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REVIEW

Maximising the duration of disease control in metastatic renal cell carcinoma with targeted agents: an expert agreement

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Abstract With six targeted agents approved (sorafenib, sunitinib, temsirolimus, bevacizumab [+interferon], everolimus and pazopanib), many patients with metastatic renal cell carcinoma (mRCC) will receive multiple therapies. However, the optimum sequencing approach has not been defined. A group of European experts reviewed available data and shared their clinical experience to compile an expert agreement on the sequential use of targeted agents in mRCC. To date, there are few prospective studies of sequential therapy. The mammalian target of rapamycin (mTOR) inhibitor everolimus was approved for use in patients who failed treatment with inhibitors of vascular endothelial growth factor (VEGF) and VEGF receptors (VEGFR) based on the results from a Phase III placebo-controlled study; however, until then, the only licensed agents across the spectrum of mRCC were VEGF(R) inhibitors (sorafenib, sunitinib and bevacizumab + interferon), and as such, a large body of evidence has accumulated regarding their use in sequence. Data show that sequential use of VEGF(R) inhibitors may be an effective treatment strategy to achieve prolonged clinical benefit. The optimal place of each targeted agent in the treatment sequence is still unclear, and data from large prospective studies are needed. The Phase III AXIS study of second-line sorafenib vs. axitinib (including post-VEGF(R) inhibitors) has completed, but the data are not yet published; other ongoing studies include the Phase III SWITCH study of sorafenib–sunitinib vs. sunitinib–sorafenib (NCT00732914); the Phase III 404 study of temsirolimus vs. sorafenib post-sunitinib (NCT00474786) and the Phase II RECORD 3 study of sunitinib–everolimus vs. everolimus–sunitinib (NCT00903175). Until additional data are available, consideration of patient response and tolerability to treatment may facilitate current decision-making regarding when to switch and which treatment to switch to in real-life clinical practice.

Keywords RCC · Sequence · Renal cell carcinoma · Tyrosine kinase inhibitor · Sorafenib · Sunitinib · Pazopanib · Bevacizumab · Everolimus · Temsirolimus

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Introduction

Metastatic renal cell carcinoma (mRCC) is an incurable disease in most cases, and as such, the aim of treatment is to prolong progression-free survival (PFS), maintain patients' quality of life and ultimately prolong overall survival (OS). Six targeted agents—sorafenib, sunitinib, temsirolimus, bevacizumab (in combination with interferon), everolimus and pazopanib—have been introduced for the treatment of advanced and/or metastatic RCC; all of these agents have demonstrated an increase in PFS [1–7]. Few of these studies have reported improvements in OS; however, this mainly relates to the confounding effects of crossover to active treatment from the placebo/comparator arm. The availability of so many agents means that many patients will likely receive treatment with multiple therapies. Indeed, how to use these agents in sequence, and how to expose patients to as many agents as possible, is an ongoing debate among the medical community and seems a logical approach to optimise patient outcomes.

Data from prospective and retrospective studies have shown that disease control may be prolonged by sequencing agents in patients with mRCC [5, 8–13], and so support this approach. As a result, several larger clinical studies, prospectively evaluating different treatment sequences, have been initiated or are planned. However, with several targeted agents now available, a Phase III study for another (axitinib) completed with data pending [14], and other agents in late-stage clinical development in mRCC (including tivozanib [15], and dovitinib [16]), it will not be possible to assess every hypothetical sequence combination in clinical trials—indeed, to evaluate the six approved agents in addition to the two late-stage investigational agents, axitinib and tivozanib, in every possible sequence, more than 40,000 trial arms would be required! Moreover, a 'one size fits all' approach may be inappropriate; instead, patient and disease characteristics, and treatment aims, should all be considered in order to tailor treatment to each individual [17]. To do this, we must review all available evidence with a view to identifying key considerations that could facilitate treatment decisions and allow us to maximise the duration of disease stabilization for all patients with mRCC.

Against this background, we convened to assess and discuss results available in the scientific literature for the treatment of mRCC with targeted agents. We used these data together with our own clinical experience to consider how we might optimise using these agents in sequence. Here, we present our expert opinion regarding the sequential use of targeted agents in patients with mRCC.

Methods

In January 2011, an expert panel including medical oncologists from across Europe considered the data of patients with mRCC following single as well as sequential use of targeted agents. This included preclinical models of resistance to molecularly targeted agents, and data from retrospective and prospective studies, as well as from our own clinical practice, for licensed agents and those in clinical development in mRCC. We shared our expert opinion on these data and also considered the unanswered questions related to the optimum sequential use of targeted agents in mRCC.

