

## Minireview

# Challenges and opportunities for converting renal cell carcinoma into a chronic disease with targeted therapies

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Optimum efficacy is the primary goal for any cancer therapy, and entails controlling tumour growth and prolonging survival as far as possible. The prognosis for patients with metastatic renal cell carcinoma (mRCC) has greatly improved with the introduction of targeted therapies. This review examines the development and efficacy of targeted agents for the management of mRCC, the challenges offered by their rapid emergence, and discusses how mRCC treatment may evolve in the future. Improvements in progression-free survival and overall survival rates, observed with targeted agents, indicate that it may now be possible to change mRCC from a rapidly fatal and largely untreatable condition into a chronic disease. The major challenges to further advances in targeted therapy for mRCC include overcoming drug resistance, identifying the most effective sequence or combination of targeted agents, optimising clinical trial design and managing the cost of treatment.

*British Journal of Cancer* (2011) **104**, 399–406. doi:10.1038/sj.bjc.6606084 www.bjcancer.com  
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**Keywords:** chronic disease; combinatorial therapy; renal cell carcinoma; sequential therapy; sunitinib malate; targeted agents

Renal cell carcinoma (RCC) accounts for almost 2% of all adult malignancies (Parkin *et al*, 2005). There are 210 000 new cases diagnosed in the world each year, with more than 63 000 of these being in Europe (Parkin *et al*, 2005; Ferlay *et al*, 2007). Worldwide and in Europe, the annual number of deaths from this disease are 100 000 and 26 000, respectively (Ferlay *et al*, 2007). At diagnosis, approximately 20–30% of patients have metastatic renal cell carcinoma (mRCC) (Motzer *et al*, 1996), and a similar percentage of those with initially localised disease will subsequently relapse and develop metastases (Antonelli *et al*, 2007).

Historically, cytokine therapy was the only systemic treatment that had any consistent activity in mRCC. However, whereas cytokine treatment, particularly high-dose interleukin 2, can be associated with complete and durable responses, these occur in only a small proportion of patients (Fisher *et al*, 2000). In addition, cytokine treatment can be associated with substantial toxicity. In a Cochrane review of interferon- $\alpha$  (IFN- $\alpha$ ) for mRCC, median overall survival (OS) for patients treated with this cytokine was found to be 11.4 months, which represented a 3.8-month improvement when compared with patients who received no immunotherapy (Coppin *et al*, 2004). In a randomised phase III study, a median OS of 17.5 months was observed in patients with mRCC, receiving high dose interleukin-2 (IL-2), compared with 13 months, for those treated with a combination of lower dose of IL-2 and IFN- $\alpha$ , but this difference was not statistically significant ( $P=0.211$ ) (McDermott *et al*, 2005). In addition, it has become clear that only patients with good prognostic features are likely to benefit from immunotherapy. This is further supported by the recent results of

McDermott *et al* (2010) who demonstrated a higher response rate in patients, who were selected based on clinical and pathological features, treated with high-dose IL-2 when compared with historical data (28 vs 14%;  $P=0.0016$ ).

The development of targeted agents for the treatment of mRCC has provided physicians with unprecedented opportunities to improve clinical outcomes for patients with mRCC. For example, compared with IFN- $\alpha$  treatment, the oral multi-targeted receptor tyrosine kinase (RTK) inhibitor, sunitinib malate (Sutent; Pfizer Inc., New York, NY, USA) doubled median progression-free survival (PFS) in a phase III trial of patients with previously untreated mRCC (Motzer *et al*, 2007). In addition, sunitinib was associated with median OS of greater than 2 years in this trial and substantial improvements in objective response rates when compared with IFN- $\alpha$  treatment (Motzer *et al*, 2007, 2009).

Optimum efficacy is the primary goal of any cancer treatment and this means controlling tumour growth as far as possible and prolonging survival. The new-targeted agents such as sunitinib, with their improved response and survival rates, have allowed this goal to be realisable for patients with mRCC. We now have the therapeutic tools that could potentially result in mRCC changing from a rapidly fatal, largely untreatable condition, into a chronic disease. Several treatment challenges must be overcome by us to maximise the potential of targeted agents, and these include the identification of predictive molecular markers, drug resistance, the identification of the most effective sequence or combination of targeted agents, efficient clinical trial design and the provision of cost-effective access to treatment for all patients with mRCC.

