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Sunitinib re-challenge in advanced renal-cell carcinoma

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Despite offering significant clinical benefits in advanced renal-cell carcinoma (RCC), the effectiveness of targeted therapies eventually declines with the development of resistance. Defining optimal sequences of therapy is therefore the focus of much current research. There is also evidence that treatment 're-challenge' may be an effective strategy in some patients. We review evidence to evaluate whether sunitinib may have value as re-challenge therapy in patients who have progressed on prior targeted therapy with sunitinib and/or an alternative tyrosine kinase inhibitor or mammalian target of rapamycin inhibitor. Re-challenge with sunitinib appears to be of clinical benefit, thus representing a feasible therapeutic option for patients with advanced RCC who are refractory to other treatments and are able to receive further therapy. These observations support hypotheses that resistance to targeted agents is transient and can be at least partially reversed by re-introduction of the same agent after a treatment break. Median progression-free survival durations appear to be shorter and response rates lower on re-challenge than following initial treatment, although a wider interval between treatments appears to increase response to sunitinib re-challenge.

Renal-cell carcinoma (RCC) represents ~2% of adult malignancies worldwide, and is increasing in incidence by 1.5–5.9% each year (McLaughlin *et al*, 2006). Most cases of RCC (70–80%) are classified as clear-cell tumours. The prognosis for advanced/metastatic RCC (a/mRCC) is poor and, before the introduction of targeted therapies, median survival time was ~10 months (Motzer *et al*, 1999). For many years, standard treatment of a/mRCC comprises interferon-α (IFN-α) and/or interleukin-2. This cytokine-based therapy resulted in modest clinical benefit but also significant toxicity (Negrier *et al*, 1998).

In the majority of cases (>50–80%), clear-cell RCC is associated with abnormalities of the *von Hippel–Lindau* (*VHL*) gene that result in dysregulation of hypoxia-inducible factor (HIF) and vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) pathways (Pantuck *et al*, 2003). The mammalian target of rapamycin (mTOR) is also activated in clear-cell RCC, and is linked to increased levels of HIF proteins and angiogenesis (Pantuck *et al*, 2003, 2007).

Over the past decade, increased knowledge regarding underlying oncogenetic mechanisms in a/mRCC has resulted in the introduction of various targeted therapies. These include the tyrosine kinase inhibitors (TKIs) sorafenib (Escudier *et al*, 2007a), sunitinib (Motzer *et al*, 2007), pazopanib (Sternberg *et al*, 2010), and axitinib (Rini *et al*, 2011), and the monoclonal antibody bevacizumab in combination with IFN-α (Escudier *et al*, 2007b; Rini *et al*, 2010). All of these agents target the VEGF/VEGFR pathway and, in the case of the TKIs, other pathways important in tumour biology. Temsirolimus (Hudes *et al*, 2007) and everolimus (Motzer *et al*, 2008) inhibit the mTOR pathway. These targeted agents have proven clinical benefit in a/mRCC (Escudier *et al*, 2007a, b, 2010; Hudes *et al*, 2007; Motzer *et al*, 2007, 2008, 2009, 2010; Sternberg *et al*, 2010, 2013; Rini *et al*, 2011; Hutson *et al*, 2013) and have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Despite the benefits of these agents, tumour cells become refractory to treatment and resistance will eventually develop in the majority of patients. Since the disease control rate is in the range of 70–80% for almost all targeted therapies, patients with a/mRCC typically go on to receive multiple single agents, and there is emerging evidence that the sequential use of targeted agents in RCC can overcome transient resistance of the tumour.

The main focus of this article will be on accumulating evidence suggesting that sunitinib (and potentially other agents targeting the VEGF pathway such as sorafenib) may have value as 're-challenge therapy' in patients who have progressed (treatment failure or

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progression after initial response) on prior targeted therapy with sunitinib and/or an alternative TKI or mTOR inhibitor.

EVIDENCE ACQUISITION

The PubMed database was searched (no defined time period) using the following terms: renal cell carcinoma; metastatic renal cell carcinoma; angiogenesis and renal cell carcinoma; targeted therapy; second-line therapy and RCC; sunitinib; Sutent; sorafenib; Nexavar; tyrosine kinase inhibitors; mTOR inhibitors; axitinib; pazopanib; immunotherapy and renal cell carcinoma; progression and renal cell carcinoma (and various author names).