Putative mechanisms of resistance to targeted therapies in RCC

RCC is a highly vascularised malignancy; therefore, anti-angiogenesis via blockade of vascular endothelial growth factor (VEGF) or the VEGF receptors (VEGFR) is an important strategy in the treatment of this disease. However, unlike other tumour types, which are thought to exhibit increased angiogenesis mainly as a result of hypoxia, angiogenic mechanisms in clear cell RCC are thought to be largely mediated by inactivation of the tumour suppressor gene, von Hippel Lindau (*VHL*) [18]. This gene encodes the VHL protein, which plays a key role in the degradation of hypoxia-inducible factor (HIF). *VHL* loss results in defective VHL protein and activated HIF, which translocates to the nucleus, resulting in transcription of various genes, including *VEGF*, platelet-derived growth factor (*PDGF*) and transforming growth factor alpha (*TGF-α*), all of which play a central role in angiogenesis and tumour progression [18].

Resistance to VEGF(R)-targeted agents

Targeted agents, such as sorafenib and sunitinib, are thought to exert a significant proportion of their therapeutic efficacy by reducing tumour angiogenesis via VEGF(R) blockade. Intrinsic resistance to VEGF(R)-targeted agents is uncommon in clear cell RCC [18]. Moreover, the development of resistance to VEGF(R)-targeted agents is also unlikely to be related to mutations in the VEGF receptors, since they are genetically stable [19]. However, given the angiogenic mechanisms in RCC described above, it is possible that acquired resistance may occur as a result of VHL-mediated upregulation of other pro-angiogenic proteins in addition to VEGF, which may provide a reversible mechanism of 'escape' for the tumour and continued angiogenesis via a switch in the cellular pathways utilised [18].

Resistance to mTOR inhibitors

Mammalian target of rapamycin (mTOR) is also a therapeutic target in RCC, with the mTOR inhibitors everolimus and temsirolimus among the treatment options for patients with advanced-stage disease. However, treatment with these agents is also associated with the development of resistance [18]. Both everolimus and temsirolimus act by blocking mTOR from interacting with its target, S6 kinase 1 (S6K1). This prevents the activation of ribosomal S6 protein, ribosomal synthesis and subsequent transcription of proteins involved in the regulation of cell growth, cell cycle progression and cellular metabolism [20]. However, as S6K1 also has a negative feedback effect on Akt, mTOR inhibition may enhance Akt activity with the potential to promote cancer cell survival [20]. In addition, as both everolimus and temsirolimus only inhibit the mTORC1 complex, this could lead to a compensatory upregulation of mTORC2, resulting in further Akt and HIF activation and continued tumour cell growth and angiogenesis [18]. For this reason, mTOR inhibitors ultimately also target angiogenesis.

Overcoming resistance to targeted therapies

Collectively, these findings indicate that all targeted agents in RCC have 'escape' pathways through which resistance to treatment may be mediated. However, evidence from a preclinical study of sunitinib-resistant skin metastases transplanted into nude mice has highlighted the importance of the tumour microenvironment—in the mice, the tumours were once again sensitive to sunitinib [21]. Similarly, in xenograft models, sorafenib-resistant tumours reacquired sorafenib sensitivity when reimplanted in untreated mice [22]. These data suggest that a change in the tumour microenvironment may 'reset' the responsiveness of the tumour to targeted therapies. This could be achieved either by providing a treatment break or by switching to another targeted therapy, both of which are therefore important considerations in establishing the optimum use of targeted agents in mRCC.

Targeted agents in sequence

VEGF(R)-targeted agents in sequence

There is an increasing body of evidence to suggest that the sequential use of VEGF(R)-targeted agents is associated with continued clinical benefit, indicating that there is no absolute cross-resistance between these agents [11]. This may be explained, at least in part, by the fact that each VEGF(R) inhibitor has a different molecular target profile (Table 1A) as well as different binding affinities for shared molecular targets (Table 1B). As acquired resistance to VEGF(R) inhibitors is thought to occur as a result of upregulation of a range of angiogenic factors to allow continued angiogenesis, a switch in VEGF(R) inhibitor may result in a change in molecular targets that is sufficient to allow continued anti-angiogenesis.

Sorafenib and sunitinib in sequence

The majority of clinical evidence to support the efficacy of switching from one VEGF(R) inhibitor to another at progression comes from studies of the approved VEGFR–tyrosine kinase inhibitors (TKIs), sorafenib and sunitinib. These include four prospective studies, thirteen retrospective studies, and the sorafenib European expanded access programme, and collectively include data from 1157 patients (Table 2).