This review examines the development and efficacy of targeted agents for the management of mRCC, discusses the challenges offered by their rapid emergence and speculates how mRCC treatment might evolve in the future.

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Received 25 August 2010; revised 25 November 2010; accepted 13 December 2010

## DEVELOPMENT AND EFFICACY OF TARGETED AGENTS

Advances in our understanding of the molecular mechanisms associated with RCC have enabled rational targets for systemic therapy to be identified. In clear cell RCC, inactivation of the *von Hippel-Lindau* gene is associated with the accumulation of both hypoxia-inducible factor 1 (HIF-1 $\alpha$ ) and HIF-2 $\alpha$ . HIF-1 $\alpha$  causes transcriptional activation of several genes, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), both of which are implicated in tumour angiogenesis and growth (Krause and Van Etten, 2005). These ligands serve as agonists for their respective RTKs, VEGF receptor (VEGFR) and PDGF receptor (PDGFR). HIF-1 $\alpha$  activity is also regulated by other growth factor and cell adhesion pathways (Motzer and Bukowski, 2006); for example, HIF-1 $\alpha$  is increased in response to growth factor binding to the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (mTOR) and Ras/Raf/mitogen-activated protein kinase signalling pathways. In contrast, HIF2- $\alpha$  has an opposing role to HIF-1 $\alpha$  with regard to gene expression, and promotes enhanced tumour growth (Toschi *et al*, 2008; Biswas *et al*, 2010). Elevation of HIF2- $\alpha$  expression also contributes towards angiogenesis (Toschi *et al*, 2008).

The formation of a multi-molecular complex between mTOR and regulatory-associated protein of mTOR (rapTOR) has a role in cell proliferation, survival and tumour angiogenesis (Le Tourneau *et al*, 2008). Upregulation of VEGF or PDGF can also stimulate activity of mTORC1 (Le Tourneau *et al*, 2008). In addition, mTOR is also able to form a complex with rapamycin-insensitive companion of mTOR (riCTOR) to form mTORC2 (Le Tourneau *et al*, 2008). Development of targeted therapies has focused on mTORC1 and other components of the HIF-1 $\alpha$  signalling pathway, aimed at reducing the effects of growth factors, including VEGF and PDGF.

Sunitinib is a multi-targeted RTK inhibitor, targeting a range of receptors including VEGFR-1, -2 and -3, PDGFR- $\alpha$  and - $\beta$ , glial cell line-derived neurotrophic factor receptor (REarranged during Transfection; RET), the receptor for macrophage colony-stimulating factor 1, FMS-like tyrosine kinase 3 receptor (FLT3) and c-KIT (Motzer *et al*, 2007). Sorafenib (Nexavar; Bayer Healthcare, Leverkusen, Germany) and pazopanib (Votrient; GlaxoSmithKline, Middlesex, UK), are also both oral multi-targeted RTK inhibitors, with sorafenib targeting VEGFR-2 and -3, PDGFR- $\beta$ , FLT3, c-KIT, RET, B-Raf and Raf-1/C-Raf (Escudier *et al*, 2009a) and pazopanib targeting VEGFR-1, -2 and -3, PDGFR- $\alpha$  and - $\beta$  and c-KIT (Sternberg *et al*, 2010a). Temsirolimus (Torisel; Pfizer Inc) and

everolimus (Afinitor; Novartis, Basel, Switzerland) are both mTOR kinase inhibitors (Hudes *et al*, 2007; Motzer *et al*, 2008) and bevacizumab (Avastin; F Hoffmann-La Roche, Basel, Switzerland) is a humanised monoclonal antibody that binds to and neutralises all major isoforms of VEGF-A (Escudier *et al*, 2010a).

