermatitis (grade 3), and although HFSR is not life threatening, it often results in dose reduction as symptoms progress to a degree where they have a detrimental effect on day-to-day activities (1,7,27). The published guidance identified in the literature search for HFSR can be split into preventative measures and management strategies (Table 3). Initial prophylaxis includes removal of any existing hyperkeratotic areas and calluses evident on a pretreatment examination of the palms and soles of the feet (71). Such areas can be protected by cushioning and treated with moisturizing creams and keratolytic agents such as urea-containing and salicylic acid–containing creams or ointments. As an *aide-mémoire*, this is sometimes referred to as the "3C" approach: Control calluses, Comfort with cushions, Cover with creams (72). During treatment, care should be taken to reduce exposure of the hands and feet to hot water and to avoid constrictive footwear, friction, and trauma arising from vigorous exercise. Shoes with padded insoles (and possibly also gloves) can be worn. There may be benefit in sparingly applying moisturizing cream to the hands and feet (28–31). In addition, it is recommended that patients are educated about the visible signs of HFSR to aid in the early detection of symptoms (28,30). Management strategies for HFSR include topical treatments for grade 1 symptoms such as appropriate use of corticosteroids (29,31). Higher grades of severity may require dose reduction or interruption of the targeted anticancer treatment and in severe or persistent cases, discontinuation of treatment (28,29). Nonetheless, to clearly define the degree of benefit that can be obtained by using the above HFSR prevention and management strategies, there is a need for dedicated studies with clear and objective endpoints.

The management strategies that were identified for anticancer therapy–related rash include topical therapies for symptomatic relief, such as intensified skin care and moisturization, as well as application of urea-containing lotion (1,38). However, the long-term use of topical steroids (eg, betamethasone) is to be avoided because it increases the risk of topical infection (33,34). A key management issue is to differentiate between nonserious rash (usually moderate in intensity, erythematous/squamous, and possibly diffuse) and serious hypersensitivity rash that can necessitate discontinuation of the targeted anticancer drug. The signs that suggest the possibility of a serious AE, such as a Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome or a Stevens–Johnson syndrome, include mucosal involvement, bullous lesions, and the association with clinical or biological symptoms such as elevated temperature, hepatitis, and hypereosinophilia.

An uncommon skin adverse effect (incidence 0.1 to <1%) that has been reported with the use of sorafenib, and not with the other drugs considered here, is the emergence of actinic keratoses, keratoacanthomas, and squamous cell carcinoma, which are benign, borderline, and malignant cutaneous neoplasias, respectively (1,40,41). This effect is probably linked to the paradoxical activation of the MAPK pathway in keratinocytes by drugs targeting Raf proteins because it is also observed, but with a higher frequency, in patients treated with more recent and specific v-raf murine sarcoma viral oncogene homolog B1 (B-Raf) inhibitors (73). Further research is required to understand fully the mechanism for cutaneous neoplasia during anticancer therapy. Early recognition of these conditions is critical, and patients should be queried about the development of any new skin lesions (41). Management of these AEs in RCC depends on the clinical situation; however, it is recommended that squamous cell carcinomas and keratoacanthomas should be surgically removed if possible (40).

Diarrhea

Anticancer treatment–related diarrhea is not only an inconvenient AE but can also be life threatening if not sufficiently managed. The severity of diarrhea can vary considerably (ranging from mild symptoms to fecal incontinence) and have a dramatic negative

Table 3. Recommendations for the monitoring and management of specific AEs*

Widely accepted measures (level of evidence†)	Unproven recommendations with some merit, based on author/expert opinion‡	Points for further research
Skin and subcutaneous		
Hand–foot skin reaction (HFSR)		
Prevention	Patient education including visuals/videos to help with early identification of grade 2 HFSR (level 4) (28,30)	Future studies with clear objective endpoints are needed to define the degree of benefit that can be obtained by using the described HFSR prevention and management strategies
A pedicure before treatment may be effective to prevent the development of HFSR in patients with plantar hyperkeratosis (level 4) (28–30).	Sorafenib: Oral vitamin B6 preparations may help prevent symptoms (level 4) (31)	Specific examples include: Use of prophylactic pedicure; value of different levels of patient education
Instruct patients to protect hands and feet		
Reduce exposure of hands and feet to hot water (level 4) (29)		
Avoid constrictive clothing (level 4) (29)		
Avoid excessive rubbing (level 4) (29)		
Patients should wear open shoes with padded soles during treatment (level 4) (29)		
Avoid vigorous exercise or activities that place undue stress on the hands and feet/no excessive sport (level 4) (29,31)		
Instruct patients on use of emollients		
Sparingly apply an alcohol-free moisturizer immediately after bathing if the skin becomes dry (level 4) (29)		
Moisturizing cream can be applied sparingly on the hands and feet (level 4) (29)		
Moisturizing cream can be worn at night under cotton gloves and socks (level 4) (29)		
Management–sorafenib		
Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption, and/or dose modification; in severe or persistent cases, permanent treatment discontinuation may be required (level 4) (1)		
Cooling foot or hand baths and shoe inlays may be used for relief of symptoms (level 4) (31)		
Sorafenib (grade 1 HFSR)		
Urea- or salicylic acid–containing exfoliants may be used on hyperkeratotic areas and topical steroids on inflammatory areas (level 4) (29,31)		
Sorafenib (grade 2 HFSR)		
A decrease of sorafenib dose to 400 mg daily for a minimum of 7 d (up to 28 d) should be considered (level 4) (29)		
If toxicity does not resolve to grade 0 or 1 following dose reduction, treatment should be interrupted for a minimum of 7 d and until toxicity has resolved to grade 0 or 1 (level 4) (29)		
When resuming treatment after dose interruption, the dose should be reduced to 400 mg daily (level 4) (29)		
If toxicity is maintained at grade 0 or 1 for a minimum of 7 d, the dose can be increased back to full dose (level 4) (29)		
Sorafenib (grade 3 HFSR)		
Minimum of 7 d treatment interruption, combined with symptomatic treatment, until symptoms return to grade 0 or 1 (level 4) (29)		
When treatment is resumed, the dose should be reduced by one dose level (ie, 400 mg daily) (level 4) (29)		
If symptoms remain at grade 0 or 1 for a minimum of 7 d, the treatment can be increased by one dose level (level 4) (29)		

(Table continues)

Table 3 (Continued).

Widely accepted measures (level of evidence†)	Unproven recommendations with some merit, based on author/expert opinion‡	Points for further research
On the third occurrence of grade 3 symptoms, sorafenib should be discontinued (level 4) (29)		
Management–sunitinib		
Sunitinib (grade 1 HFSR)	Sunitinib: In cases where an additional cause of foot problems exists, for example, diabetes, patients need to pay especially careful attention to symptoms (level 4) (32)	
Thick soled shoes, local corticoid, vitamin A, and urea creams may provide symptomatic relief (28,30) (level 4)		
Sunitinib (grade 2 HFSR)		
If reaction occurs early (eg, week 1), treatment can be discontinued until symptoms return to grade 0 or 1; treatment should be restarted at a reduced dose of 37.5 mg/d (level 4) (28)		
If reaction occurs late (eg, week 4), treatment should be discontinued and the next cycle dose discussed with patient; treatment may be restarted at a dose of 50 mg/d or at a reduced dose of 37.5 mg/d (level 4) (28)		
Taking sunitinib in the evening may help to reduce the severity of hand–foot syndrome because the maximum plasma concentration is then reached during the night when patients are less likely to be active (level 4) (28)		
Sunitinib (grade 2/3 HFSR)		
Wearing a hydrocolloidal bandage may be helpful (level 4) (30)		
Rash (and other dermatologic events)		
Management–sorafenib		
Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption, and/or dose modification of sorafenib, or in severe or persistent cases, permanent discontinuation of sorafenib (level 4) (1)	Aloe vera–containing gels may be effective (level 4) (34)	Future studies will need to investigate if there is an increase in severity of skin toxicities when TKIs are combined with other cancer treatments compared with TKI monotherapy
Topical emollients and topical imidazole derivatives may be used (level 4) (29)		Future studies will need to assess the tolerability profile of newer targeted agents in combination with other cancer therapies
Body lotions containing exfoliative alpha hydroxyl acid components may be used, and sun exposure should be avoided after treatment (level 4) (33)		Further studies are needed to corroborate a recent subgroup analysis that showed no association between treatment outcome with sorafenib and facial skin eruption (level 3) (39)
Avoid the long-term use of topical steroids (eg, betamethasone) because they increase the risk of topical infection (level 4) (33,34)		
Topical corticosteroids should be used judiciously (level 4) (35,36)		
Symptomatic relief can be achieved with topical emollients, topical imidazole derivatives, or topical steroids (level 4) (29,35,36)		
No intervention is required for grade 1 erythema and flushing (level 4) (33)		
Seborrhoeic dermatitis-like rash on the face and scalp can be treated with antifungals (eg, ketoconazole 2% cream/ciclopirox 1% cream) (level 4) (29)		
Antihistamines may be used (level 4) (37)		

(Table continues)

Table 3 (Continued).