Relevant articles were also identified using the 'related citations' function of PubMed, and from the bibliographies of identified references. Abstracts from the 2009, 2010, 2011, and 2012 American Society of Clinical Oncology (ASCO) annual meetings, ASCO Multidisciplinary Genitourinary Cancers Symposia, American Urological Association (AUA), European Association of Urology (EAU) and European Society for Medical Oncology (ESMO) annual congresses were also searched.

EVIDENCE SYNTHESIS

Sunitinib for first-line treatment of a/mRCC. Sunitinib was initially shown to be effective in phase II trials in patients with cytokine-refractory a/mRCC, representing the basis for a conditional approval by the FDA and EMA (Motzer *et al*, 2006a, b). These findings led to a pivotal phase III trial comparing sunitinib with IFN-α (Motzer *et al*, 2007). This trial demonstrated that the use of sunitinib in treatment-naïve patients with metastatic clear-cell RCC resulted in significant improvements in median progression-free survival (PFS; 11 *vs* 5 months; $P<0.001$) and objective response rate (ORR; 47% *vs* 12%; $P<0.001$) compared with IFN-α, while overall survival (OS) was of borderline significance (26.4 *vs* 21.8 months; $P=0.051$); the study had not been designed to demonstrate any OS benefit (Motzer *et al*, 2009).

Results from an expanded-access programme of 4577 patients treated with sunitinib also showed clinical benefit (median PFS, 9.4 months). Interestingly, this data set reported clinical activity among older patients, those with brain metastases, and patients with non-clear cell a/mRCC (Gore *et al*, 2009, 2012). Recent reports show that sunitinib is active and feasible in patients >70 years old (De Giorgi *et al*, 2013; Hutson *et al*, 2014), and has increased efficacy compared with sorafenib in patients with papillary (non-clear cell) a/mRCC (median PFS 11.9 *vs* 5.1 months ($P<0.001$) (Choueiri *et al*, 2008). Notably, sunitinib has also been associated with cases of complete remission (CR) in metastatic RCC (Albiges *et al*, 2012).

Until recently sunitinib has been the main first-line treatment of choice in patients with good- or intermediate-risk a/mRCC (EAU Guidelines; Ljungberg *et al*, 2010). Indeed, the recently updated ESMO Clinical Practice Guidelines recommend sunitinib with the highest level of evidence (IA) in this setting (Escudier *et al*, 2012). Similarly, the latest Guidelines of the National Comprehensive Cancer Network (NCCN) recommend sunitinib (Category 1) as one of the options for the first-line treatment of advanced clear-cell RCC (National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, 2014).

Studies comparing the efficacy of sunitinib with other agents (or in combination with other agents *vs* single-agent therapy) as first-line treatment have recently been completed or are ongoing. In the COMPARZ study of first-line treatment of locally advanced and/or metastatic RCC (NCT00720941), pazopanib reached the primary end point of non-inferiority compared with sunitinib for PFS, and had some safety and quality of life advantages (Motzer *et al*, 2013b). However, sunitinib remains to be one of the standard first-line treatments for a/mRCC and, to date, is still the most widely prescribed drug in this setting. A multicentre, open-label, randomised phase III study is investigating the multipeptide cancer vaccine, IMA901, and whether this treatment can prolong OS when added to standard first-line therapy with sunitinib in patients with metastatic and/or locally advanced RCC (NCT01265901). An international phase III randomised trial of autologous dendritic cell immunotherapy, AGS-003, also plans to determine whether there is an OS benefit when given as first-line therapy in combination with standard treatment for a/mRCC *vs* standard treatment alone (ADAPT; NCT01582672).