Sunitinib is approved multinationally for the treatment of mRCC, and is a reference standard of care for the first-line treatment of patients with mRCC (Escudier *et al*, 2010b). Other targeted agents that are approved in the first-line setting include temsirolimus for the treatment of mRCC patients, with poor prognostic factors, and the combination of bevacizumab plus IFN- $\alpha$ . Sorafenib is approved for patients with mRCC who have failed, or are considered unsuitable for, cytokine therapy. Everolimus is approved for the treatment of patients with mRCC following the failure of treatment with sunitinib or sorafenib (Escudier *et al*, 2010b). Most recently, pazopanib has been approved in the USA for the treatment of advanced RCC, and received conditional approval in Europe for the treatment of advanced RCC in the first-line setting and in patients with previous cytokine therapy. In contrast to sunitinib, sorafenib and pazopanib, temsirolimus and bevacizumab both have single targets and are administered intravenously. Everolimus also has a single target, but is orally administered.

Additional targeted agents are currently under investigation for mRCC. Those in phase III of development include axitinib, an orally administered multi-targeted receptor RTK inhibitor (Rini *et al*, 2007; Rixe *et al*, 2007) and tivozanib, an oral VEGFR-targeted tyrosine kinase inhibitor (Bhargava *et al*, 2009). Both these agents are similar in terms of mechanisms of action to the currently available VEGF-targeted therapies, and differ from these agents on the basis of affinities for the various receptors (Eskens *et al*, 2008; Schmidinger and Bellmunt, 2010). The clinical efficacy demonstrated by the targeted agents approved for the treatment of mRCC, and the most promising of those currently in development, are summarised in Tables 1–3.

## TARGETED AGENTS AND DRUG RESISTANCE

Targeted agents have significantly improved the prognosis for patients with mRCC; however, complete responses are rare and the majority of patients develop drug resistance, as exemplified by the fact that their disease progresses during treatment (Sosman *et al*, 2007). Drug resistance is the underlying reason for the growth and spread of tumours in the presence of systemic treatment, and it is the main barrier against long-term tumour control.

**Table 1** Clinical efficacy data for targeted agents approved in Europe/USA for the treatment of mRCC in the first-line setting

	Number of patients (N)	Median PFS (months)	P-value	Median OS (months)	P-value
Sunitinib (Motzer <i>et al</i> , 2009)	375	11	<0.001	26.4	0.051
vs IFN- $\alpha$	360	5		21.8	0.049 <sup>a</sup>
Temsirolimus <sup>†</sup> (Hudes <i>et al</i> , 2007)	209	5.5	0.0001	10.9	0.0069
vs IFN- $\alpha$	207	3.1		7.3	
Bevacizumab (plus IFN- $\alpha$ ) (Escudier <i>et al</i> , 2010a)	327	10.2	<0.0001	23.3	0.1291
vs IFN- $\alpha$	322	5.4		21.3	
Bevacizumab (plus IFN- $\alpha$ ) (Rini <i>et al</i> , 2009b, 2010b)	369	8.5	<0.0001	18.3	0.069
vs IFN- $\alpha$	363	5.2		17.4	
Sorafenib (Escudier <i>et al</i> , 2009b)	97	5.7	0.504	NR	NA
vs IFN- $\alpha$	92	5.6			
Pazopanib (Sternberg <i>et al</i> , 2010a, b) (overall)	290	9.2	<0.0001	22.9	0.224
vs placebo (overall)	145	4.2		20.5	
Treatment-naïve patients	155	11.1	<0.0001	NR	NA
vs placebo	78	2.8			

Abbreviations: IFN- $\alpha$  = interferon- $\alpha$ ; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival. <sup>a</sup>P-values by pre-planned unstratified and stratified log-rank test, respectively. <sup>†</sup>Patients stratified into the poor-risk prognostic category on the basis of three of six risk features (five pre-defined Memorial Sloan-Kettering Cancer Centre risk factors plus multiple sites of organ metastases).

**Table 2** Clinical efficacy data for targeted agents approved in Europe/USA for the treatment of mRCC in the second-line setting

	Number of patients (N)	Primary treatment	Median PFS (months)	P-value	Median OS (months)	P-value	
Sorafenib (Escudier <i>et al.</i> , 2009a)	451	Systemic therapy with cytokines	5.5	<0.001	17.8	0.0287	
vs placebo	452		2.8		14.3		
Everolimus (Escudier <i>et al.</i> , 2008; Motzer <i>et al.</i> , 2009, 2010) (overall)	272	Previous VEGF inhibitor therapy (sunitinib, sorafenib or both; bevacizumab permitted); systemic therapy with cytokines	4.9	<0.001	14.8	0.177	
vs placebo (overall)	138		1.9		14.4		
refractory to sunitinib	124		3.9		NR		NA
vs placebo	60		1.8				
refractory to sorafenib	77		5.9		NR		NA
vs placebo	42	2.8					
Pazopanib (Sternberg <i>et al.</i> , 2010a, b) (overall)	290	Previous systemic therapy with cytokines	9.2	<0.0001	22.9	0.224	
vs placebo (overall)	145		4.2		20.5		
cytokine-pre-treated patients	135		7.4		NR		NA
vs placebo	67		4.2				

Abbreviations: NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival.