Widely accepted measures (level of evidence†)	Unproven recommendations with some merit, based on author/expert opinion‡	Points for further research
Patients with unusual lesions anywhere on the body should be examined by a dermatology consultant to rule out malignancy (level 4) (37) In cases of skin erosion, the dose may need to be reduced or treatment stopped (level 4) (34,37)		
Management–sorafenib/sunitinib Intensified skin care and application of moisturizing lotion are useful supportive measures (level 4) (38) Treatment of rash with topical application of urea-containing lotion (5% urea ointment, methylprednisolone) or short*pulse oral corticosteroid therapy in refractory patient (level 4) (38) Gentle soaps, body washes, antidandruff shampoos, and corticosteroid shampoos may be used (fluocinonide 0.05%) (level 4) (33,36)		
Other skin AEs Prevention Early recognition of actinic keratoses and keratoacanthomas is crucial; patients receiving sorafenib should be queried about the development of any new skin lesions (level 3) (40,41) Patients treated with sorafenib require periodic dermatologic evaluations (level 3) (41) Patients treated with sorafenib need to avoid excessive sun exposure (level 3) (41).		
Management in RCC When the surgical removal of squamous cell carcinoma or keratoacanthomas is required, sorafenib treatment can be interrupted; however, if patients have metastatic RCC and appear to benefit from sorafenib, treatment should not be interrupted and surgical removal of the skin lesion undertaken where possible (level 4) (42,43)		
Management in other conditions (ovarian cancer) If limited options exist for the underlying disease (ovarian cancer), continue sorafenib treatment and use surgical procedures or bexarotene for squamous cell carcinoma (level 4) (44)		
Diarrhea Diet Avoid foods that would aggravate the diarrhea (level 4) (15,38) Favor food that can slow GI motility, for example, bananas, rice, apples, toast (level 4) (27,33) Avoid high-fiber food, stool softeners, and fiber supplements (level 4) (15,28,31)	TKIs: Consult with a dietician before starting therapy (level 4) (28,30) Consider the use of bulking agents (Benefiber or Metamucil [psyllium] to reduce frequency of bowel movement (level 4) (27,28,30)	More research is needed on the effects of diet and if the timing of a targeted therapy has any influence on the frequency/severity of diarrhea
Dehydration management General: Aggressive oral rehydration with fluids containing water, salt, and sugar (level 4) (15,30,31,45)		
Pharmacological management Loperamide/diphenoxylate, standard dose (4 mg), followed by 2 mg/4 h or after every loose stool. More aggressive regimen: 4 mg, then 2 mg/2 h (level 4) (15,30,33,38) Tincture of opium (one teaspoon in water every 3–4 h), morphine, or codeine (level 4) (45)	Sunitinib: Loperamide 30 min before eating (level 4) (27,28) Sorafenib: Loperamide 30 min before treatment (level 4) (33)	

(Table continues)

Table 3 (Continued).

Widely accepted measures (level of evidence†)	Unproven recommendations with some merit, based on author/expert opinion‡	Points for further research
Budesonide can be used to treat low- to medium-grade inflammatory bowel disease (level 4) (45)	For severe/persistent diarrhea, consider somatostatin analogs (e.g. octreotide), starting dose 100–150 μg, subcutaneous intravenous delivery three times per day (sc/iv twice a day), titrated up to 500 μg twice a day or continual iv infusion of (20–50 μg/h) (level 4) (45)	
Dose adjustments For grade 3–4 diarrhea, interrupt treatment and/or reduced dose until symptoms subside to grade 1 (level 4) (31,33)		
Oral or upper GI complications		
General management Everolimus: Use mouthwashes (without alcohol or peroxide) and topical treatments. Do not use antifungal agents unless fungal infection has been diagnosed (level 3) (6,46) General: In severe cases endoscopy may be considered (level 4) (38) Dietary management Foods that do not require significant chewing (level 4) (15) Avoid spicy/salty/acidic food and spirits; sweets are often well tolerated (level 4) (28,30,31,38)	TKIs: Switch to a pediatric toothpaste (level 4) (28,30)	Clinical studies comparing the various treatment options should be undertaken
Pharmacological management Dexpanthenol sugar-coated tablets, dexpanthenol cream, agents to protect the mucus membrane (Orabase, Gelcair, magic mouthwash), topical steroids, narcotic analgesics for pain relief (eg, lidocaine solutions, combinations of topical lidocaine may be helpful) (level 4) (15,31,38,47) Mouth rinses (eg, sage tea, sodium chloride/baking soda solutions, with/without acetaminophen [paracetamol], and morphine or codeine sulfate) as prophylactics (level 4) (15,28,30,31) For fungal infection, use oral fluconazole (Diflucan) 200 mg twice a day for 7–14 d, local clotrimazole (Canesten topical): prophylaxis 10 mg troche dissolved 3–5 times daily for 14 d, amphotericin B or pantoprazole. Ketoconazole is contraindicated because it may increase kinase inhibitor concentrations (level 4) (15,38) Regular use of antacids (level 4) (34,38) Mucositis may result in epistaxis, and intensified care (nose ointment with fatty/oily ingredients) should be applied to the nasal mucosa (level 4) (38) Sorafenib/sunitinib: Do not take proton pump inhibitors within 2 h of receiving treatment (interferes with drug absorption/metabolism) (level 4) (27)	General: Proton-pump inhibitors can be used to treat stomatitis/esophagitis (level 4) (34,38)	
Dose reductions and interruptions Early intervention can help to avoid dose reductions (level 4) (27,31,47) Treatment interruption/dose reductions prevent recurrent severe mucositis. Grade 3 mucositis may resolve after 1 wk off of treatment (level 4) (31,38,47) Sunitinib: If patients develop ulcers, delay treatment by 2–3 d (level 4) (28)		
Anorexia/weight loss		
General management Supplementation with parenteral or enteral feeding has limited efficacy (Ensure, Boost) (level 4) (15)		
Pharmacological management		

(Table continues)

Table 3 (Continued).

Widely accepted measures (level of evidence†)	Unproven recommendations with some merit, based on author/expert opinion‡	Points for further research
General: Progestins (megestrol acetate, 160–800 mg every day; medroxyprogesterone acetate) improve appetite and reduce or reverse cancer cachexia (level 4) (15,48,49) Corticosteroids (dexamethasone 4 mg every day) or megestrol acetate (level 4) (15,49)		
Fatigue and anemia		
Fatigue-related monitoring General: Monitor for other causes of fatigue such as anemia, hypothyroidism, cardiomyopathy, dehydration (level 4) (15,28,31,38)	Sunitinib: At the end of cycle 2, check on the level of fatigue and its potential impact on QoL. If QoL is compromised, reduce the dose of treatment if other strategies fail (level 4) (28)	More patient preference and QoL studies are needed into the merits of the various management strategies
Non-pharmacological management AE education and counseling about coping strategies can motivate patients to remain on therapy (level 4) (28,30,50) Encourage patients to conserve energy, to reschedule activities to periods of peak energy and to stay active to promote sleep (level 4) (27,28,30,31,38,50) Contributing factors can be managed by stress management, relaxation techniques, and nutritional support (level 4) (47,50)		
Pharmacological management Treat patients for anemia (level 4) (50) Dose adjustments Grade 3 or 4 fatigue requires treatment interruption or adjustment (level 4) (15)	Consider tricyclic antidepressants, selective serotonin reuptake inhibitors (eg, paroxetine [20 mg every day], venlafaxine [37.5 mg twice a day], methylphenidate, or sleep medication (level 4) (15) Sunitinib: In macrocytic anemia, treat with B12 if there is a B12 or folate deficiency (level 4) (51)	
Hypothyroidism		
Sunitinib Before starting sunitinib measure thyroid function and treat any existing hypothyroidism (level 3) (3,13) All patients should be observed closely for signs and symptoms of thyroid dysfunction on sunitinib treatment. Patients with signs and/or symptoms suggestive of thyroid dysfunction should have laboratory monitoring of thyroid function performed (level 2) (3)	Use preventative measures such as vitamin B12 and iron supplements (level 4) Measure TSH on day 1 of every cycle (level 4) (13) In the case of "overt" or "subclinical" hypothyroidism (with increase thyroid peroxidase or thyroglobin Ab, hypercholesterolemia, thyroid nodules, or thyroid complaints) treat with levothyroxine therapy and measure TSH on day 1 of every cycle (level 4) (13) If TSH reaches 0.5–2.5 mIU/L with improvement of symptoms continue TKI and levothyroxine with TSH monitoring on day 1 of every cycle If TSH reaches 0.5–2.5 mIU/L without improvement of symptoms continue levothyroxine and consider other causes and TKI reduction or withdrawal	Prospective evaluation of safety, efficacy, dosing, and timing of replacement therapy Is early detection beneficial and should patients with subclinical hypothyroidism be considered for hormone replacement therapy?
Hyperglycemia		
For patients treated with mTOR inhibitors (4,6)		

(Table continues)

Table 3 (Continued).

Widely accepted measures (level of evidence†)	Unproven recommendations with some merit, based on author/expert opinion‡	Points for further research
Optimize glycemic control in diabetic patients before initiating treatment (level 2) (4,6) Advise patients to report excessive thirst or increase in volume of frequency of urination (level 2) (4) Monitor fasting serum glucose before initiating treatment and periodically thereafter (level 3) (4,6) Adapt doses of or initiate insulin and/or hypoglycemic agent therapy (level 2) (4,6)		
Gastrointestinal perforation (GIP)		
Monitoring		
Monitor patients for early signs of GIP, such as fever, abdominal pain, constipation, and vomiting (level 2) (4,52,53)	Identify patients at high risk of GIP before treatment: evidence of past diverticulitis or ulcers, radiation exposure, recent sigmoidoscopy or colonoscopy, resection of the primary tumor, gastrointestinal obstruction, and multiple previous surgeries (level 4)	Identification of specific risk factors Identification of better specific diagnostic markers
Management of GIP		
Discontinue treatment (level 1) (1,5). Prompt surgical assessment (level 3) (52)	Nonoperative treatment may be viable, for example, immediate bowel rest, intravenous fluid resuscitation, intravenous broad-spectrum antibiotics, and/or percutaneous intra-abdominal catheter (level 2/3) (54) Bevacizumab: A case of successful treatment of colonic perforation with endoscopic stenting has been reported (level 4) (55)	Assessment of possibility of retreating patients who recover from GIP (52)
Hypertension		
BP monitoring		
Bevacizumab: monitor BP before, and following, each infusion (more frequently if BP is elevated) (level 4) (5); TKIs: monitor BP at least weekly, during the first 12 weeks of therapy. May be reduced thereafter if no BP elevations (level 4) (56)	Home monitoring may aid early detection of hypertension. Patients should be provided with prospectively set, individualized, thresholds (systolic and diastolic) for contacting their HCP (level 4) (14,38,47,56–58)	
Baseline diagnosis and control of hypertension should be based on 24-h BP monitoring (level 2) (56) For an individual patient, BP should be monitored using the same equipment throughout management (level 4) (28)		
Control of hypertension		
Control hypertension before administration of bevacizumab or TKIs (level 4) (5)	ACE inhibitors and ARBs may be useful in this indication (level 4) (15,35,47,59)	Identification of optimal pharmacological management of hypertension in patients receiving targeted agents
Treat hypertension as needed with standard antihypertensive therapy (appropriate for the individual situation of the affected patient) (level 4) (1–3,5)	A calcium channel blocker can be added if needed (level 4) (35,38,47,60)	
If severe hypertension develops, suspend targeted therapy (and resume once hypertension is appropriately controlled) or permanently discontinue if medical control is not possible or hypertension becomes life threatening (level 4) (1–3,5)	Non-dihydropyridine calcium channel blockers (verapamil, diltiazem) should be avoided because they may interfere with metabolism via CYP3A4 (15,28,31,38,61) Dihydropyridines, such as amlodipine and nifedipine, should be preferred (31,38)	

(Table continues)

Table 3 (Continued).