The four prospective studies all evaluated sorafenib as second-line therapy and reported progression-free survival (PFS) benefits in this setting ranging from 3.7 to ≥8 months [23–26]. Similarly, data from retrospective studies all

Table 1 Differences in (A) the molecular target profile of VEGFR–TKIs and (B) binding affinities of shared molecular targets

A

Sunitinib targets [53]	Sorafenib targets [54, 55]	Pazopanib targets [56]	Axitinib targets [57]
PDGFR-β	PDGFR-β	PDGFR-β	PDGFR-β
c-KIT	c-KIT	c-KIT	c-KIT
FLT-3	FLT-3		
RET	RET		
VEGFR-2, -3	VEGFR-2, -3	VEGFR-2, -3	VEGFR-2, -3
VEGFR-1		VEGFR-1	VEGFR-1
PDGFR-α		PDGFR-α	PDGFR-α
	c-RAF		
	b-RAF		
CSF-1R		CSF-1R	

B

Target	IC_{50} (nM)			
	Sunitinib [58]	Sorafenib [55]	Pazopanib [56]	Axitinib [58]
VEGFR-1	2	–	10	1.2
VEGFR-2	10	90	30	0.25
VEGFR-3	17	20	47	0.29
PDGFR-β	8	57	84	1.7
EGFR	880	>10,000	>20,000	–
c-KIT	10	68	74	1.6
FGFR1	880	580	140	230
Flt-3	14	58	>20,000	–
c-RAF	–	6	–	–
CSF-1R	100	–	146	–

Table 2 Summary of studies evaluating the sequential use of sorafenib and sunitinib in mRCC

Study	Number of patients	
	SuSo	SoSu
Prospective studies		
Di Lorenzo (phase II) [23]	52	–
Garcia (phase II) [24]	27	–
Mancuso et al. (phase II) [25]	13	–
Sepulveda et al. (prospective) [26]	20	–
EU-ARCCS (expanded access) [10]	69	–
Retrospective studies		
Buchler [27]	138	122
Choueiri [28]	7	31
Dudek [29]	20	29
Elfiky [59]	–	62
Herrmann [52]	54	33
Heuer [35]	–	44
Kontovinis [60]	35	–
Porta [13]	99	90
Richter [31]	5	5
Sablin [32]	22	68
Tamaskar [33]	5	4
Wang [36]	28	53
Zimmermann [34]	–	22
Total	594	563
	1,157	

SuSo Sunitinib → Sorafenib, *SoSu* Sorafenib → Sunitinib

showed that further PFS benefits were achieved by switching from one VEGFR–TKI to the other, either with sorafenib followed by sunitinib (SoSu) or sunitinib followed by sorafenib (SuSo). Notably, they also suggested that the observed PFS benefit was generally greater with SoSu than with SuSo [10, 13, 27–36] (Fig. 1). This hypothesis, which may have a sound biological basis [37], is being evaluated further in the ongoing randomized, Phase III, open-label SWITCH study [38]; the primary objective is to determine whether SoSu is superior to SuSo in terms of PFS from randomization to progression/death on second-line therapy in treatment-naïve patients with mRCC.

Data for other VEGF(R) inhibitors in sequence

Initial Phase II data for the investigational VEGF(R) inhibitors axitinib and linifanib also suggest no absolute cross-resistance, with median PFS 5.4–7.4 in patients refractory to VEGF(R) inhibitors (Table 3) [12, 39]. In addition, the Phase III AXIS study of axitinib compared with sorafenib in patients who had progressed on one prior therapy, which could include a VEGF(R) inhibitor [14], has completed; the data are expected to be presented at the 2011 meeting of the American Society of Clinical Oncology. The licensed agent, pazopanib, has also shown efficacy post-VEGF(R) inhibitor therapy—in an ongoing Phase II study of patients with mRCC who progressed on or were intolerant to first-line sunitinib or bevacizumab, preliminary data from 41 patients showed a median PFS for pazopanib of 11.9 months [40]. Various other key studies investigating the benefits of VEGF(R) inhibitors in sequence are ongoing (Table 4), including further studies of axitinib in sequential therapy [15, 41, 42].