Resistance to targeted therapy in advanced RCC. Besides primary resistant tumours (which are thought to be characterised by a completely different molecular pathogenesis), RCC tumours develop acquired or adaptive resistance to targeted therapy. Tumours with primary refractoriness to first-line TKI treatment are possibly characterised by a different pathogenesis (Porta *et al*, 2012a), involving gene mutations other than (or in addition to) *VHL* (e.g., *SETD2* and *BAP1* have been shown to correlate with poor prognosis and aggressive disease in non-metastatic patients) (Hakimi *et al*, 2013; Joseph *et al*, 2013). Loss of BAP1 protein expression is an independent marker of poor prognosis in patients with low-risk clear-cell RCC (Joseph *et al*, 2013). The predictive nature of these mutations for targeted agents remains to be determined in ongoing studies.

With acquired resistance, preclinical data suggest that tumour and environmental changes may allow for continued perfusion and tumour growth with less dependence on VEGF (Rini and Atkins, 2009a). While the mechanisms of resistance are not fully understood, it is generally acknowledged that resistance can develop when genetic alterations result in the activation of a previously inhibited pathway (an 'escape' pathway) to compensate for the drug-inhibited pathway, or prevent the drug from binding to its targets by altering the drug–target interaction (Rini and Atkins, 2009a; Zama *et al*, 2010; Hutson *et al*, 2011).

Clinical data suggest that resistance to targeted agents is transient, since changing to a different line of treatment can result in tumour regression (Rini and Atkins, 2009a), thus supporting a 'resistance reset phenomenon' reported by Hutson *et al* (2011). As the different TKIs and mTOR inhibitors have specific targeted activity and differing pharmacokinetic profiles, it can be hypothesised that each will be associated with a different compensatory tumour response, thus facilitating the use of several sequential regimens of these agents in a/mRCC without the development of cross-resistance (Porta *et al*, 2012b).

This hypothesis is supported by a number of clinical studies in which targeted agents, given in sequence, have been used successfully (see below), and also by data suggesting that sunitinib is able to inhibit pathways implicated in resistance to bevacizumab; indeed, sunitinib was associated with substantial clinical benefit (ORR 23%; median PFS 30.4 weeks; median OS 47.1 weeks) in 61 patients with metastatic RCC who were refractory to bevacizumab/cytokine therapy in a phase II multicentre study (Rini *et al*, 2008). Additionally, a near-CR was reported in two bevacizumab-refractory patients following sequential use of sunitinib (Heng *et al*, 2007). To date, attempts to overcome resistance with other strategies, such as dose increases and combination therapy, have failed, mainly due to tolerability issues.

Optimal treatment sequence in a/mRCC and the role of sunitinib as a second-line therapy. A number of trials and clinical reports have shown the feasibility of using TKIs and/or mTOR inhibitors in the second-line treatment of a/mRCC. Indeed, based on the recently updated ESMO Clinical Practice Guidelines (Escudier *et al*, 2012), both axitinib (level IB evidence (ESMO

Guidelines Corrigendum, 2013) and everolimus (level IIA) are currently recommended first-choice therapy in patients who have previously received first-line treatment with a VEGF(Rs)-pathway inhibitor, while sorafenib (level IA), axitinib (level IA), pazopanib (level IIA) and sunitinib (level IIIA) are recommended after first-line cytokine therapy.

Several ongoing trials are attempting to more clearly establish the optimal sequencing of targeted treatment for patients with a/mRCC. Although switching to mTOR inhibition following TKI failure appears to be logical in terms of targeting a putatively different signalling pathway, clinical benefit has also been reported following use of a different TKI in TKI-refractory patients at the time of disease progression (Park *et al*, 2012). Indeed, the concept of switching to an agent with a different mechanism of action (e.g., TKI followed by mTOR inhibitor) has been challenged by some authors (Porta *et al*, 2012b), and a number of retrospective studies using sequences of sunitinib/sorafenib or sorafenib/sunitinib as first- and second-line therapies have now been performed (Porta *et al*, 2011; Procopio *et al*, 2012). Data from >850 patients have shown enhanced clinical benefit following TKI–TKI therapy with sunitinib and sorafenib, indicating that there is no complete cross-resistance between these two agents (Rini and Atkins, 2009a; Stenner *et al*, 2012). A phase III trial of 512 patients who had progressed on sunitinib showed no significant PFS difference between temsirolimus and sorafenib as second-line therapy (4.3 *vs* 3.9 months), although median OS was significantly longer with sorafenib (12.3 *vs* 16.6 months, $P=0.01$) (Hutson *et al*, 2013). In the phase III AXIS trial (NCT00678392), axitinib significantly improved PFS compared with sorafenib in patients who had progressed on sunitinib. Longer duration of prior sunitinib treatment was associated with significantly longer OS in those who switched to sorafenib, underscoring the relevance of VEGF sensitivity on prognosis in RCC (Escudier *et al*, 2013).The phase III GOLD trial prospectively compared third-line sorafenib *vs* dovitinib (an inhibitor of fibroblast growth factor receptor, VEGFR and PGDFR) in patients with metastatic RCC who had progressed on one VEGF-targeted therapy and one mTOR-targeted therapy. There were no significant differences in PFS (3.7 months with dovitinib, 3.6 months with sorafenib) or OS (11.1 and 11.0 months, respectively) (Motzer *et al*, 2014). This trial provides landmark outcome data supporting further re-exposure to VEGF TKI in this third-line setting.