Widely accepted measures (level of evidence†)	Unproven recommendations with some merit, based on author/expert opinion‡	Points for further research
Cardiovascular events		
Pretreatment evaluation		
TKIs in patients with cardiac risk factors and/or history of coronary artery disease: Detailed cardiovascular history and physical examination for signs and symptoms of heart failure (62)	In rare cases, it may be helpful to include a BNP or chest image (level 4) (62)	Evidence-based recommendations are needed. The predictive value of cardiac investigations should be specifically investigated: future trials of TKIs and other drugs that affect the VEGF pathway should include careful monitoring of cardiac effects.
Noninvasive evaluation of left ventricular function to detect subclinical cardiovascular disease (level 3) (3)		
On-treatment monitoring		
The primary focus should be on-going close monitoring for clinical signs and symptoms of heart failure (level 3) (3)	Sunitinib:	Clinical trials to evaluate the use of biomarkers in early detection of cardiac AEs
	In patients with cardiac risk factors perform an echo cardiogram every 3–6 mo [co-author recommendation]	
	Electrocardiogram at baseline, on day 7 and then whenever other medications are initiated [co-author recommendation]	Evaluation of echo cardiogram with newly developed measures of diastolic function such as tissue velocity imaging of the early diastole, strain, and strain rate
Diagnosis and management		
Exclude other etiologies of heart failure, including hypothyroidism anemia, and pulmonary embolism	A BNP test can help with diagnosis in patients with clinical symptoms [co-author recommendation]	Data on optimal therapy for cardiotoxicity induced targeted therapy are lacking
Sunitinib: In the presence of clinical manifestations of CHF, discontinuation of sunitinib is recommended. Sunitinib should be interrupted and/or the dose reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline (level 3) (3)		
Standard heart failure management (level 4) (62)		
Hemorrhage		
Minimize risk by controlling hypertension		
Minor bleeding		
Patients receiving bevacizumab or TKIs should be educated about the management of minor bleeding such as epistaxis (level 4)		
Grade ≥3 bleeding		
Bevacizumab and TKIs: Any grade 3 or 4 hemorrhage should result in treatment discontinuation (level 2) (1,3,5)		
Bevacizumab warning:		
Do not administer bevacizumab to patients with serious hemorrhage or recent hemoptysis (level 1) (5)		
Anticoagulation		
Patients receiving sorafenib and concomitant treatment with anticoagulants may be periodically monitored by complete blood counts (platelets), coagulation factors, and physical examination (level 4) (1)	Low-dose aspirin may continue in patients on bevacizumab (level 3) (63)	Definition of balance of risk between thromboembolism and bleeding in patients receiving TKIs or bevacizumab
Caution should be exercised before initiating oral anticoagulant therapy in patients treated with bevacizumab (level 4) (5)		

(Table continues)

Table 3 (Continued).

Widely accepted measures (level of evidence†)	Unproven recommendations with some merit, based on author/expert opinion‡	Points for further research
Thromboembolism		
Thromboprophylaxis		
In general, thromboprophylaxis is recommended for hospitalized cancer patients (in the absence of bleeding or other contraindications) (level 2) (64)	Low-dose aspirin may continue in patients on bevacizumab (level 3) (63)	Identification of markers of VTE or ATE risk
		Assessment of impact of prophylaxis in ambulatory patients receiving targeted agents for RCC
Treatment		
Low–molecular weight heparins (level 2) (65)		More information is needed on when to start or stop oral anticoagulant prophylaxis and which type of anticoagulants to use in patients receiving agents therapies for RCC
Dose interruptions/modifications		
Grade 3 VTE: dose interruption, restarting treatment if anticoagulation therapy is effective, and patients do not present a risk of hemorrhage (level 4) (5)		
Grade 4 VTE or ATE: discontinue treatment (level 4) (5)		
Wound healing		
Bevacizumab should be discontinued at least 28 d before elective surgery and restarted after 28 d or when the wound is fully healed (level 1) (5)		
TKIs and mTORs should be interrupted (at least 1 week) before surgery and not reinitiated until adequate wound healing has occurred (level 3) (1–4,6,66)		Clearer definition of minimum period of treatment discontinuation around elective surgery for all agents
Pneumonitis		
Monitoring	Management (4,6,67)	
Patients receiving temsirolimus or everolimus should be monitored for clinical respiratory symptoms indicative of interstitial lung disease, for example, hypoxia, pleural effusion, cough, or dyspnea (level 3) (4,6)	Radiological changes only: monitor (level 3)	
	Radiological changes and moderate symptoms: consider temporary treatment interruption (level 3)	
Where symptoms are observed diagnosis should be based on pulmonary function tests, chest x-ray and/or CT scan and appropriate diagnostic tests to exclude opportunistic infection (level 3) (4,6)	Radiological changes and increasing clinical symptoms in conjunction with a decrease in diffusing capacity of the lung: drug discontinuation and corticosteroid treatment. Treatment may be restarted at a lower dose on recovery to grade 1 (level 3)	

* Suggestions for management of hepatotoxicity, observed with sunitinib and pazopanib, are not presented in the table owing to lack of data. However, one recent report found that transaminase elevations to three or more times the upper limit of normal spontaneously recovered to grade 0 or baseline levels in 30% of patients treated with pazopanib, and 29% of patients were managed with a dose interruption, although subsequent rechallenge resulted in recurrence in 32% of these patients (68). Specific gene polymorphisms may account, in part, for pazopanib-related ALT elevations and hyperbilirubinemia (69,70). ACE = angiotensin converting enzyme; ALT = alanine aminotransferase; ARB = angiotensin II receptor blockers; ATE = arterial thromboembolism; BP = blood pressure; BNP = Brain-type (B-type) natriuretic peptide; CHF = congestive heart failure; CT = computed tomography; CYP3A4 = member of cytochrome P_{450} family; HCP = health-care provider; QoL = quality of life; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor; TSH = thyroid-stimulating hormone; VTE = venous thromboembolism.

† Levels of evidence: level 1 = at least one randomized controlled trial; level 2 = at least one well-designed controlled study without randomization, or one other type of well-designed quasi-experimental study; level 3 = well-designed nonexperimental studies, such as comparative studies, correlation studies and case reports; level 4 = evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.

‡ Recommendations that the authors consider to have some merit but that are not supported by clinical data.

impact on a patient's quality of life, as well as physical and emotional well-being. In addition to increased bowel movement, patients may experience abdominal pain, cramping, proctitis, and anal or perianal skin erosion. Some patients may also develop aversions to some foods or stop eating, which can lead to weight loss, malnutrition, fatigue, and depression (74).

Because diarrhea is one of the most common AEs of anticancer therapy (Table 1), there are a number of published clinical guidelines for the management of diarrhea in cancer patients (75–78). Although these guidelines are not RCC or targeted therapy specific (and were therefore not uncovered by our search strategy), they warrant consideration because they may be beneficial in the management of diarrhea associated with the TKIs (27). Guidelines suggest that patients should be educated about treatment-related diarrhea and encouraged to keep diaries listing episodes, their severity, and accompanying symptoms of diarrhea (78); this may help clinicians to optimize management strategies.

The management strategies that we identified from the literature generally fall into four categories: diet, dehydration management, pharmacological interventions, and dose adjustments (Table 3). Regarding diet, patients are often advised to avoid foods that may aggravate diarrhea; they are also encouraged to consume foods that may increase the consistency of their stools. Because patients can become dehydrated after experiencing particularly long or severe episodes of diarrhea, dehydration management is vital in these cases. Pharmacological interventions such as loperamide are widely used for managing anticancer therapy–related diarrhea; however, there is currently no consensus on when during the course of anticancer treatment loperamide should be taken. For patients who experience grade 3 or 4 AEs, dose adjustments in anticancer therapies may be necessary. However, once the severity of diarrhea subsides, optimal treatment dosing should be reinstated so as not to unnecessarily compromise the efficacy of therapy.

Oral or Upper Gastrointestinal Complications

Oral and upper gastrointestinal complications of targeted therapies include mucositis, stomatitis, xerostomia (dry mouth), ageusia (taste loss), and dysgeusia (taste disturbance) (1–6). Mucositis is characterized by painful inflammation and ulceration of the mucous membranes lining the digestive tract, whereas stomatitis more specifically refers to inflammation of the mucous lining of the mouth. Both AEs are associated with pain, which can in turn lead to difficulty speaking, eating, or opening the mouth. Stomatitis is commonly associated with sunitinib (3,79), bevacizumab + IFN-α (5), temsirolimus (4,22), and everolimus (6,80) treatment but is not common in patients on sorafenib therapy (Table 1).

Although there are a number of management strategies available for treating both targeted therapy–related stomatitis and mucositis, there is no consensus on which strategy is the most effective (Table 3). However, a meta-analysis carried out by Worthington et al. (81) assessed the effectiveness of prophylactic agents for preventing stomatitis in patients receiving chemotherapy (81). Results from their analysis suggest that amifostine, Chinese medicine (that involved mixtures of five or 11 herbs including honeysuckle flower, licorice root, and magnolia bark), hydrolytic enzymes (pepsin, trypsin and chymotrypsin, or wobe-mugos preparation of enzymes), and ice chips may be beneficial in preventing or reducing the severity of stomatitis (81).