Taken together, the data suggest that VEGF(R) inhibitors each have distinct biological and clinical profiles, in terms of both efficacy and tolerability, and that switching from one VEGF(R) inhibitor to another at progression certainly provides clinical benefit in some patients. Importantly, these data therefore indicate that VEGF(R) inhibitors should be considered as individual agents rather than as a drug class.

mTOR inhibitors in sequence

Everolimus

The largest dataset for mTOR inhibitors in sequence comes from the RECORD-1 study—a prospective Phase III, randomized, double-blind, placebo-controlled study that evaluated treatment with everolimus in 416 patients with mRCC who had progressed after treatment with sorafenib and/or sunitinib [5, 43]. In this study, more than three-quarters (79%) of patients had received two or more prior therapies (which, as well as sorafenib/sunitinib could have included bevacizumab, interleukin-2 and/or interferon-alpha) and so received everolimus/placebo as a third-line or later treatment. Everolimus was associated with a median PFS of 4.9 months in the overall population versus 1.9 months for placebo (hazard ratio [HR] 0.33; 95% confidence interval [CI] 0.25–0.43; $P < 0.001$) [5]. Analysis of PFS with everolimus compared with placebo according to prior VEGFR–TKI showed that everolimus was as effective after two VEGFR–TKIs as it was after one and also appeared to be more effective post-sorafenib than post-sunitinib. Everolimus also provided a PFS benefit in patients who had received bevacizumab in addition to sorafenib and/or sunitinib (Table 4 [5, 44]). Notably, prior sunitinib treatment was prognostic of decreased PFS and OS in a multivariate analysis; although this may be related to a bias in TKI selection, it could also suggest an element of cross-resistance between sunitinib and everolimus [5]. It is important to stress that direct comparisons are not possible between the RECORD-1 data and those for sequential therapy with multiple VEGFR–TKIs. The everolimus Phase III study used a placebo control arm, and this is likely to have lead to a larger HR for the median PFS than would have been observed had an active control arm been used.

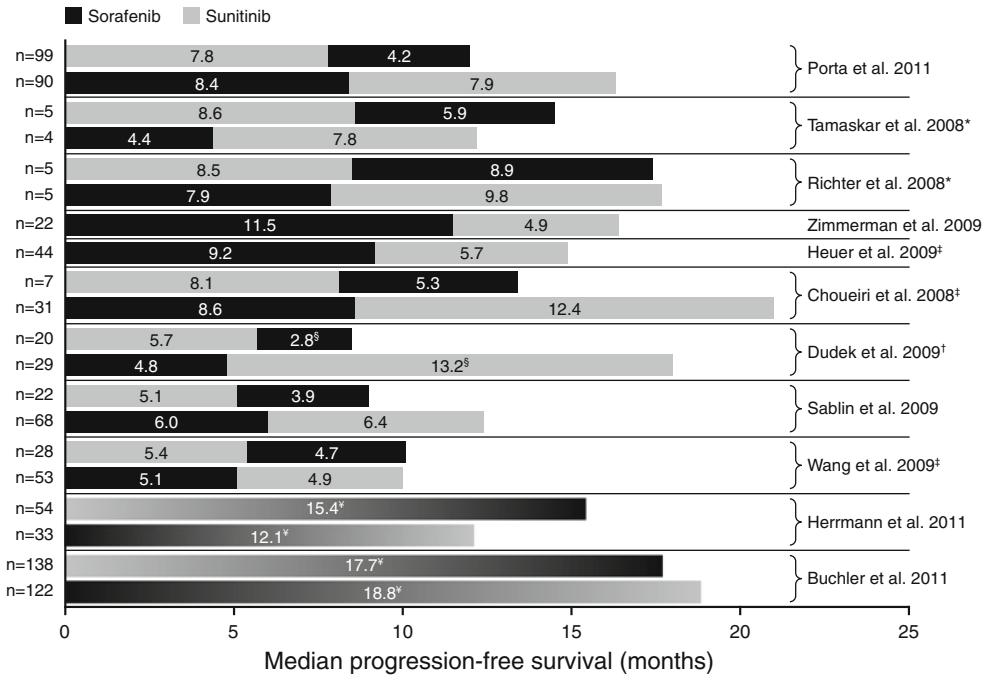

Fig. 1 Summary of retrospective studies reporting the clinical benefit of sequential therapy with SoSu and SuSo in mRCC. Adapted from Porta et al. [11], Copyright 2010 San Lucas Medical. From European Journal of Clinical and Medical Oncology, 2010, volume 4, issue 2. Reprinted with permission from San Lucas Medical. *Mean PFS; †Median time to progression; ‡Median treatment duration; §Calculated by subtracting first/second median from overall median; ¥Overall PFS. Studies that reported second-line PFS only are not shown. Data are from Porta et al. [13], Tamaskar et al. [33], Richter et al. [31] (PFS data published in Merseburger et al. [10]), Zimmerman et al. [34], Heuer et al. [35]; Choueiri et al. [28], Dudek et al. [29], Sablin et al. [32], Wang et al. [36], Herrmann et al. [52] and Buchler et al. [27]