Prospective efficacy data have recently been presented from a phase III sequential study to treat RCC (SWITCH) (Michel *et al*, 2014); this study directly compared sunitinib–sorafenib *vs* sorafenib–sunitinib sequential therapeutic approaches (NCT00732914). Adverse events leading to permanent discontinuation were reported in 18.6% of patients receiving first-line sorafenib and in 29.5% of those receiving first-line sunitinib. However, fewer patients crossed over to second-line therapy with sorafenib than to second-line sunitinib. There was no significant difference between treatment arms in efficacy end points; both sequences provided therapeutic benefit. However, treatment with second-line therapies outside the protocol could explain the similar OS seen with the two sequencing strategies (Michel *et al*, 2014).

Finally, the phase II RECORD-3 study (NCT00903175) is comparing the efficacy and safety of everolimus *vs* sunitinib as first-line treatment, followed by the alternative drug as second-line therapy (Motzer *et al*, 2013a). According to the first presentation of the results of this study, median PFS was 7.9 months (95% confidence interval (CI): 5.6–8.2) for first-line everolimus and 10.7 months (95% CI: 8.2–11.5) for first-line sunitinib. The hazard ratio (first-line everolimus/first-line sunitinib) was 1.43 (95% CI: 1.15–1.77). A trend towards increased OS was also observed with first-line sunitinib, although confirmation of these data is required in the final OS analysis. The sequence associated with optimal clinical benefit was therefore first-line sunitinib followed by everolimus; hence, the authors concluded that the treatment paradigm remains unchanged.

Clinical evidence suggesting the feasibility of re-challenge with targeted agents. Although the current long-term treatment strategy in a/mRCC is to give multiple sequential treatments using different agents, there are increasing numbers of studies and case reports suggesting that re-challenge with a specific drug can be of therapeutic benefit. These data are in-line with earlier preclinical studies in which transplantation of sunitinib- or sorafenib-resistant tumours into untreated mice resulted in re-acquired sensitivity to the respective agents (Hammers *et al*, 2010; Zhang *et al*, 2011). Porta *et al* (2012b) have suggested that the responsiveness of the tumour may therefore be altered by a change in the tumour microenvironment. In the clinic, this could possibly be achieved by switching to a different targeted therapy, but also by a treatment break followed by re-challenge with the same therapeutic agent.

Sunitinib re-challenge. There have been no prospective clinical trials reported on sunitinib re-challenge as third-line therapy (after other targeted therapies such as everolimus, sorafenib, and axitinib) in a/mRCC, although there are several ongoing trials, including an observational (prospective and retrospective) study in patients treated with sunitinib in first-line and re-challenged with sunitinib in third- and fourth-line (NCT01827254), a prospective phase II study involving several Italian centres ('RETRY' study; EUDRACT n. 2012-000473-23) and a further prospective phase II Dutch trial (NTR3711).