Xerostomia is commonly associated with sunitinib treatment (3,79) but is not commonly related to any of the other targeted therapies. Severe cases of xerostomia can cause difficulty in speech and eating, can lead to a rise in the number of tooth cavities, and can make the mouth vulnerable to infection.

Ageusia and dysgeusia do not generally affect the physical well-being of a patient; however, they can both have an impact on psychological well-being and the ability of some patients to perform tasks associated with daily living (eg, a chef's ability to work); this in turn can have a large negative impact on a patient's quality of life. No recommendations were found from the literature on how to treat targeted therapy–related ageusia and dysgeusia; however, some studies suggest that zinc replacement, palliative measures (eg, use of mints, sugarless chewing gums, and bicarbonate mouthwashes), niacin, and vitamin A may help relieve dysgeusia (82). In addition, it may be necessary to switch treatments to another anticancer drug within the same class to treat severe or particularly distressing cases of ageusia and dysgeusia (82).

Anorexia/Weight Loss

Anorexia, which presents as dramatic weight loss, may be caused by decreased or a complete loss of appetite that may or may not be related to treatment-related nausea, vomiting, oral pain, diarrhea, and loss or disturbance of taste. Anorexia-related symptoms, which include weakness, fatigue, depression, tooth loss, and organ damage, can have a negative impact on health-related quality of life, affect a patient's ability to perform daily tasks, and can result in death in severe cases.

Phase III studies of targeted therapies report anorexia occurring at a rate of 36% (83), 32% (22), 16% (23), and 22% (12) in patients treated with bevacizumab + IFN-α, temsirolimus, everolimus, and pazopanib, respectively, and 14% (80) with sorafenib. Although anorexia was not reported in the sunitinib phase III trial in metastatic RCC, anorexia and decreased appetite are reported as a combined AE in the summary of product characteristics for sunitinib (occurring at a rate of 37.7%) (3).

There are few studies that address the management of targeted therapy–related anorexia, which may worsen cachexia in patients with RCC (Table 3); however, this topic has been widely addressed in several other general publications (84–89). General pharmacological interventions recommended for treating anorexia and cachexia include megestrol acetate (48,87), eicosapentaenoic acid diester (86), medroxyprogesterone acetate (88), and mixtures of beta-hydroxyl beta-methyl butyrate, glutamine, and arginine (85). Other interventions for treating anorexia and cachexia involve giving patients simple dietary advice, prescribing artificial saliva, mouthwash, and prokinetic antiemetics (84).

Fatigue

Fatigue presents as a distressing, persistent, subjective sense of emotional, physical, and/or cognitive tiredness or exhaustion (50). Because the etiology of fatigue is often multifactorial—arising as an AE of anticancer therapy, as a symptom of the underlying illness, and/or as a sign of hypothyroidism, anemia, depression, sleep disturbances, or pain (50)—it is often difficult to manage. However,

the initial step is to exclude treatable causes, notably anemia (see below), thyroid dysfunction, poor sleep, and depression. Once treatable causes have been excluded or managed, the patient may be further helped by the teaching of coping strategies.

Cancer-related fatigue is common, occurring in around 75% of patients with metastatic disease (50). Targeted therapy–related fatigue is also common, occurring in 20% (23) to 51% (90) of patients. The frequent occurrence (Table 1) and high impact of fatigue on quality of life means that effective management is important. However, there is lack of consensus. For example, although some sources state that dose modifications in targeted therapies are rarely necessary (30), others suggest that for grade 3 or 4 fatigue, dose modification, or interruption should be considered (15). Because depression is a common cause of fatigue, antidepressants are sometimes considered an option. However, not all authors recommend them for reducing the severity of fatigue (15,47,50). There is also disagreement on whether patients suffering from fatigue should rest (28,30,50) or maintain everyday activities (27,31,38). However, there appears to be agreement that patients should be educated and counseled about coping strategies because this can motivate them to remain on therapy (28,30,31,38).

Anemia

Anemia is a common but reversible AE of therapy with targeted agents, occurring in less than 10% (91) to 91% of patients (23). Along with fatigue, symptoms include shortness of breath, paleness of the skin, and, in severe cases, heart failure. Anemia and myelosuppression may occur particularly with those agents that target fms-related tyrosine kinase 3 (Flt-3), such as sunitinib (92).

Hypothyroidism

Hypothyroidism is a very common AE associated with sunitinib and is also noted with other agents in the class. The European summary of product characteristics reports an incidence of hypothyroidism of 14% in patients receiving sunitinib for RCC in phase II and phase III clinical trials (3). Results from subsequent small clinical studies suggest that the incidence may be higher, ranging from 27% to 85% (93–96). The management of hypothyroidism is important for controlling associated symptoms such as fatigue. Most authors agree that any preexisting hypothyroidism should be detected and treated before starting sunitinib treatment, as recommended in the European summary of product characteristics (3). There is less consensus on the extent of monitoring required once treatment with sunitinib is in progress. For example, Wolter et al. (94) suggest measuring thyroid-stimulating hormone (TSH) on days 1 and 28 in the first four cycles of sunitinib treatment, arguing that hypothyroidism generally develops early during the course of treatment and may be most effectively diagnosed with this intensive monitoring. If TSH levels remain normal, these authors recommend reducing the frequency of monitoring to once every three cycles (on day 28). In contrast, Torino et al. (13) propose measurement of TSH on day 1 of every cycle of sunitinib treatment (as detailed in Table 3). Although measurement of TSH at day 28 of the cycle (at the end of the 4-week sunitinib treatment period) may increase the chances of early detection of thyroid dysfunction, this dysfunction may prove to be transient and/or subclinical and not warrant therapy. Elevated TSH levels measured on day 1 of the cycle (at the end of the 2-week rest period) are more likely to indicate clinically relevant thyroid damage requiring further investigation and, if appropriate, initiation of corrective therapy (13).

The high incidence of hypothyroidism in patients receiving sunitinib raises the question as to whether this is a class effect of TKIs. Hypothyroidism was not listed as a common AE in phase III studies of either sorafenib or pazopanib (12,83,91); however, the European summary of product characteristics for pazopanib notes that hypothyroidism was common across RCC phase II and III studies (incidence, 4%) (2). A retrospective study of 39 patients treated with sorafenib (97) did identify thyroid dysfunction attributable to the drug in eight (21%) patients, although only two of these patients had clinical symptoms requiring treatment (97); a prospective study in Japanese patients (98) suggested that hypothyroidism may occur more frequently in Japanese than in Western patients (98). On the basis of these results, the authors suggested that thyroid function tests are warranted before treatment with sorafenib (97). Other authors also cite this study (97) as justification for extending recommendations for thyroid function monitoring to include all patients treated with TKIs.

Hyperglycemia

Hyperglycemia is a very common AE of the mTOR inhibitors temsirolimus and everolimus (4,6). In both diabetic and nondiabetic patients, it may be prudent to monitor fasting serum glucose before initiating treatment with everolimus or temsirolimus and periodically thereafter. In diabetic patients, optimization of glycemic control is recommended before initiating treatment. Advising patients to report excessive thirst or any increase in the volume or frequency of urination will help with early identification of problems (4,6). Hyperglycemia can be relatively simply treated with dietary modifications and an increase in the dose of, or initiation of, insulin and/or hypoglycemic agent therapy.

Gastrointestinal Perforation (GIP)

GIP is a rare but potentially fatal complication that has been reported in association with all the targeted agents except (to date) everolimus (1–5). GIP has been most comprehensively documented in patients treated with bevacizumab. A meta-analysis (52) of 17 randomized studies, including more than 12 000 patients with colorectal cancer, breast cancer, pancreatic cancer, non–small cell lung cancer, or RCC, reported an overall incidence of GIP of 0.9% in patients receiving bevacizumab. The relative risk (RR) of GIP compared with control subjects was highest in patients with colorectal cancer (RR = 3.10, 95% confidence interval [CI] = 1.26 to 7.63) or RCC (RR = 5.67, 95% CI = 0.66 to 48.42) (52). An increased risk was also associated with metastatic disease and with a higher dose of bevacizumab (5 vs 2.5 mg/kg). The authors of this meta-analysis (52) suggest that to identify patients at high risk of GIP, an assessment of the patient's history should include evidence of past diverticulitis or ulcers, radiation exposure, recent sigmoidoscopy or colonoscopy, resection of the primary tumor, gastrointestinal obstruction, and multiple previous surgeries.

Patients treated with targeted agents, particularly bevacizumab, should be monitored for early signs of GIP. Early diagnosis of GIP is complicated by the fact that targeted agents are commonly

associated with gastrointestinal AEs, and monitoring for signs such as fever, abdominal pain, constipation, and vomiting may not be sufficient. Further analysis of cases of GIP in patients with RCC treated with targeted agents may help to identify more specific diagnostic markers. For example, in a report (99) of two patients receiving sunitinib for RCC, GIP was observed in association with colonic pneumatosis with right-sided colonic involvement, lactate elevation, and previous high-dose interleukin 2 exposure (99).

Any case of GIP should result in discontinuation of anticancer therapy and appropriate treatment of the perforation. The European summaries of product characteristics for bevacizumab and sorafenib clearly recommend permanent discontinuation of these agents in the case of GIP (1,5). However, in patients who were responding to targeted therapy, recovery from GIP and appropriate management of the underlying causes may allow retreatment, maybe at a reduced dose (52). There are no specific recommendations for the management of GIP in patients receiving targeted anticancer therapies. Considering the increased risk of bleeding and wound-healing complications in patients taking VEGF-targeted agents (particularly bevacizumab), nonsurgical interventions may be preferable to surgery. A study of 24 patients with bevacizumab-associated GIP (54) suggested that nonoperative treatments, such as placement of a percutaneous intra-abdominal catheter, bowel rest, and intravenous antibiotics, may be viable options (54). Further studies are warranted to investigate this possibility, as well as that of subsequent retreatment with targeted agents after the occurrence of GIP.