Table 3 Phase II studies reporting the clinical benefit of investigational agents in mRCC sequential therapy

Investigational agent	Patients	*n*	PFS (months)	OS (months)
Axitinib [12]	Sorafenib-refractory	62	7.4	13.6
Linifanib [39]	Sunitinib-refractory	53	5.4	13.3

Table 4 Efficacy of everolimus compared with placebo in previously treated mRCC patients in RECORD-1

Patients	Hazard ratio (95% CI)	PFS (months)		*P* value
		Everolimus	Placebo	
Overall population [5]	0.33 (0.25–0.43)	4.9	1.9	<0.001
Prior sorafenib [5]	0.25 (0.16–0.42)	5.9	2.8	NR
Prior sunitinib [5]	0.34 (0.23–0.51)	3.9	1.8	NR
Prior sorafenib and sunitinib [5]	0.32 (0.19–0.54)	4.0	1.8	NR
Prior bevacizumab and sorafenib and/or sunitinib [44]	0.30 (0.13–0.68)	5.8	1.8	0.001

NR Not reported

Temsirolimus

There are very limited data available regarding the use of temsirolimus after VEGF(R) inhibitors. Data from one retrospective and two prospective studies, each comprising low patient numbers ($n = 13$–30), showed that treatment with temsirolimus after a VEGFR–TKI was associated with a PFS benefit of 1.4–4.6 months [8, 45, 46]. In a slightly larger, retrospective study of 87 patients with mRCC and intermediate or poor prognosis, temsirolimus after a VEGF(R) inhibitor (including bevacizumab, sunitinib, sorafenib, axitinib and others) was associated with a PFS benefit of 3.9 months [9].

Important considerations for sequential treatment options

Given that available data suggest that switching from one VEGF(R) inhibitor to another at progression is associated with clinical benefit and that PFS with everolimus was similar in patients who had received one or two previous VEGFR–TKIs, one rational sequencing approach may be to exhaust treatment with different VEGF(R) inhibitors before switching to an mTOR inhibitor. This hypothesis is supported by a retrospective analysis, which is not without bias, of data from 216 patients with mRCC who had received a first-line VEGF(R) inhibitor [47]. Patients who received a VEGF(R) inhibitor as their second-line therapy had a longer median time to treatment failure (TTF) than those who received an mTOR inhibitor as their second-line therapy (median TTF: 4.9 vs. 2.5 months, respectively [$P = 0.014$]) (Fig. 2) [47].

Notably, a later analysis of the same database, but now including more patients, has called into question the hypothesis that patients with primary refractory disease following VEGF(R) inhibition will receive greater benefit from a subsequent mTOR inhibitor rather than switching to a different VEGF(R) inhibitor. In the especially hard-to-treat subgroup of patients with primary refractory disease after VEGF(R) inhibitor therapy, subsequent treatment with a different VEGF(R) inhibitor resulted in similar outcomes to those reported following a switch to an mTOR inhibitor. Indeed, there was no significant difference in response rate, PFS or OS between treatment groups (10 vs. 6% [P = NS], 2.8 vs. 2.0 months [$P = 0.069$] and 7.9 vs. 4.7 months [$P = 0.40$], for those receiving second-line VEGF(R) inhibitor vs. mTOR inhibitor, respectively) [48]. These findings are particularly interesting given that such patients had been considered by some experts in this field to be the most 'logical' candidates to switch to an mTOR. There is a clear need for the prospective studies of VEGF(R) inhibitors compared with mTOR inhibitors in patients with primary refractory disease after VEGF(R) inhibition.