To date, most data on sunitinib re-challenge have been reported from retrospective studies and small case series (Table 1) (Paule and Brion, 2010; Shablak *et al*, 2010; Zama *et al*, 2010; Grünwald *et al*, 2011; Nagyivanyi *et al*, 2012). In a multicentre retrospective analysis, 5 of 23 (22%) patients with sunitinib-refractory a/mRCC achieved an objective partial response on re-challenge with sunitinib (Zama *et al*, 2010). Patients had previously received sunitinib (the partial response rate after initial sunitinib treatment was 65%), had experienced disease progression or intolerance, and had subsequently received at least one additional antitumour therapy before sunitinib was given a second time. The median PFS was 13.7 months with initial sunitinib treatment and 7.2 months with sunitinib re-challenge (Figure 1). Of note, PFS was longer following re-challenge than with initial treatment in six patients (32%). Treatment toxicity on re-challenge was acceptable; no substantial new toxicity or increased severity of prior toxicity was noted.

The interval between sunitinib treatments appeared to have an impact on response to re-challenge; patients with an interval of >6 months between sunitinib treatments had a median PFS of 16.5 months (compared with 6.0 months in those who were re-challenged within 6 months). Objective response rate and PFS on sunitinib re-challenge were similar to the rates reported in trials of sequential VEGF pathway inhibitors: one with sunitinib in bevacizumab-refractory RCC (Rini *et al*, 2008) and the other with axitinib in sorafenib-refractory RCC (Rini *et al*, 2009b), providing support for the central role of the VEGF pathway in the pathogenesis of a/mRCC. No significant outcome differences on re-challenge were noted according to the type or number of intervening treatments.

In another study involving 13 patients who had progressed on sunitinib and an mTOR inhibitor, sunitinib re-challenge resulted in a median PFS of 6.9 months (*vs* a median PFS of 21 months after initial sunitinib treatment). Following sunitinib re-challenge, 12 of 13 (92%) patients derived clinical benefit, with 2 patients experiencing a PR and 10 patients stable disease (Grünwald *et al*, 2011). Patients received sunitinib re-challenge a median of 13 (range: 2.9–25.2) months after initial sunitinib treatment, and immediately after failure of an mTOR inhibitor.

Table 1. Sunitinib re-challenge in a/mRCC: summary of data from retrospective trials and patient case reports

	Number of patients	Patient characteristics	Initial sunitinib efficacy data	Re-challenge efficacy data
Zama *et al* (2010)	23	Male: 78% Median age: 59 years Clear-cell histology: 100% KPS: 90–100% MSKCC risk group: intermediate = 74%	PR rate: 65% Median PFS: 13.7 months	ORR: 22% Median PFS: 7.2 months Median interval before re-challenge: 6.7 months
Grünwald *et al* (2011)	13	Male: 62% Median age: 58 years Clear-cell histology: 92% Papillary histology: 8% ECOG PS: 0 (69%), 1 (31%) MSKCC risk group: intermediate = 62% Patients failed sunitinib and mTOR inhibitor	ORR: 69% (CR: 15%; PR: 54%) Clinical benefit (CR/PR or SD) rate: 92% Median PFS: 21.0 months	ORR: 15% (PR) Clinical benefit (PR or SD) rate: 92% Median PFS: 6.9 months Median interval before re-challenge: 13 months
Nagyivanyi *et al* (2012)	9	Male: 89% Median age: 59 years Clear-cell histology: 100%	Median PFS: 13.7 months	Clinical benefit (PR or SD) rate: 67% Median PFS: 6.8 months
Shablak *et al* (2010)	2	Male: 100% 61 years and 69 years Sunitinib discontinued during radiotherapy for new metastases	SD after 6 and 13 months of sunitinib treatment	Ongoing survival after a further 18 and 13 months of treatment
Paule and Brion (2010)	1	Female 54 years Clear-cell histology Lung and bone metastases Sequential treatment with suntinib, sorafenib and everolimus	PD after 13 months of treatment	Mixed response: reduction in bone metastases; progression of lung metastases PFS: 4 months

Abbreviations: CR = complete remission; ECOG PS = Eastern Cooperative Oncology Group performance status; KPS = Karnofsky Performance Scale; MSKCC = Memorial Sloan-Kettering Cancer Center; ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