Hypertension

Arterial hypertension is a common AE of inhibitors of the VEGF pathway, reported at a frequency of between 12% and 41% in patients treated with sorafenib, sunitinib, bevacizumab + IFN-α, or pazopanib (1,3,5,12,79,83,91). These incidences may be underestimated because they were based on measurements taken at predefined visits during clinical trials; more detailed prospective evaluation may be necessary to reveal the true incidence of hypertension. Management of angiogenesis inhibitor–related hypertension (Table 3) is frequently based on the current guidelines of the European Society of Hypertension (100) but should be optimized on a case-by-case basis.

Prompt diagnosis of hypertension may help to prevent serious complications, such as intracranial hemorrhage and heart failure (15,16), and maintain patients on treatment for longer periods. In this respect, blood pressure (BP) monitoring is clearly important; however, there is general disagreement about when and how BP should be measured (14,15,31,38,47,56–58). The routine use of home BP monitoring may be valuable in standard care for early detection and accurate assessment of BP changes (38,47,57,58). In a small prospective study (56) in 10 patients treated with sunitinib, home measurements based on 24-hour BP monitoring at baseline and after 2, 4, and 6 weeks of treatment revealed two cases of hypertension that would not otherwise have been detected (56). When home monitoring, patients need to be provided with individualized thresholds for contacting their health-care provider. For example, patients with additional risk factors and rising BP may need earlier intervention, even if their BP is within what are usually considered to be normal limits (14,56,58).

When it arises, hypertension should be treated promptly as needed with standard antihypertensive therapy (appropriate for the individual situation of the patient) (1–3,5). Although it is generally admitted that angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) are useful in this indication, no clear recommendation for antihypertensive agents can be made because there is a lack of controlled studies addressing the treatment of hypertension in patients with RCC. Some antihypertensive medications might prove more effective in treating anti–VEGF-associated hypertension and be better tolerated; in addition, certain antihypertensive medications can interfere with antineoplastic activity by modulating VEGF expression and reducing the antiangiogenic effect of targeted therapies (101–103). Large trials (101,102) in patients with diabetic nephropathy clearly indicate that antihypertensives that target the renin–angiotensin–aldosterone system have renoprotective effects. Both ACE inhibitors and ARB are able to lower the intraglomerular pressure independent of any change in systemic BP by dilation of the efferent arteriole of the glomerulus. Furthermore, they have antiproteinuric effects, which may contribute to protection of renal function. However, enalapril and candesartan can inhibit myocardial angiogenesis (103).

Because VEGF is known to increase endothelial nitric oxide (NO), the hypertensive effect of anti-VEGF compounds is considered by some to be mediated by the drop in endothelial NO synthetase. Antihypertensives that increase endogenous NO (eg, nitrates, phosphodiesterase inhibitors, or the beta-blocker nebivolol) might be of particular interest and merit evaluation in prospective clinical trials (34,104,105). Calcium channel blockers (CCBs) may reduce microvascular rarefaction and improve angiogenesis. In a prospective randomized trial (106) investigating approaches to minimizing dose interruptions and reductions of the experimental VEGF-targeted agent cediranib, a low dose of CCB 3–7 days before starting therapy reduced the incidence of severe hypertension from 18/63 patients without prophylaxis to 1/63 patients with prophylaxis (106). However, CCB prophylaxis did not result in fewer dose reductions or dose interruptions in cediranib therapy. Concerns have been raised over the safety of CCBs, particularly non-dihydropyridines, because they interfere with CYP3A4 activity (15,28,61,103). Thus, dihydropyridines, such as amlodipine and nifedipine, may be preferable (103), although nifedipine has been shown to induce VEGF secretion (107). Diuretics also have been used successfully to manage increases in BP arising from cancer treatment; however, thiazide-type diuretics should be used cautiously, particularly in patients prone to dehydration or hypercalcemia (35,58). Results from this literature review suggest that further clinical studies are needed to identify optimal treatments for managing targeted therapy–related hypertension.

Cardiovascular Events

Of the targeted agents used in RCC, sunitinib is most frequently associated with cardiovascular events. Although cardiovascular events are not all that common, they can be life threatening and thus require careful monitoring (Table 3). Few studies have prospectively examined the cardiotoxicity of TKIs in the treatment of RCC with defined cardiac endpoints. Therefore, evidence-based recommendations are lacking, and future trials of TKIs and other

drugs that affect the VEGF pathway should include careful monitoring of cardiac effects. Some such studies are already in progress, such as the SWITCH study of sequential use of sorafenib followed by sunitinib and vice versa, in which cardiotoxicity will be analyzed by means of echocardiography and measurement of N-terminal fragment of pro B-type natriuretic peptide (NT-proBNP), with a planned interim analysis after 100 patients in each arm have completed the study (www.clinicaltrials.gov, NCT00732914).

Generally VEGF-targeted agents should be used with caution in any patients with clinically significant cardiovascular disease or preexisting congestive heart failure, and these patients should be closely monitored for clinical signs of heart failure (3,5). Periodic measurement of LVEF using echocardiography, magnetic resonance imaging, or multigated acquisition gives an assessment of systolic cardiac function and is the most common method of monitoring cardiac function during cancer treatment (108–110). However, LVEF alone is not an adequate early marker of cardiac damage; other methods to assess cardiac function during cancer treatment are being investigated, for example, biomarkers, or identification of subclinical changes, such as changes in diastolic function (16,62,108–113). Any left ventricle dysfunction could be exacerbated or even caused by other AEs such as hypothyroidism or hypertension; therefore, these conditions should be carefully monitored and managed.

Where targeted agent–related congestive heart failure is diagnosed, the treatment strategy is unclear; data on optimal therapy are lacking. TKI-induced cardiac dysfunction generally responds well to standard heart failure management for nonischemic cardiomyopathy, as outlined by the American Heart Association/American College of Cardiology and the Heart Failure Society of America (62). However, because in most cases TKI treatment will be withheld, we do not really know if the recovery is attributable to the heart failure treatment or to stopping the TKIs. Anecdotal reports suggest that left ventricular dysfunction may be at least partially reversed on cessation of TKI therapy.

Wound Healing

Bevacizumab has been shown to adversely affect the process of wound healing, and the European summary of product characteristics includes a black box warning recommending treatment discontinuation for at least 28 days either side of elective surgery or after emergency surgery (5). Signs of wound dehiscence or infection should be regularly monitored (5,53).

Effects of mTOR inhibitors on wound healing have been documented (4,6) in the field of transplantation surgery, in which these agents are widely used (albeit at a different dose). Impaired wound healing was reported as an AE in three (1%) patients during the temsirolimus phase III study in RCC. Caution is therefore advised when using these agents in patients undergoing surgery; however, there are no clear recommendations regarding the optimal duration of treatment interruption before or after surgery.

Prospective studies have not been conducted on the effects of the TKIs sorafenib, sunitinib, and pazopanib on wound healing, although one study (114) found that in RCC patients undergoing cytoreductive nephrectomy or resection of retroperitoneal recurrence, rates of incision-related complications were similar between patients treated with preoperative sorafenib, sunitinib, or bevacizumab and those who underwent up-front surgery (114). Given the antiangiogenic action of these agents, it is generally recommended that treatment be interrupted at least 1 week before any scheduled major surgery, with resumption of therapy based on clinical judgment of adequate wound healing (1–3). Guidance on the necessary duration of treatment interruption is lacking, with suggestions ranging from 7 to 14 days (1,3,66). Further studies, or further analysis of data obtained during clinical use, are needed to better understand the effects of TKIs on wound healing and the minimum duration of treatment discontinuation around elective or emergency surgery.

Hemorrhagic Events

Minor hemorrhagic events are relatively common in patients treated with targeted agents; the most common event reported in patients treated with bevacizumab, sunitinib, temsirolimus, and everolimus is epistaxis, which usually resolves without medical attention (79,83,90,91). Bleeding events with sorafenib in the phase III TARGET trial were mostly grade 1 in severity and were reported in 15% of patients; rates of severe hemorrhage were similar in the sorafenib (3%) and placebo arms (2%) (115). The impact of minor bleeding events can be limited by good patient education (Table 3) (116).

Life-threatening hemorrhagic events are rarer than minor hemorrhagic complications. In the case of bevacizumab, serious hemorrhage appears to be more frequently associated with specific tumor types such as non–small cell lung cancer or cancer of the gastrointestinal tract (5). A point of disagreement is whether patients with metastases of the central nervous system (CNS) should receive treatment with bevacizumab + IFN-α. A severe CNS hemorrhage during a phase I study of bevacizumab (117) led to the exclusion of such patients in subsequent clinical trials. As a result, there are no data on the use of bevacizumab in this group of patients. In contrast, subgroup analyses and case studies have indicated that the TKIs sorafenib and sunitinib can be safely administered to patients with CNS metastases that have been irradiated (9,118–120).

The risk of serious hemorrhage can be minimized by good control of hypertension. Clearly, with any agent that increases the risk of bleeding, care should be taken in patients who require concomitant treatment with anticoagulants, and this is of relevance to the problem of prevention of thromboembolic events.

Venous (VTE) and Arterial Thromboembolism (ATE)

VTE is a common complication in cancer patients (65,121). Risk factors include age older than 65 years, previous VTE events, and surgery (65,121). The role that targeted agents play in modifying the risk of VTE is difficult to clarify. Treatment-related VTE, including pulmonary embolism and deep vein thrombosis, was reported in approximately 2% of patients in clinical studies of sunitinib for RCC and in 3% of patients in clinical studies of temsirolimus for RCC, including some fatal outcomes (3,4). The European summary of product characteristics for bevacizumab does not report VTE as a common AE in patients with RCC. However, a meta-analysis of 15 studies (122) investigating the treatment of various solid tumors with bevacizumab, with or without other antineoplastic agents, suggested that there is an increased

risk of VTE in patients who received this agent (122). The overall incidence of VTE in patients treated with bevacizumab was 12% for all grades and 6% for high-grade VTE, with the highest risk reported in patients with non–small cell lung cancer or colorectal cancer. The AVOREN phase III study reported an incidence of 2% of grade 3 or worse VTE in patients with RCC with a relative risk of 2.86 (95% CI = 0.62 to 13.24) (83,122).