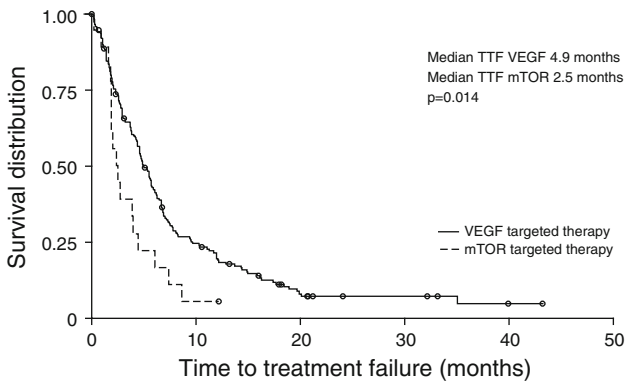

Fig. 2 Median time to treatment failure in patients with mRCC who received second-line therapy with either a VEGF(R) inhibitor or an mTOR after first-line treatment with a VEGF(R) inhibitor (retrospective study). Reprinted from Urology, 76, Vickers MM et al., Clinical outcome in metastatic renal cell carcinoma patients after failure of initial vascular endothelial growth factor-targeted therapy, Pages 430–434, Copyright (2010), with permission from Elsevier

Taken together, these findings indicate that the optimum sequence of VEGF(R) and mTOR inhibitors is yet to be defined. To address this, various ongoing studies are prospectively evaluating different sequencing strategies of mTOR and VEGF(R) inhibitors (Table 5), and the results of these studies are eagerly awaited.

Clinical trials versus clinical practice: challenges and unanswered questions

Many of our treatment decisions in clinical practice are based on the evidence from clinical trials. However, the strict inclusion criteria, and hence narrowly defined patient populations, may mean that findings from clinical studies do not translate easily into real-world clinical practice. Moreover, with various targeted therapies available, and patients receiving treatment with multiple therapies, it would be unfeasible to evaluate all possible treatment sequence permutations within the context of a clinical study in order to determine the optimum sequencing approach. Importantly, absence of high-level evidence (i.e. level 1 evidence) for each treatment sequence does not mean an absence of activity. Therefore, as clinicians, we should also take into account our own clinical experience together with the patient and disease characteristics when making treatment decisions and considering whether to switch treatment and which treatment to switch to. For example, did the patient tolerate the previous therapy? Were toxicities manageable? How did the disease respond to previous treatment, and for what duration? In doing this, we may be able to tailor treatment to each individual patient and to optimise outcomes as far as possible until data from further ongoing clinical studies become available.

When to switch?

Key considerations regarding the decision to switch therapy (regardless of whether this is a switch to a VEGF[R] inhibitor or an mTOR inhibitor) are response to treatment and tolerability (Table 6). The subsequent treatment decision appears most obvious in patients who had a long-term response and tolerated prior therapy—these patients may derive benefit from an agent of the same class. However, in patients with a short-term, mixed or no response, the decision is less clear cut; the main points for

Table 5 Key ongoing and planned studies of VEGF(R) and/or mTOR inhibitors in sequence in mRCC

Study name and ClinicalTrials.gov identifier	Treatment arms	Estimated enrolment	Patients	Primary outcome measure	Key secondary efficacy measures	Estimated primary completion date
SWITCH	Sor → Sun	346	Treatment naïve and cytokine unsuitable	Overall PFS	OS	Mar-13
NCT00732914 [38]	Sun → Sor				Disease control rate	
RECORD-3	Eve → Sun	390	Treatment naïve	First-line PFS	Second-line PFS	Apr-13
NCT00903175 [61]	Sun → Eve				OS	
					Response rate	
					Patient-reported outcomes	
404	Tem	480	Prior sunitinib	PFS	Response rate	Jun-11
NCT00474786 [62]	Sor			Tolerability	OS	
PISCES	Paz → Sun	161	Treatment naïve	Patient preference for Paz or Sun	Fatigue	Oct-11
NCT01064310 [63]	Sun → Paz				Quality of life	
TIVO-1	Tiv	500	Treatment naïve	PFS	OS	Dec-11
NCT01030783 [15]	Sor		1 prior therapy excluding VEGF(R)- or mTOR-targeted therapy		Response rate	
TIVO-1 extension	Tiv → Tiv	500	Patients from TIVO-1	Long-term safety	OS	Mar-12
NCT01076010 [42]	Sor → Sor		Patients with clinical benefit on Tiv continue on Tiv		PFS	
	Sor → Tiv		Patients with clinical benefit on Sor continue on Sor		Response rate	
			Patients progressing on Sor switch to Tiv			
Unnamed Ax study	Ax	447	Treatment naïve	PFS	OS	Aug-11
NCT00920816 [41]	Sor		One previous therapy (sunitinib, cytokines or both)		Response rate	
GOLD	Dov	550	One prior VEGF(R) inhibitor AND one prior mTOR inhibitor	PFS	OS	May-13
NCT01223027 [16]	Sor				Response rate	
					Patient-reported outcomes	
START	Bev → Eve	240	Treatment naïve	Time to overall treatment failure	Not reported	Jan-13
NCT01217931 [64]	Bev → Paz		Prior immunotherapy			