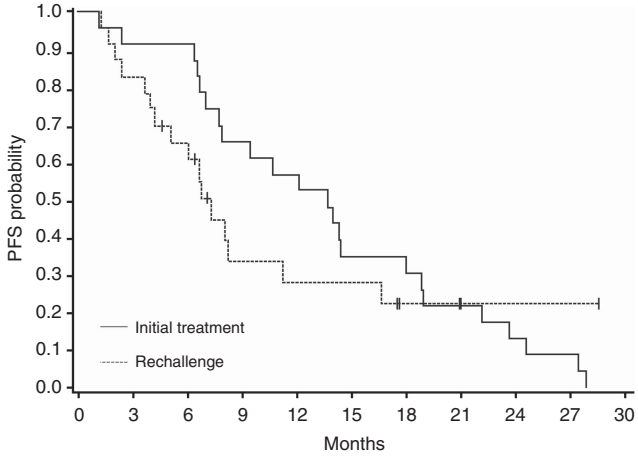

Figure 1. Progression-free survival with sunitinib: initial treatment and re-challenge (from Zama *et al*, 2010).

Further retrospective data were recently reported for nine patients who were re-challenged with sunitinib after failing at least two previous therapies, including sunitinib. Median PFS with initial sunitinib treatment was 13.7 months, and following re-challenge was 6.8 months (Nagyivanyi *et al*, 2012). The investigators concluded that sunitinib re-challenge was a valid third-line treatment option in sunitinib-responsive patients after previous TKI or mTOR inhibitor therapy.

There are several case reports describing the successful use of sunitinib as re-challenge therapy. Shablak *et al* (2010) reported on re-treatment with sunitinib in two patients following a break for radiotherapy to treat new metastases occurring during initial sunitinib therapy. In both cases, recommencing sunitinib resulted in symptomatic relief and disease stabilisation, and the patients were still alive after 18 and 13 months.

Also of interest was a case study in which re-challenge with sunitinib resulted in a reduction in bone metastases and a PFS of 4 months in a patient with a/mRCC and lung and bone metastases who had previously received sequential treatment with sunitinib, sorafenib, and everolimus (Paule and Brion, 2010). Despite the observed reduction in bone metastases in this patient, progression was observed in lung metastases that had previously responded during the first exposure to sunitinib. Notably, disease progression was not seen in mediastinal lymph-node metastases. While the reasons for this mixed response are unclear, it seems likely that intratumour heterogeneity may have a role. Such heterogeneity has recently been described in primary renal carcinomas and associated metastatic sites (Gerlinger *et al*, 2012). Gerlinger *et al* identified gene-expression signatures of both good and poor prognosis in different regions of the same tumour and suggested that such heterogeneity arises from tumour adaptation through Darwinian selection.

Five patients at IRCCS San Matteo University Hospital Foundation (four of good prognostic risk and one of intermediate risk) have received sunitinib re-challenge, three as a third-line treatment and two in the fourth-line (Table 2). All patients received first-line sunitinib and subsequent therapy with sorafenib and/or everolimus, and all achieved a partial response following first-line sunitinib, with a duration of therapy ranging from 8.5 to 18 months. Sunitinib re-challenge (as third- or fourth-line

Table 2. Single-centre experience with sunitinib re-challenge in 5 patients with a/mRCC

N	Sex	Age (years)	MSKCC score before first-line therapy	Heng score before first-line therapy	First-line therapy	Duration of first-line therapy (months)	Best response	Second-line therapy	Duration of second-line therapy (months)	Best response	MSKCC score before third-line therapy	Heng score before third-line therapy	Third-line therapy	Duration of third-line therapy (months)	Best response	MSKCC score before fourth-line therapy	Heng score before fourth-line therapy	Fourth-line therapy	Duration of fourth-line therapy (months)	Best response
1	M	63	Good	Good	Sunitinib	9.5	PR	Sorafenib	7	SD			Everolimus	5.5	SD	Int	Int	Sunitinib	6	SD
2	M	57	Good	Int	Sunitinib	11.5	PR	Everolimus	4.5	SD	Int	Int	Sunitinib	6	SD					
3	F	72	Int	Int	Sunitinib	8.5	PR	Sorafenib	5.5	SD			Everolimus	4	SD	Poor	Poor	Sunitinib	5	SD
4	M	60	Good	Good	Sunitinib	18	PR	Everolimus	10	PR	Int	Int	Sunitinib	8	SD					
5	M	59	Good	Good	Sunitinib	10	PR	Everolimus	7.5	SD	Good	Int	Sunitinib	7	SD					

Abbreviations: a/mRCC = advanced/metastatic renal-cell carcinoma; F = female; Int = intermediate; M = male; MSKCC = Memorial Sloan-Kettering Cancer Center; PR = partial response; SD = stable disease. Shaded cells show sunitinib re-challenge (third- and fourth-line therapy).

treatment) resulted in disease stabilisation in all patients. The duration of third-line sunitinib therapy was 6, 7, and 8 months, and the duration of fourth-line sunitinib was 5 and 6 months, respectively.