**Table 3** Clinical efficacy data for targeted agents in development for the treatment of mRCC

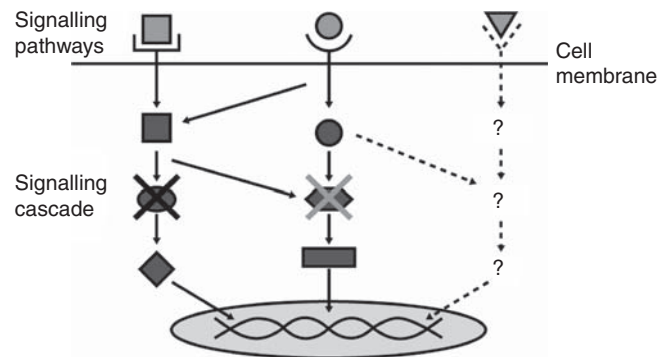
	Study design	Median PFS (months)	P-value	Median OS (months)	P-value
Reyorafenib (Eisen <i>et al.</i> , 2009)	First line, phase II	8.3	NA	NR	NA
Tivozanib (Bhargava <i>et al.</i> , 2009)	First line, phase II	11.8	NA	NR	NA
Axitinib (Rixe <i>et al.</i> , 2007)	Second line, phase II	15.7 <sup>a</sup>	NA	29.9	NA
Axitinib (Rini <i>et al.</i> , 2007; Dutcher <i>et al.</i> , 2008)	Second line, phase II	7.4	NA	NR	NA
Refractory to sunitinib and sorafenib		7.1			
Refractory to cytokines and sorafenib		9			
Refractory to sorafenib		7.7			
Linifanib (Tannir <i>et al.</i> , 2009)	Second line, phase II	5.4	NA	15.7	NA
Cediranib (Mulders <i>et al.</i> , 2009)	First/second line, phase II	12.1	0.017	NR	NA
vs placebo		2.8			

Abbreviations: NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival. <sup>a</sup>Reported as time to progression.

Resistance to targeted agents in mRCC may develop as a result of the multiplicity of pathways involved in regulating HIF-1 $\alpha$  activity, some of which have not yet been identified. A particular targeted agent may effectively inhibit one or more pathways, but resistance can result from the development of other molecular and cellular processes that 'bypass' this effect (Figure 1). These include additional mutations, feedback loops compensating for inhibition through gene upregulation, increased angiogenesis or the activation of downstream mediators (Sosman *et al.*, 2007). Furthermore, some of these bypass mechanisms may not even involve the VEGF pathway. For example, a preclinical study demonstrated that upregulation of proangiogenic pathways, through increased expression of IL-8, contributed towards evasion of anti-angiogenic effects mediated by sunitinib (Huang *et al.*, 2010).

Rini and Flaherty (2008) have described three clinical patterns of resistance in patients with mRCC: a small group (15–20%), which is resistant to therapy from the outset of treatment, a larger group that demonstrates early-tumour regression followed by a short period of stability then disease progression (6–12 months from the start of therapy) and finally a subgroup of patients that exhibit tumour response over several months followed by a prolonged period of stable disease, without the appearance of new lesions.

Additional reasons for the development of resistance to treatment may include pharmacokinetic resistance to treatment whereby the pharmacokinetic activity of the treatment may be affected by interaction with cellular proteins or structure such as transport pumps (Schmidt, 2008). Non-compliance with oral treatment may also result in the development of resistance to treatment (Schmidt, 2008).