Table 5 continued

Study name and ClinicalTrials.gov identifier	Treatment arms	Estimated enrolment	Patients		Primary outcome measure	Key secondary efficacy measures	Estimated primary completion date
	Eve → Bev						
	Eve → Paz						
	Paz → Bev						
	Paz → Eve						

Ax axitinib, *Bev* bevacizumab, *Dov* dovitinib (also known as TKI258), *Eve* everolimus, *Paz* pazopanib, *PFS* progression-free survival, *OS* overall survival, *Sor* sorafenib, *Sun* sunitinib, *Tem* temsirolimus, *Tiv* tivozanib

consideration are outlined in Table 6. There is no definitive cut-off in the medical literature of what constitutes a long-term versus short-term response and, indeed, we were unable to gain agreement on a suitable cut-off, given that this will depend on multiple factors, including the line of treatment, and clinicians must often use their clinical judgement. That said, we believe that an appropriate, approximate indicator across patient populations would be ~6 months. The definition of stable disease may also differ between clinical practice and clinical trials and may not necessarily be aligned with the RECIST definition—in clinical practice, some physicians may consider any increase in lesion size to constitute progressive disease necessitating a change of treatment, if additional drugs are available, rather than the ≥20% increase specified in the RECIST criteria. Crucially, there is a need for additional data to drive treatment decisions, particularly with regard to subsequent therapy in patients with primary refractory disease.

Treatment rechallenge—is it feasible?

An additional unanswered question is what to use in patients who have failed multiple targeted therapies. Rechallenge with an agent that the patient has already received may be a rational approach in countries where not all marketed agents are available, or when treatment options have been exhausted. In such situations, treatment rechallenge may allow patients the possibility of receiving additional treatment. For example, in a retrospective analysis in 14 patients with mRCC who had relapsed following prior treatment with sorafenib as well as other agents during the intervening period, sorafenib rechallenge was associated with a clinical benefit rate of 67% and a median PFS of 4.3 months [49]. Similarly, a retrospective analysis in 23 patients with mRCC who had relapsed following prior treatment with sunitinib as well as other agents found that sunitinib rechallenge was associated with a partial response rate of 22% and a median PFS of 7.2 months. Interestingly, patients with a >6 month interval between sunitinib treatments had a longer PFS with sunitinib rechallenge than those who received sunitinib rechallenge within 6 months [50].

Key considerations for treatment rechallenge include prior response and tolerability to the treatment that is being reintroduced, and the reason for originally stopping the treatment. For example, if a patient has demonstrated a long-term response to a first-line VEGF(R) inhibitor, and then progressed on a second-line mTOR inhibitor, rechallenge with the initial VEGF(R) inhibitor may be a viable treatment strategy, providing that any toxicities with the first-line VEGF(R) inhibitor were manageable. One school of thought is that using an mTOR inhibitor between

Table 6 Key considerations in the decision to switch treatment

Response to first targeted therapy	Considerations for subsequent therapy
No response	Tolerability of previous therapy
	Agent with different targets and/or different affinities for shared targets
Short-term response	Nature of response on previous therapy
	Tolerability of previous therapy
Long-term response	Agent with a similar target and toxicity profile
Mixed response (different responses in different target lesions)	Is it in the patient's best interest to switch?
	Site(s) of progressive disease
	Tolerability of previous therapy
	Patient's symptoms
	e.g. if liver metastasis has responded, but bone metastasis has progressed, it may be appropriate to continue current therapy, as bone metastases are notoriously difficult to treat
Additional consideration	
Tolerability	
Tolerable AEs	If patient responded to prior therapy, agent with a similar safety profile
Intolerable AEs	Agent with a different toxicity profile

VEGF(R) inhibitor treatments could offer a 'break' from VEGF(R) inhibition, in effect "resetting" the tumour microenvironment prior to reinitiating VEGF(R) inhibition. Importantly, switching from one VEGF(R) inhibitor to another at progression may achieve the same goal; certainly, data from retrospective analyses have shown that sequential therapy with VEGF(R) inhibitors can provide additional clinical benefit. As VEGF(R) inhibitors have different molecular profiles and binding affinities for shared molecular targets, these differences could be sufficient to offer a 'break' from inhibition of specific molecular targets and achieve a similar "resetting" of the tumour microenvironment as could be achieved by a switch to an mTOR inhibitor.