According to our experience and opinion, sunitinib re-challenge should be considered, in clinical practice, as an option in third-line therapy (as an alternative to sorafenib) after first-line sunitinib and second-line everolimus, especially when PFS with first-line sunitinib was particularly long (over the average reported in randomised clinical trials). Specific local regulatory limitations may influence this choice, either positively or negatively.

There is similar (although far more limited) experience with sorafenib re-challenge in advanced RCC. A small, retrospective analysis of patients who received sorafenib re-challenge after failed treatment (sunitinib, everolimus, and other treatments) provides further support that re-introduction of the same VEGFR inhibitor is of clinical benefit (Nozawa *et al*, 2012).

CONCLUSIONS

There is increasing evidence of the central role of the VEGF/VEGFR pathway in the development of a/mRCC and good rationale for continuous inhibition of this pathway due to the frequent mutation of the *VHL* tumour suppressor gene in RCC (also seen in sporadic forms of the disease). This molecular hallmark renders this cancer particularly dependent on angiogenesis and thus susceptible to angiogenesis inhibition with targeted agents.

Sunitinib is currently the most commonly used targeted agent for the first-line treatment of good- and intermediate-risk a/mRCC and, from the data summarised here, also seems to represent an important therapy option in later lines of treatment in those patients refractory to other agents. While ongoing studies are helping to better understand whether specific sequences of targeted agents may be more active than others, there is increasing evidence to suggest that re-challenge with sunitinib (and other TKIs such as sorafenib) is of clinical benefit in patients with a/mRCC. Although the PFS achieved on re-challenge appears to be shorter than that observed with first-time use, in-line with the so-called 'law of diminishing returns', re-challenge represents a feasible option in patients who are refractory to other treatments and are able to receive further therapy. These observations are consistent with data indicating that resistance may be mediated by transient mechanisms that can be at least partially reversed by treatment with a different agent or re-introduction of the same agent after a treatment break.

Even though similarity in their mechanism of action makes all the available TKIs theoretically suitable for use after a first TKI and an mTOR inhibitor, there are limited data currently available on pazopanib use beyond first line.

Several recently reported and ongoing trials are helping to provide additional clarity on optimal sequencing of targeted agents in a/mRCC so that, in the future, specific sequences of therapy that include treatment re-challenge can be tailored to the individual patient. A greater understanding of the specific mechanisms underlying resistance of RCC tumours to the different targeted therapies will also be of importance when making recommendations regarding optimal treatment sequences in the future. While large prospective trials are required to further evaluate and confirm the benefits of treatment re-challenge, the currently available data suggest that sunitinib re-challenge represents an important and feasible therapeutic option for the future treatment of patients with a/mRCC.

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CONFLICT OF INTEREST

CP has acted as a speaker or consultant for Pfizer Oncology, GSK, Hoffmann-La Roche, Bayer-Schering Pharma, Novartis Pharma, Astellas, Aveo Pharmaceuticals, Boehringer-Ingelheim, and Recordati; he has also received research grants from Bayer-Schering Pharma and Novartis Pharma.Chiara Paglino has acted as a speaker for Pfizer Oncology, Hoffmann-La Roche, GSK and Bayer-Schering Pharma.VG has acted as a speaker or consultant for Pfizer Oncology, Novartis, GSK, Hoffmann-La Roche, Astellas, Aveo Pharmaceuticals, and Bayer-Schering Pharma.

AUTHOR CONTRIBUTIONS

Camillo Porta contributed to conception and design; Camillo Porta, Chiara Paglino, and VG contributed to acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content.

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