**Figure 1** Resistance to targeted agents may occur through target bypass mechanisms. A targeted agent (denoted by X in the figure) may effectively inhibit the signalling cascade of one or more pathway (denoted by the light grey square and circle in the figure). However, the presence of a 'bypass' mechanism may allow this inhibition to be circumvented by signalling along an unknown or unrelated pathway (denoted by the light grey triangle in the figure), resulting in resistance to the targeted therapy.

The mode of action of targeted agents will affect the strategies that will be utilised to overcome drug resistance. Multi-targeted agents may provide the most effective option for combating drug resistance because of involvement of multiple signalling pathways in the pathology of RCC. Differential responses to targeted agents have been observed between tumours within the same patient, and also between tumours within the same organ. This indicates

variances in resistance between tumour clones and the use of multi-targeted agents, such as sunitinib or sorafenib, instead of single-targeted agents, might be most effective at simultaneously blocking, both known and unknown, angiogenic and proliferation pathways.

A major consideration in devising the optimal treatment strategy to overcome drug resistance, and thus optimising long-term therapy with targeted agents in mRCC is how best to use these agents in sequence or in combination. Data in favour of either sequencing or combining targeted agents for mRCC are currently limited, and as discussed below, clinical studies are ongoing to investigate both these approaches.

## SEQUENTIAL THERAPY WITH TARGETED AGENTS

Targeting different pathways through sequential therapy should offer benefit in terms of overcoming resistance to individual agents. It also enables a treatment continuum to be achieved, maintaining patients on treatment without progression for as long as possible. Sequential therapy has the potential to change mRCC into a chronic disease that can be managed for long term through the administration of targeted agents in sequence. It should also enable full dosages of targeted agents to be administered, ensuring that optimal drug levels are achieved without the additional toxicity that often occurs with combinatorial approaches. There is emerging evidence that dose is important with the targeted agents in this disease. The results of a meta-analysis of data from sunitinib studies indicated that higher sunitinib exposure is associated with higher efficacy with respect to longer times to tumour progression and OS (Houk *et al*, 2010). In practice, clinicians are currently using targeted agents in a sequential manner for patients with mRCC, although concerns remain regarding cross-resistance between the different agents, and there are many questions regarding the optimal sequence for obtaining maximal clinical benefit from the available targeted therapies.

Current data indicate that there is a degree of non-cross-resistance between the different targeted agents. A retrospective study by Tamaskar *et al* (2006) found that both sunitinib and sorafenib demonstrated anti-tumour activity in patients refractory to previous anti-angiogenic therapy. In particular, clinical benefit was observed in patients receiving sorafenib following previous therapy with sunitinib and *vice versa*. Similarly, a lack of cross-resistance between sunitinib and sorafenib was observed in another retrospective analysis of 90 patients, supporting sequential use of these agents in the treatment of mRCC (Sablin *et al*, 2007). The results of a randomised phase II study of sorafenib alone and in combination with low-dose IFN- $\alpha$  following previous first-line sunitinib treatment in patients with mRCC are awaited (CONCERT study) (<http://www.clinicaltrials.gov>).

Incomplete cross-resistance has also been demonstrated between sunitinib and bevacizumab. Rini *et al* (2008) treated 61 bevacizumab-refractory patients with sunitinib; an objective response rate of 23% (95% CI: 13.2–35.5) and median PFS of 30.4 weeks (95% CI: 18.3–36.7) were achieved. All these data suggest that resistance to one VEGF-targeted therapy can be overcome by another agent that also targets this pathway.

Interestingly, transient resistance to the same agent has also been observed. In a recent retrospective review of 23 patients, re-challenge with sunitinib in patients with disease progression on sunitinib and other therapies, resulted in 5 patients (22%) achieving PR and 17 patients (74%) achieving SD (Rini *et al*, 2010 a). Re-challenge was associated with a median PFS of 7.2 months compared with 13.7 months on initial treatment ( $P=0.04$ ). In addition, patients with more than 6 months between sunitinib treatments had significantly longer PFS than those receiving re-treatment with sunitinib within 6 months (16.5 and 6.0 months, respectively). The results described here indicate the potential for

re-treating with an agent despite the occurrence of resistance at first treatment and have implications for achieving a continuum of treatment in these patients.