An increased frequency of ATE has been recorded in multiple trials of bevacizumab across tumor types. A pooled analysis (123) including 1745 patients from five randomized trials reported an overall incidence of 4% of ATE in patients with non–small cell lung cancer, colorectal, or breast cancer who received bevacizumab combined with chemotherapy and suggested an increased risk of ATE associated with bevacizumab (123). The risk of ATE was also increased in patients older than 65 years of age and in those who had previously experienced an ATE. In the AVOREN phase III study, four (2%) patients in the bevacizumab arm had an ATE compared with one patient in the placebo arm. ATE such as cardiac ischemia and/or infarction occurred in around 3% of patients treated with sorafenib or pazopanib in clinical studies of RCC patients.

ASCO and American College of Chest Physician guidelines provide general recommendations about the prophylaxis and treatment of thrombosis in cancer patients (64,124). Further information may be obtained from a recent review of VTE guidelines (125). In general, anticoagulation prophylaxis is not recommended for ambulatory patients with cancer receiving systemic treatment (124); whether the increased risk of thrombotic events with some targeted agents warrants prophylaxis in ambulatory patients remains unclear. Clearly, acetylsalicylic acid (ASA) or other antiplatelet drugs should be used with caution in association with anti-VEGF agents because of the increased risk of bleeding. A small number of studies suggest that ASA or warfarin can be used to control thrombotic complications in patients receiving bevacizumab with no significant increase in bleeding events (65,121); however, these results are preliminary, and no specific recommendations can be made. Further studies are needed to better define the balance of risk between thromboembolic and hemorrhagic complications.

Pneumonitis

Pneumonitis is a common AE associated with the mTOR inhibitors temsirolimus and everolimus (4,6). A review of cases arising during the phase III clinical study of everolimus suggests that the risks associated with noninfectious pneumonitis can be effectively managed by early recognition and prompt intervention (6,67). Because noninfectious pneumonitis in the absence of symptoms is not life threatening and does not affect quality of life, it is not necessary to routinely monitor patients with chest x-rays or computed tomographic scans. However, patients treated with mTOR inhibitors should be carefully monitored for signs and symptoms of respiratory illness, which should be rapidly investigated further when identified (as outlined in Table 3). The optimal management of this AE in patients treated with mTOR inhibitors is not yet clearly defined. In clinical practice, use of corticosteroids to manage everolimus-associated pneumonitis may be commonplace (126); however, initial recommendations from the manufacturer suggest that moderate symptoms can be managed with dose reductions or temporary treatment interruption and that discontinuation of everolimus and initiation of corticosteroid treatment is only necessary where severe symptoms are present (6,67).

Concluding Remarks

With the advent of targeted therapies for RCC and their positive impact on overall survival, patients are increasingly treated for long periods of time, raising challenges in how to manage the associated AEs. Multiple toxic effects have been reported with targeted agents, some of which differ greatly from those traditionally associated with the cytotoxic agents or immunotherapy. There are also some notable differences between the AE profiles of the various classes of targeted agents. Dermatologic and gastrointestinal AEs are those most commonly reported with TKIs; hypertension has also frequently been observed. Bevacizumab + IFN-α is also associated with gastrointestinal disorders, in addition to general AEs such as fatigue and headache. By contrast, with mTOR inhibitors, treatment-related infections, pneumonitis, and metabolic disorders are generally the most common AEs.

This review found many articles detailing a large number of different investigations for monitoring AEs and interventions for AE management, but the supportive evidence for the suggested management strategies is generally very weak. Data relating to the management of treatment-related AEs are largely anecdotal, and there are few consensus recommendations for AE management strategies. There is thus an unmet need for systematic evaluation of AE monitoring strategies to separate those that are useful from those that are not, thereby avoiding subjecting patients to a barrage of unnecessary tests.

In this review, we focused on strategies for monitoring and managing AEs to avoid dose or drug schedule modifications where possible. However, although beyond the scope of this review, an assessment of the incidence and consequences of dose modifications and alternative dose schedules would certainly be worthy of further study. For example, sunitinib regimens other than the 4/2 schedule have entered clinical practice, despite few data on their efficacy (127,128).

In conclusion, some suggestions for management of AEs, based mainly on expert opinion, can be made. In particular, there are clear recommendations for the management of dermatologic and oral/gastrointestinal AEs, which are some of the most common associated with targeted therapies. This review highlights that surprisingly few strong data exist to guide management of side effects of these widely used drugs. There is a clear need for systematic investigation of management strategies for AEs related to targeted therapies for RCC.

References

1. *EU SmPC Nexavar.* http://www.ema.europa.eu/humandocs/Humans/EPAR/nexavar/nexavar.htm. Accessed November 8, 2010.
2. *EU SmPC Votrient.* http://www.ema.europa.eu/humandocs/Humans/EPAR/votrient/votrient.htm. Accessed November 8, 2010.
3. *EU SmPC Sutent.* http://www.ema.europa.eu/humandocs/Humans/EPAR/sutent/sutent.htm. Accessed November 8, 2010.
4. *EU SmPC Torisel.* http://www.ema.europa.eu/humandocs/Humans/EPAR/torisel/torisel.htm. Accessed November 8, 2010.

5. *EU SmPC Avastin.* http://www.ema.europa.eu/humandocs/Humans/EPAR/avastin/avastin.htm. Accessed November 8, 2010.
6. *EU SmPC Afinitor.* http://www.ema.europa.eu/humandocs/Humans/EPAR/afinitor/afinitor.htm. Accessed November 8, 2010.
7. Anderson R, Jatoi A, Robert C, et al. Search for evidence-based approaches for the prevention and palliation of hand-foot skin reaction (HFSR) caused by the multikinase inhibitors (MKIs). *Oncologist.* 2009; 14(3):291–302.
8. Hutson TE, Bellmunt J, Porta C, et al. Long-term safety of sorafenib in advanced renal cell carcinoma: follow-up of patients from phase III TARGET. *Eur J Cancer.* 2010;46(13):2432–2440.
9. Gore ME, Szczylik C, Porta C, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. *Lancet Oncol.* 2009;10(8):757–763.
10. Porta C, Szczylik C, Bracarda S, et al. Short- and long-term safety with sunitinib in an expanded access trial in metastatic renal cell carcinoma (mRCC). *J Clin Oncol.* 2008;26. Abstract 5114.
11. Sternberg CN, Hawkins RE, Szczylik C, et al. A randomized, double-blind phase III study (VEG105192) of pazopanib (paz) versus placebo (pbo) in patients with advanced/metastatic renal cell carcinoma (mRCC): updated safety results. *J Clin Oncol.* 2011;29. Abstract 313.
12. Sternberg CN, Szczylik C, Lee E, et al. A randomized, double-blind phase III study of pazopanib in treatment-naive and cytokine-pretreated patients with advanced renal cell carcinoma (RCC). *J Clin Oncol.* 2010;28(6): 1061–1068.
13. Torino F, Corsello SM, Barnabei A, et al. Hypothyroidism related to tyrosine kinase inhibitors: an emerging toxic effect of targeted therapy. *Nat Rev Clin Oncol.* 2009;6(4):219–228.
14. Bamias A, Lainakis G, Manios E, et al. Could rigorous diagnosis and management of hypertension reduce cardiac events in patients with renal cell carcinoma treated with tyrosine kinase inhibitors? *J Clin Oncol.* 2009; 27(15):2567–2569.
15. Bhojani N, Jeldres C, Patard JJ, et al. Toxicities associated with the administration of sorafenib, sunitinib, and temsirolimus and their management in patients with metastatic renal cell carcinoma. *Eur Urol.* 2008;53(5): 917–930.
16. Khakoo AY, Plana JC, Champion JC, et al. Heart failure associated with sunitinib malate: a multitargeted receptor tyrosine kinase inhibitor. *Cancer.* 2008;112(11):2500–2508.
17. *US PI Votrient.* http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022465s002lbl.pdf. Accessed November 8, 2010.
18. *US PI Sutent.* http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021938s010s011s014s015lbl.pdf. Accessed November 8, 2010.
19. Grunwald V, Miller K, Machiels J, et al. An international expanded access program (EAP) of RAD001 (everolimus) in patients with metastatic renal cell carcinoma (mRCC) who are intolerant or have progressed after prior vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI). *Ann Oncol.* 2010;21(suppl 8):viii274. Abstract 877PD.
20. Pelz H. Compassionate use-program (CUP) temsirolimus in patients with advanced renal cell carcinoma in Germany. *Eur Urol Suppl.* 2009;8(4):183. Abstract 251.
21. Amato RJ, Jac J, Giessinger S, et al. A phase 2 study with a daily regimen of the oral mTOR inhibitor RAD001 (everolimus) in patients with metastatic clear cell renal cell cancer. *Cancer.* 2009;115(11): 2438–2446.
22. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med.* 2007;356(22): 2271–2281.
23. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet.* 2008;372(9637):449–456.
24. Albiges L, Caramella C, Dromain C, et al. Interstitail pneumonitis during RAD-001 treatment: incidence by blinded radiological analysis. *Eur J Cancer Suppl.* 2009;7(2):427. Abstract PD-7114.
25. Pablo M, Hudes G, Dutcher J, et al. Radiographic findings of drug-induced pneumonitis and clinical correlation in patients with advanced renal cell carcinoma treated with temsirolimus. *Eur J Cancer Suppl.* 2009; 7(2):426. Abstract PD-7113.
26. Schmidinger M, Bellmunt J. Plethora of agents, plethora of targets, plethora of side effects in metastatic renal cell carcinoma. *Cancer Treat Rev.* 2010;36(5):416–424.
27. Wood LS. Managing the side effects of sorafenib and sunitinib. *Commun Oncol.* 2006;3(9):558–562.
28. Negrier S, Ravaud A. Optimisation of sunitinib therapy in metastatic renal cell carcinoma: adverse-event management. *Eur J Cancer Suppl.* 2007;5(7): 12–19.
29. Robert C, Mateus C, Spatz A, et al. Dermatologic symptoms associated with the multikinase inhibitor sorafenib. *J Am Acad Dermatol.* 2009;60(2): 299–305.
30. Roigas J. Clinical management of patients receiving tyrosine kinase inhibitors for advanced renal cell carcinoma. *Eur Urol Suppl.* 2008;7(9): 593–600.
31. Ivanyi P, Winkler T, Ganser A, et al. Novel therapies in advanced renal cell carcinoma: management of adverse events of sorafenib and sunitinib. *Dtsch Arztebl Int.* 2008;105(13):232–237.
32. Guenova E. Palmar-plantar erythrodysesthsia secondary to sunitinib treatment resulting in necrotic foot syndrome aggravated by background diabetic vascular disease. *Arch Dermatol.* 2008;144(8):1081–1082.
33. Wood LS, Manchen B. Sorafenib: a promising new targeted therapy for renal cell carcinoma. *Clin J Oncol Nurs.* 2007;11(5):649–656.
34. Porta C, Paglino C, Imarisio I, et al. Uncovering Pandora's vase: the growing problem of new toxicities from novel anticancer agents. The case of sorafenib and sunitinib. *Clin Exp Med.* 2007;7(4):127–134.
35. Porta C, Szczylik C. Tolerability of first-line therapy for metastatic renal cell carcinoma. *Cancer Treat Rev.* 2009;35(3):297–307.
36. Rosenbaum SE, Wu S, Newman MA, et al. Dermatological reactions to the multitargeted tyrosine kinase inhibitor sunitinib. *Support Care Cancer.* 2008;16(6):557–566.
37. Wood LS. Targeted therapies for advanced renal cell carcinoma: part II—sorafenib. *Oncology Nursing News.* 2007;(November/December): 37–38.
38. Grunwald V, Heinzer H, Fiedler W. Managing side effects of angiogenesis inhibitors in renal cell carcinoma. *Onkologie.* 2007;30(10):519–524.
39. Autier J, Escudier B, Wechsler J, et al. Prospective study of the cutaneous adverse effects of sorafenib, a novel multikinase inhibitor. *Arch Dermatol.* 2008;144(7):886–892.
40. Arnault JP, Wechsler J, Escudier B, et al. Keratoacanthomas and squamous cell carcinomas in patients receiving sorafenib. *J Clin Oncol.* 2009; 27(23):e59–e61.
41. Dubauskas Z, Kunishige J, Prieto VG, et al. Cutaneous squamous cell carcinoma and inflammation of actinic keratoses associated with sorafenib. *Clin Genitourin Cancer.* 2009;7(1):20–23.
42. Hong DS, Reddy SB, Prieto VG. Cutaneous squamous cell carcinoma and inflammation of actinic keratoses associated with sorafenib. *Arch Dermatol.* 2008;144(6):779–782.
43. Kong HH, Cowen EW, Azad N. Keratocanthomas associated with sorafenib therapy. *J Am Acad Dermatol.* 2007;56(1):171–172.
44. Marquez CB, Smithberger EE, Bair SM. Multiple keratocanthomas arising in the setting of sorafenib therapy: novel chemoprophylaxis with bexarotene. *Cancer Control.* 2009;16(1):66–69.
45. Cherny NI. Evaluation and management of treatment-related diarrhea in patients with advanced cancer: a review. *J Pain Symptom Manage.* 2008; 36(4):413–423.
46. *US PI Afinitor.* http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022334s6lbl.pdf. Accessed November 8, 2010.
47. Bellmunt J. The oncologist's view: targeted therapies in advanced renal cell carcinoma. *Eur Urol Suppl.* 2008;7(2):55–62.
48. Loprinzi CL, Ellison NM, Schaid DJ, et al. Controlled trial of megestrol acetate for the treatment of cancer anorexia and cachexia. *J Natl Cancer Inst.* 1990;82(13):1127–1132.
49. Turner JS, Cheung EM, George J, et al. Pain management, supportive and palliative care in patients with renal cell carcinoma. *BJU Int.* 2007;99(5, pt B):1305–1312.
50. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Cancer-Related Fatigue.* http://www.nccn.org/. Accessed February 17, 2010.