Improved diagnostic and prognostic techniques are needed

The issues considered above highlight the wealth of data that are available from retrospective and small prospective studies, as well as from our own clinical practice, to facilitate our treatment decisions while we await the results from ongoing large prospective studies. However, a number of additional challenges still remain. For example, there is a need for better diagnostic and prognostic techniques to inform treatment decisions. The identification of reliable biomarkers of treatment resistance, response and/or tolerability could facilitate selection of the most appropriate treatment for each individual patient. This is a particularly difficult task given the substantial heterogeneity even among RCC patients who all have the VHL mutation [51]. It may be that biomarkers of resistance to mTOR inhibitors will be discovered more easily than those for resistance to VEGF(R) inhibitors. Finally, there is an urgent need for improved imaging techniques to enable better characterisation of tumours and a fuller understanding of disease progression, thereby enabling physicians to make the most informed and appropriate treatment decisions for each individual patient. Thus, although advances made over the past 5 years have improved the prognosis for patients with mRCC, further work is required if we are to move towards a tailored treatment approach and maximise outcomes for our patients.

Conclusions and expert agreement

Data from ongoing clinical studies evaluating different treatment sequences are expected to shed further light on how best to use targeted agents in sequence, particularly with regard to the efficacy of using different VEGF(R) inhibitors in sequence compared with switching to an mTOR inhibitor. However, until these data are available, the expert agreement described here, based on existing data and our own clinical experience, sets into context the possible sequence options available to maximise the duration of disease control for patients with mRCC.

1. Advances in the treatment of metastatic RCC mean that many patients will be treated long term and will receive multiple therapies. Within this context, sequencing targeted agents may provide patients with the most optimal outcomes

2. It is logical to suggest that patients will benefit from being exposed to as many treatments as possible in sequence, bearing in mind that there may be a risk of cumulative toxicity
3. The optimal treatment sequence has not yet been identified and will vary depending on the patient, necessitating a patient-focused approach
4. Clinical trials are evaluating various sequences of targeted agents. However, with multiple agents approved or in development for the treatment of metastatic RCC, it would not be feasible to evaluate all sequences within clinical trials
5. RCC is VEGF-driven throughout the course of the disease
6. All targeted agents in RCC (VEGF[R] inhibitors and mTOR inhibitors) have 'escape' pathways through which resistance to treatment may be mediated

6.1. Resistance in RCC is not due to mutations but is due to switches in the players/pathways

7. TKIs have different target profiles and different affinities for shared targets. This may explain, in part, the apparent non-absolute cross-resistance between TKIs
8. Retrospective studies and case reports suggest that the use of multiple TKIs (including 3 or more) in sequence may provide prolonged disease control

8.1. TKIs should be considered in terms of the individ ual drugs, not as a class

9. In a patient who has received VEGF(R) → mTOR and progressed, rechallenge with another VEGF(R) inhibitor may be a viable treatment strategy

9.1. Use of an mTOR in a patient who has progressed could offer a 'break' from VEGF(R) resistance, but use of a VEGF(R) inhibitor should be resumed afterwards

10. Physicians should consider both tolerability and disease progression patterns when considering whether to switch treatment and which treatment to switch to

10.1. Tolerability

10.1.1. If a patient is unable to tolerate a given agent, it may be logical to suggest that treatment should be switched to an agent that does not demonstrate overlapping toxicities.

10.1.2. If a patient progresses on treatment and toxicity has been manageable, subsequent treatment decisions could be based on an agent that shares a similar toxicity profile

10.2. Disease progression

10.2.1. A long-term responder may derive benefit from an agent of the same class

10.2.2. A short-term responder may derive benefit from an agent of either the same class or a different class, depending on the nature of the response and tolerability on the first agent

10.2.3. The optimal subsequent treatment in a non-responder remains to be determined

10.2.4. In a patient showing a mixed response (defined as different responses in different target lesions), physicians must first consider whether it is in the patient's best interest to continue on the existing treatment or switch to another agent, taking into account factors such as sites of progressive disease, tolerability and patient symptoms

11. Ultimately, no definitive conclusions as to which sequences are most suitable for which patients (e.g. multiple TKIs in sequence, the sequence TKI → TKI → mTOR and the sequence TKI → mTOR → TKI) can be drawn until the data from ongoing clinical trials investigating such sequences are available
12. There is a need to identify reliable biomarkers of treatment resistance and/or treatment response in order to select the most appropriate treatment in each patient
13. Improved imaging techniques are also required to enable better characterisation of tumours and thus a fuller understanding of disease progression pattern. This would enable physicians to make the most informed treatment decision possible

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