The first randomised phase III study to investigate sequential targeted therapy in mRCC showed clinical efficacy for the sequence of sunitinib or sorafenib, followed by everolimus (RECORD-1) (Escudier *et al*, 2008; Motzer *et al*, 2008, 2010). In this study, patients who had failed earlier anti-VEGF therapy, 71% of whom had received sunitinib previously, were treated with either everolimus or placebo. The median PFS was 4.9 vs 1.9 months for those treated with everolimus or placebo, respectively ( $P<0.001$ ; hazard ratio (HR) 0.33 (95% CI: 0.25–0.43)). Improvements in PFS with everolimus relative to placebo were observed across all Memorial Sloan–Kettering Cancer Center (MSKCC) prognostic risk groups. Patients pre-treated with sunitinib achieved a median PFS of 3.9 vs 1.8 months when treated with everolimus or placebo, respectively ( $P<0.001$ ; HR 0.34 (95% CI: 0.23–0.51)). Everolimus-treated sorafenib-refractory patients achieved a median PFS of 5.9 vs 2.8 months for those treated with placebo ( $P<0.001$ ; HR 0.25 (95% CI: 0.16–0.42)). Patients refractory to both sunitinib and sorafenib achieved a median PFS of 4.0 months when treated with everolimus compared with 1.8 months for those treated with placebo ( $P<0.001$ ; HR 0.32 (95% CI: 0.19–0.54)).

Sequential treatment has also been investigated with the VEGF inhibitor, axitinib. In a phase II study, median PFS was 7.1, 9.0, and 7.7 months for those mRCC patients who had received previous treatment with sunitinib and sorafenib, cytokines and sorafenib, or sorafenib alone, respectively (Dutcher *et al*, 2008). The phase III AXIS study investigates axitinib in 540 patients with mRCC who have experienced failure on a first-line treatment, including sunitinib, bevacizumab plus IFN- $\alpha$ , temsirolimus or cytokines (<http://www.clinicaltrials.gov>). A phase III study comparing sorafenib with temsirolimus (INTORSECT study) will also investigate sequential therapy in an estimated 440 patients who have failed first-line sunitinib (Bhojani *et al*, 2008).

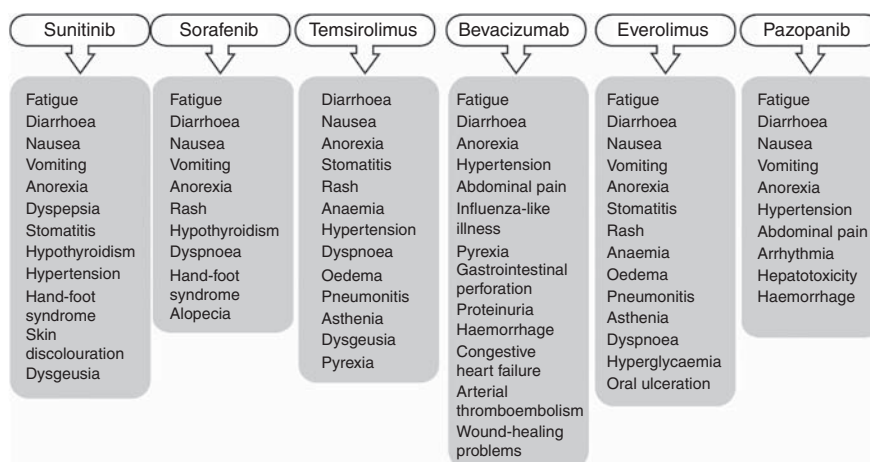
In the context of sequential therapy, adequate management of treatment-related toxicity can allow patients to remain on treatment for long periods and help maximise the clinical benefit of targeted agents. The toxicity profile of each of the targeted agents approved for the treatment of mRCC is well defined (Figure 2), and strategies to manage treatment-related adverse events are being refined (Bhojani *et al*, 2008). In addition, clinicians' familiarity with targeted agents is increasing and this experience is accompanied by the ability to manage treatment-related adverse events more effectively. Effective therapy management involves optimisation of dose, maximising treatment duration and a proactive approach to the management of toxicities.

## COMBINATION THERAPY WITH TARGETED AGENTS

Combining therapeutic agents may also overcome drug resistance and allow for the simultaneous inhibition of multiple signalling pathways. These combinations could consist of agents blocking a single target, single and/or multi-targeted agents, and targeted agents combined with cytotoxics, cytokines or other therapeutic agents. This approach presupposes knowledge of all the signalling pathways involved in the development and continuing growth of a tumour. Furthermore, any potential clinical benefit must be balanced against the potential increase in toxicity associated with combining therapeutic agents.