51. Hands DJ, Eccles B, Geldart TR. An underinvestigated toxicity of sunitinib: red cell macrocytosis. *J Clin Oncol.* 2011;29(suppl 7). Abstract 371.
52. Hapani S, Chu D, Wu S. Risk of gastrointestinal perforation in patients with cancer treated with bevacizumab: a meta-analysis. *Lancet Oncol.* 2009;10(6):559–568.
53. Blowers E, Hall K. Managing adverse events in the use of bevacizumab and chemotherapy. *Br J Nurs.* 2009;18(6):351–356.
54. Badgwell BD, Camp ER, Fieg B, et al. Management of bevacizumab-associated bowel perforation: a case series and review of the literature. *Ann Oncol.* 2008;19(3):577–582.
55. Ezzedine S, Bege T, Berdah S, et al. Endoscopic management of colonic perforation owing to angiogenesis inhibitors. *Surg Laparosc Endosc Percutan Tech.* 2010;20(6):e230–e232.
56. Bamias A, Lainakis G, Manios E, et al. Diagnosis and management of hypertension in advanced renal cell carcinoma: prospective evaluation of an algorithm in patients treated with sunitinib. *J Chemother.* 2009;21(3):347–350.
57. Azizi M, Chedid A, Oudard S. Home blood-pressure monitoring in patients receiving sunitinib. *New Engl J Med.* 2008;358(1):95–97.
58. Jain M, Townsend RR. Chemotherapy agents and hypertension: a focus on angiogenesis blockade. *Curr Hypertens Rep.* 2007;9(4):320–328.
59. Roodhart JM, Langenberg MH, Witteveen E, et al. The molecular basis of class side effects due to treatment with inhibitors of the VEGF/VEGFR pathway. *Curr Clin Pharmacol.* 2008;3(2):132–143.
60. Ivanyi P, Pencs N, Winkler T, et al. Cardiovascular AE, hypertension and antihypertensive therapy during sunitinib treatment in patients with metastatic renal cell carcinoma (mRCC) - a retrospective analysis of 72 patients. *Ann Oncol.* 2011;21(suppl 8):viii297. Abstract 946.
61. Hutson TE, Figlin RA, Kuhn JG, et al. Targeted therapies for metastatic renal cell carcinoma: an overview of toxicity and dosing strategies. *Oncologist.* 2008;13(10):1084–1096.
62. Chen MH. Cardiac dysfunction induced by novel targeted anticancer therapy: an emerging issue. *Curr Cardiol Rep.* 2009;11(3):167–174.
63. Hambleton J, Skillings J, Kabbinavar F, et al. Safety of low-dose aspirin (ASA) in a pooled analysis of 3 randomized, controlled trials (RCTs) of bevacizumab (BV) with chemotherapy (CT) in patients (pts) with metastatic colorectal cancer (mCRC). *J Clin Oncol.* 2005;23(16S):3554.
64. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest.* 2008;133(6 Suppl):381S–453S.
65. Elice F, Rodeghiero F, Falanga A, et al. Thrombosis associated with angiogenesis inhibitors. *Best Pract Res Clin Haematol.* 2009;22(1):115–128.
66. Thibault F, Billemont B, Richard F, et al. Perioperative use and surgical complications of sunitinib in metastatic renal cell carcinoma. *J Urol.* 2008;179(4):169.
67. White DA, Camus P, Endo M, et al. Noninfectious pneumonitis after everolimus therapy for advanced renal cell carcinoma. *Am J Resp Crit Care Med.* 2010;182(3):396–403.
68. Goodman VL, Wang Q, Pandite LN, et al. Incidence and management of hepatic toxicity in pazopanib-treated patients. *Ann Oncol.* 2011;21(suppl 8):viii282. Abstract 904P.
69. Xu CF, Reck BH, Goodman VL, et al. Association of the hemochromatosis gene with pazopanib-induced transaminase elevation in renal cell carcinoma. *J Hepatol.* 2011;54(6):1237–1243.
70. Xu CF, Reck BH, Xue Z, et al. Pazopanib-induced hyperbilirubinemia is associated with Gilbert's syndrome UGT1A1 polymorphism. *Br J Cancer.* 2010;102(9):1371–1377.
71. Lacouture ME, Wu S, Robert C, et al. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. *Oncologist.* 2008;13(9):1001–1011.
72. Wood LS, Lemont H, Jatoi A, et al. Practical considerations in the management of hand-foot skin reaction caused by multikinase inhibitors. *Commun Oncol.* 2010;7(1):23–29.
73. Robert C, Arnault JP, Mateus C. RAF inhibition and induction of cutaneous squamous cell carcinoma. *Curr Opin Oncol.* 2011;23(2):177–182.
74. Hogan CM. The nurse's role in diarrhea management. *Oncol Nurs Forum.* 1998;25(5):879–886.
75. Tuchmann L, Engleking C. Cancer-related diarrhea. In: Gates RA, Fink RM, eds. *Oncology Nursing Secrets.* 2nd ed. Philadelphia, PA: Hanley and Belfus; 2001:310–322.
76. Benson AB III, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol.* 2004;22(14):2918–2926.
77. Richardson G, Dobish R. Chemotherapy induced diarrhea. *J Oncol Pharm Pract.* 2007;13(4):181–198.
78. O'Brien BE, Kaklamani VG, Benson AB III. The assessment and management of cancer treatment-related diarrhea. *Clin Colorectal Cancer.* 2005;4(6):375–381.
79. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2009;27(22):3584–3590.
80. Escudier B, Ravaud A, Oudard S, et al. Phase-3 randomised trial of everolimus (RAD001) vs placebo in metastatic renal cell carcinoma. *Ann Oncol.* 2008;19(s8). Abstract 720.
81. Worthington HV, Clarkson JE, Eden OB. Interventions for preventing oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev.* 2007;(4):CD000978. doi:10.1002/14651858. CD000978.pub4.
82. Arcavi L, Shahar A. [Drug related taste disturbances: emphasis on the elderly]. *Harefuah.* 2003;142(6):446–450.
83. Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet.* 2007;370(9605):2103–2111.
84. Andrew IM, Waterfield K, Hildreth AJ, et al. Quantifying the impact of standardized assessment and symptom management tools on symptoms associated with cancer-induced anorexia cachexia syndrome. *Palliat Med.* 2009;23(8):680–688.
85. Berk L, James J, Schwartz A, et al. A randomized, double-blind, placebo-controlled trial of a beta-hydroxyl beta-methyl butyrate, glutamine, and arginine mixture for the treatment of cancer cachexia (RTOG 0122). *Support Care Cancer.* 2008;16(10):1179–1188.
86. Fearon KC, Barber MD, Moses AG, et al. Double-blind, placebo-controlled, randomized study of eicosapentaenoic acid diester in patients with cancer cachexia. *J Clin Oncol.* 2006;24(21):3401–3407.
87. Lesniak W, Bala M, Jaeschke R, et al. Effects of megestrol acetate in patients with cancer anorexia-cachexia syndrome—a systematic review and meta-analysis. *Pol Arch Med Wewn.* 2008;118(11):636–644.
88. Madeddu C, Maccio A, Panzone F, et al. Medroxyprogesterone acetate in the management of cancer cachexia. *Expert Opin Pharmacother.* 2009;10(8):1359–1366.
89. Mazzotta P, Jeney CM. Anorexia-cachexia syndrome: a systematic review of the role of dietary polyunsaturated Fatty acids in the management of symptoms, survival, and quality of life. *J Pain Symptom Manage.* 2009;37(6):1069–1077.
90. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med.* 2007;356(2):115–124.
91. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol.* 2009;27(20):3312–3318.
92. Kumar R, Crouthamel MC, Rominger DH, et al. Myelosuppression and kinase selectivity of multikinase angiogenesis inhibitors. *Br J Cancer.* 2009;101(10):1717–1723.
93. Rini BI, Tamaskar I, Shaheen P, et al. Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst.* 2007;99(1):81–83.
94. Wolter P, Stefan C, Decallonne B, et al. The clinical implications of sunitinib-induced hypothyroidism: a prospective evaluation. *Br J Cancer.* 2008;99(3):448–454.
95. Riesenbeck LM, Bierer S, Hoffmeister I, et al. Hypothyroidism correlates with a better prognosis in metastatic renal cancer patients treated with sorafenib or sunitinib. *World J Urol.* 2011;29(6):807–813.
96. Shinohara N, Takahashi M, Kamishima T, et al. The incidence and mechanism of sunitinib-induced thyroid atrophy in patients with metastatic renal cell carcinoma. *Br J Cancer.* 2011;104(2):241–247.

97. Tamaskar I, Bukowski R, Elson P, et al. Thyroid function test abnormalities in patients with metastatic renal cell carcinoma treated with sorafenib. *Ann Oncol.* 2008;19(2):265–268.
98. Miyake H, Kurahashi T, Yamanaka K, et al. Abnormalities of thyroid function in Japanese patients with metastatic renal cell carcinoma treated with sorafenib: a prospective evaluation. *Urol Oncol.* 2010;28(5):515–519.
99. Flaig TW, Kim FJ, Schoen J, et al. Colonic pneumatosis and intestinal perforations with sunitinib treatment for renal cell carcinoma. *Invest New Drugs.* 2009;27(1):83–87.
100. Mancia G, De Backer G, Dominiczak A, et al. 2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens.* 2007;25(6):1105–1187.
101. Brenner BM, Cooper ME, de ZD, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* 2001;345(12):861–869.
102. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* 2001;345(12):851–860.
103. Wu S, Chen JJ, Kudelka A, et al. Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis. *Lancet Oncol.* 2008;9(2):117–123.
104. Dirix LY, Maes H, Sweldens C. Treatment of arterial hypertension (AHT) associated with angiogenesis inhibitors. *Ann Oncol.* 2007;18(6):1121–1122.
105. Oliver JJ, Melville VP, Webb DJ. Effect of regular phosphodiesterase type 5 inhibition in hypertension. *Hypertension.* 2006;48(4):622–627.
106. Langenberg MH, van Herpen CM, De Bono J, et al. Effective strategies for management of hypertension after vascular endothelial growth factor signaling inhibition therapy: results from a phase II randomized, factorial, double-blind study of Cediranib in patients with advanced solid tumors. *J Clin Oncol.* 2009;27(36):6152–6159.
107. Miura S, Fujino M, Matsuo Y, et al. Nifedipine-induced vascular endothelial growth factor secretion from coronary smooth muscle cells promotes endothelial tube formation via the kinase insert domain-containing receptor/fetal liver kinase-1/NO pathway. *Hypertens Res.* 2005;28(2):147–153.
108. Altena R, de Vries EG, Gietema JA, et al. Cardiovascular toxicity caused by cancer treatment: strategies for early detection. *Lancet Oncol.* 2009;10(4):391–399.
109. Force T, Kerkelae R. Cardiotoxicity of the new cancer therapeutics—mechanisms of, and approaches to, the problem. *Drug Discov Today.* 2008;13(17–18):778–784.
110. Telli ML, Witteles RM, Fisher GA, et al. Cardiotoxicity associated with the cancer therapeutic agent sunitinib malate. *Ann Oncol.* 2008;19(9):1613–1618.
111. Chen MH, Rupnick MA, Chu TF, et al. Cardiotoxicity associated with sunitinib—Authors' reply. *Lancet.* 2008;371(9620):1245.
112. Chu TF, Rupnick MA, Kerlela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet.* 2007;370(9604):2011–2019.
113. Wong MK, Jarkowski A. Response to sorafenib after sunitinib-induced acute heart failure in a patient with metastatic renal cell carcinoma: case report and review of the literature. *Pharmacotherapy.* 2009;29(4):473–478.
114. Margulis V, Matin SF, Tannir N, et al. Surgical morbidity associated with administration of targeted molecular therapies before cytoreductive nephrectomy or resection of locally recurrent renal cell carcinoma. *J Urol.* 2008;180(1):94–98.
115. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med.* 2007;356(2):125–134.
116. Gobel BH. Nursing considerations of bevacizumab use in multiple tumor types. *Oncol Nurs Forum.* 2007;34(3):693–701.
117. Gordon MS, Margolin K, Talpaz M, et al. Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. *J Clin Oncol.* 2001;19(3):843–850.
118. Massard C, Zonierek J, Gross-Goupil M, et al. Incidence of brain metastases in renal cell carcinoma treated with sorafenib. *Ann Oncol.* 2010;21(5):1027–1031.
119. Ranze O, Hofmann E, Distelrath A, et al. Renal cell cancer presented with leptomeningeal carcinomatosis effectively treated with sorafenib. *Onkologie.* 2007;30(8–9):450–451.
120. Stadler WM, Figlin RA, McDermott DF, et al. Safety and efficacy results of the advanced renal cell carcinoma sorafenib expanded access program in North America. *Cancer.* 2010;116(5):1272–1280.
121. Zangari M, Fink LM, Elice F, et al. Thrombotic events in patients with cancer receiving antiangiogenesis agents. *J Clin Oncol.* 2009;27(29):4865–4873.
122. Nalluri SR, Chu D, Keresztes R, et al. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. *JAMA.* 2008;300(19):2277–2285.
123. Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst.* 2007;99(16):1232–1239.
124. Lyman GH, Khorana AA, Falanga A, et al. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. *J Clin Oncol.* 2007;25(34):5490–5505.
125. Khorana AA, Streiff MB, Farge D, et al. Venous thromboembolism prophylaxis and treatment in cancer: a consensus statement of major guidelines panels and call to action. *J Clin Oncol.* 2009;27(29):4919–4926.
126. Cauley DH, Atkinson BJ, Corn PG, et al. Everolimus-associated pneumonitis (EAP) in metastatic renal cell cancer patients (mRCC): a single-center experience. *J Clin Oncol.* 2011;29(suppl 7). Abstract 332.
127. Bjarnason GA, Khalil B, Williams R, et al. Effect of an individualized dose/schedule strategy for sunitinib in metastatic renal cell cancer (mRCC) on progression-free survival (PFS): correlation with dynamic microbubble ultrasound (DCE-US) data. *J Clin Oncol.* 2011;29(suppl 7). Abstract 356.
128. Motzer RJ, Hutson TE, Olsen MR, et al. Randomized phase II multicenter study of the efficacy and safety of sunitinib on the 4/2 versus continuous dosing schedule as first-line therapy of metastatic renal cell carcinoma: renal EFFECT trial. *J Clin Oncol.* 2011;29. Abstract LBA308.

Notes

The authors are grateful to 7.4 Limited for providing editorial support on this review, with financial support from Bayer HealthCare Pharmaceuticals. T. Eisen has received honoraria from Novartis, Astra Zeneca, AVEO, Bayer and Pfizer, has been an advisory board member for Bayer, Pfizer, Novartis, Astra Zeneca and AVEO, and has received research funding from Bayer and Pfizer. C. N. Sternberg has received honoraria from GSK, Pfizer, Novartis, and Bayer. P. Mulders has been an advisory board member for Bayer, Pfizer, Novartis, AstraZeneca, and GSK and has received research funding from Bayer. L. Pyle has received honoraria from Novartis, GSK, Bayer, and Pfizer and has been an advisory board member for Bayer, Pfizer, Novartis, and GSK. S. Zbinder has received a research grant from Roche and has received honoraria from AstraZeneca. B. Escudier has received honoraria from Novartis, Roche, AVEO, Bayer, GSK, and Pfizer and has been an advisory board member for Bayer, Pfizer, Novartis, GSK, and AVEO. C. Robert and H. Izzedine declare no potential conflicts of interest.

Bayer HealthCare Pharmaceuticals supported publication of this article by providing editorial support through literature research on request of the author or via an independent agency directly paid by Bayer. However, Bayer has not generated the content of the publication or made any other financial contributions directly to the author. In addition, Bayer did not have any involvement in the design of the study; the collection, analysis, and interpretation of the data; the writing of the review; or the decision to submit the review for publication.

Affiliations of authors: Cambridge University Health Partners, Cambridge, UK (TE); San Camillo and Forlanini Hospitals, Rome, Italy (CNS); Institut Gustave Roussy, Villejuif, France (CR, BE); Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands (PM); Royal Marsden Hospital, London, UK (LP); University Hospital, Bern, Switzerland (SZ); Pitié-Salpêtrière Hospital, Paris, France (HI).