Combination therapies are currently under investigation in several ongoing and planned clinical trials. These include several studies evaluating bevacizumab in combination with temsirolimus, everolimus and sorafenib (Merchan *et al*, 2007; Sosman *et al*, 2008; Whorf *et al*, 2008). Two phase I studies have evaluated sunitinib in combination with bevacizumab for the treatment of solid tumours,





**Figure 2** Most common and side effects of interest reported with the six licensed targeted agents for mRCC.

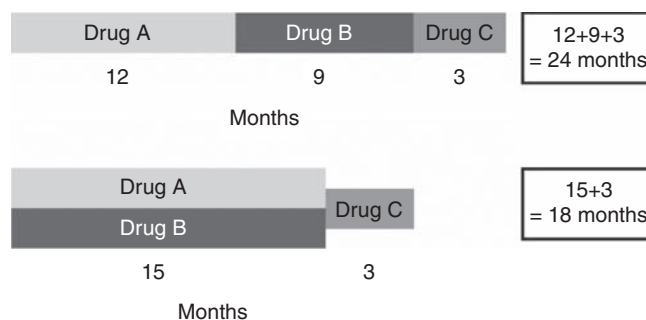
including mRCC (Feldman *et al*, 2007; Rini *et al*, 2010c). Results from these studies have noted that the combination is associated with significant toxicity at full-doses of sunitinib and bevacizumab (Feldman *et al*, 2007; Rini *et al*, 2009a). Similarly, treatment of patients with mRCC using sorafenib in combination with bevacizumab does not seem to be possible at full doses of both drugs (Sosman *et al*, 2006). A further phase I study, in which temsirolimus was combined with sunitinib, was terminated because of dose-limiting toxicity observed at low-starting doses of both agents (Patel *et al*, 2009). Sorafenib plus IFN- $\alpha$ 2b demonstrated clinical activity for the first-line treatment of patients with mRCC, but the toxicity profile of this combination has limited its development in relation to the use of full doses of both these agents within such a combination (Ryan *et al*, 2007). Another study, evaluating the efficacy of bevacizumab combined with everolimus demonstrated clinical activity of the combination for the treatment of patients with advanced RCC, although the efficacy results did not demonstrate a clear advantage for the combination over single agent, sequential treatment and the occurrence of grades 3–4 proteinuria was higher than expected in this study (Hainsworth *et al*, 2010). The results of these early studies demonstrate the potential for detrimental effects for the combination of therapeutic agents. Further larger studies are required to determine the clinical applicability if any, of other targeted agent combinations.

It is also important to consider the therapeutic options that are possible or available following the use of combination-targeted agent therapy. The development of resistance to combination-targeted therapy could negatively impact subsequent treatment. This theoretical consideration relates to the possibility that combination therapy will 'use' up active treatment options, and denies the potential for the repeated 'beneficial' interventions that the single-agent sequential therapy strategy affords (Figure 3).

## TARGETED AGENTS AND CLINICAL TRIAL DESIGN

The approval of sunitinib, sorafenib, temsirolimus, everolimus, bevacizumab plus IFN- $\alpha$  and pazopanib in Europe for the treatment of mRCC, resulted in the establishment of evidence-based recommendations and a treatment algorithm that can be used to achieve optimal clinical benefit with these agents. Data from randomised phase III clinical trials were, of course, an essential element in this process (Escudier *et al*, 2010b).

A large number of new targeted therapeutic compounds are currently under investigation for mRCC. Using traditional 'pick the winner' trials to demonstrate the efficacy of these agents



**Figure 3** Treatment strategies with targeted agents involve a sequential or a combinatorial approach; single-agent sequential therapy may cause tumour shrinkage but may also slow disease progression and, therefore, turn mRCC into a chronic disease.

in mRCC could result in the failure of some compounds, as current trial designs and statistical methods may not be sensitive enough to evaluate their therapeutic benefits, particularly as they relate to subgroups of mRCC patients, for example, those with comorbidities, histological and molecular subtypes.

In addition, the end points used in phase II and III clinical trials might not always be appropriate for assessing the efficacy of new agents (Medina *et al*, 2007). Standard cytotoxic agents rely on response rates, time to tumour progression, PFS and OS as clinical end points to assess efficacy. Targeted therapies may have both a cytotoxic and a cytostatic effect, complicating assessment of response to treatment. As such, clinical benefit consisting of a partial response and/or disease stabilisation, that is, 'slowing' of disease progression could be a clinically relevant new parameter of efficacy. It is this concept, together with the strategy of single-agent sequential therapy, which could transform mRCC into a chronic condition (Figure 3). The most appropriate end points for assessing efficacy of new targeted agents are currently under debate. Biomarkers serving as surrogates for efficacy, functional imaging technology and a focus on new clinical end points, are all required to help further develop this area of novel therapeutics (Medina *et al*, 2007; Sessa *et al*, 2008).

Biomarkers may identify patients with the potential to benefit from targeted therapy, and may be predictive of response, allowing a more individualised approach to prognostication and treatment. The expression of several molecular markers, including circulating VEGF, endostatin and cell surface markers, such as CD31, may all be relevant in this context (Sessa *et al*, 2008). These biomarkers may be useful in predicting treatment outcomes in mRCC, but they

have not yet been validated for use in routine clinical practice. Imaging studies can also contribute towards determining the efficacy of an agent under development, providing useful information regarding early-treatment response by monitoring alterations in tumour vasculature and angiogenesis (Sessa *et al*, 2008). However, the implementation of multiple assessments for each patient could prove to be prohibitively costly (Sessa *et al*, 2008).

## ACCESS TO TARGETED AGENTS

Considerations of cost can impact the availability, timing and duration of treatment with targeted therapies. It may also influence the choice of treatment strategy used to overcome drug resistance and how response to therapy is assessed. Commissioners and providers of healthcare are increasingly looking to achieve the most cost-effective outcomes by balancing clinical efficacy against patient management costs, for example, costs of managing adverse events and drug pricing. Recently, the cost-effectiveness of sunitinib for the first-line treatment of patients with mRCC was evaluated by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom. The NICE Assessment Group developed an analysis model to evaluate the cost-effectiveness of sunitinib in comparison with IFN- $\alpha$  as well as the other therapies approved for the treatment of mRCC, and concluded that sunitinib provided a cost-effective option for the treatment of patients with mRCC in the first-line setting.

The NICE finding mirrors the economic analyses conducted using data from phase II and III trials of sunitinib, sorafenib, bevacizumab plus IFN- $\alpha$  and temsirolimus vs IFN- $\alpha$  as first-line therapy for patients with mRCC in the USA, Sweden and Spain (Oudard *et al*, 2010). On the basis of indirect treatment comparisons, these analyses identified sunitinib as a cost-effective alternative to sorafenib, bevacizumab plus IFN- $\alpha$  and temsirolimus in the first-line treatment of patients with mRCC. Cost-effectiveness ratios of sunitinib vs other therapies were within

the established threshold that society is willing to pay for health benefits.

## CONCLUSION

The development of targeted agents has substantially improved the prognosis for patients with mRCC and has the potential to convert mRCC into a chronic disease.

Challenges in achieving this goal include:

- identifying and optimising the most appropriate sequence or combination of agents.
- development of molecular biomarkers to better identify the patients who are likely to benefit from a particular agent.
- imaging techniques as predictive markers of efficacy to minimise the time on treatment for those patients who will not respond to a particular agent.
- developing appropriate clinical trial designs and statistical methods to test new therapies.
- overcoming drug resistance by more new agents, or sequential or combination therapies.
- managing the cost barriers against treatment.

## ACKNOWLEDGEMENTS

Medical writing support was provided by Minal Kotecha at ACUMED (Tytherington, UK) and was funded by Pfizer Inc. MG is funded by the NIHR (UK) as part of the Royal Marsden Hospital Biomedical Research Centre Grant.

## Conflict of interest

Martin Gore has received honoraria from, and served on, the Speakers Bureau and Advisory Boards of Pfizer, Bayer, Wyeth, Roche and GSK. James Larkin has received honoraria from, and served on, the advisory boards of Pfizer, Bayer, GSK, AVEO and Novartis.

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