Does a reasonable treatment approach beyond second-line exist?

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1. Introduction

In the 1990s, the outlook for a metastatic renal-cell carcinoma (mRCC) patient was particularly bleak, as the disease was resistant to conventional chemotherapy and only small subsets of patients responded to immunotherapy. This outlook improved in 2005 with the introduction of sorafenib, the first targeted therapy; it was followed by the development of other tyrosine kinase inhibitors (TKIs): namely, sunitinib, pazopanib, axitinib, the monoclonal antibody bevacizumab (directed at vascular endothelial growth factor, VEGF) which was used in combination with interferon (IFN) and the inhibitors of the mammalian target of rapamycin (mTORis) everolimus and temsirolimus. Despite the number of available options, sequencing questions remain key, and the choice for first- and second-line treatment is still controversial.

However, there is a consensus that VEGF inhibition is the standard of care for first-line treatment in most cases. The choice of first-line treatment is informed by the results of large randomised clinical trials which have included prognostic models in their design and analysis [1–3]. Recent guidelines have suggested that low- and intermediate-risk patients are candidates for sunitinib, pazopanib or a combination of bevacizumab and interferon, while temsirolimus should be an option for high-risk patients [4].

Second-line therapy for patients with mRCC of the clear-cell type is still an evolving field. All the targeted agents mentioned above have activity in patients previously exposed to cytokine therapy; however, only the orally administered mTOR inhibitor everolimus is approved for patients failing prior treatment with sorafenib and/or sunitinib [5]. Recent data have shown that axitinib, a selective VEGFR TKI, significantly improves progression-free survival (PFS) compared to sorafenib in patients who have previously been treated with sunitinib [6]. Based on these two studies, both agents are currently approved and are used as standard treatment in patients failing a first-line treatment with VEGF inhibitors; they are part of the most recent guidelines [4].

Beyond second-line, there is no consensus and no "officially" approved drug. However, for the first time, the European Society for Medical Oncology (ESMO) guidelines recently opened the gate for third-line options [4]. This chapter is intended to clarify possible options after second-line treatment in mRCC.

Two sequences are currently standard of care, and approved regimen: TKI (or VEGF inhibitor) followed by everolimus, or TKI (or VEGF inhibitor) followed by axitinib. The proposed third-line strategy will depend on this sequence (Table 1).

2. Treatment after TKI (or VEGF inhibitor) followed by everolimus

There is no randomised study demonstrating the activity of any approved agent after this sequence. However, there are some retrospective data suggesting that another TKI can induce clinical benefit in patients still eligible to receive targeted agents [7,8]. In a retrospective database study, third-line sorafenib appeared active and feasible after first-line sunitinib and second-line everolimus or temsirolimus in terms of toxicity profile and median PFS [7]. Recently, 36 patients from French sites who received a TKI after everolimus within the RECORD-1 study have been reported [8]. The received TKI after everolimus was sunitinib in 17 patients, sorafenib in 15 and dovitinib (TKI258) in four. The response rate with TKI re-treatment was 8%, and the disease control rate (response plus stable disease) was 75%. Median PFS with each component of the TKI–everolimus–TKI sequence was 10.7 months (range 1.8–28.5), 8.9 months (range 1.7–34.6) and 8.2 months (95% confidence interval (CI) 5.2–11.9), respectively. Median overall survival from the start of everolimus was 29.1 months (95% CI 21.1 – not reached [NR]), suggesting a benefit in using TKI in this setting.

Another option after the TKI–everolimus sequence is re-challenge with the previous TKI [9]. Re-challenge with the same agent has been examined in those with prior response; for example, in a retrospective study, 23 patients who exhibited long response with sunitinib first-line treatment

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Table 1 – Third-line treatment in metastatic renal-cell cancer (mRCC).

Histology and setting	Previous treatment	Standard	Option
Clear-cell third line	Post 2 TKIs	Everolimus	Clinical trial
	Post TKI and mTOR	TKI (sorafenib, axitinib)	Clinical trial
Non-clear-cell histology		Clinical trial	As for clear cell

were re-challenged with sunitinib after progression on prior sunitinib were reported. Upon re-challenge, five patients (22%) reached a PR. The median PFS with initial sunitinib was 13.7 months and 7.2 months with re-challenge. Those with >6-month interval between sunitinib treatments had a longer PFS with re-challenge (median PFS, 16.5 versus 6.0 months, $P = 0.03$). Substantial new or increased severity of toxicities was not reported during re-challenge.

Finally, newer TKIs have also demonstrated activity in this setting. In a recent phase I/II clinical trial of dovitinib, an inhibitor of multiple-receptor tyrosine kinases, including fibroblast growth factor receptor (FGFr) and VEGF receptor (VEGFr), in patients with mRCC refractory to standard therapies, 8 of 10 patients previously treated with a TKI–everolimus sequence achieved disease control, with one patient experiencing a partial response [10]. This has been convincing enough to launch a large prospective phase III trial comparing sorafenib and dovitinib in patients who have received one TKI and one mTOR inhibitor (ClinicalTrials.gov. NCT identifier: 01223027). This trial, known as the GOLD trial, has completed enrolment and will be reported shortly.

Interestingly, first-line PFS, with 6 months taken as cut-off parameter, appears to be an important prognostic factor for survival and thus for the likelihood of benefit of second- and third-line treatments [11].

3. Treatment after TKI (or VEGF inhibitor) followed by axitinib

There is currently no evidence that a third TKI after two TKIs has activity, although axitinib has shown some efficacy after sunitinib and sorafenib, with a response rate of 7% and a PFS of 7.1 months in a small number of patients [12].

By contrast, there is level I evidence that everolimus is active after two TKIs, as recognised in the recent ESMO guidelines [4]. In the aforementioned phase III RECORD-1 trial, everolimus was compared with placebo in patients following sorafenib and/or sunitinib [5]. Among patients who received one previous TKI median PFS was 5.4 months versus 1.9 months (HR, 0.32; $P < 0.001$), and among those who received two previous TKIs median PFS was 4.0 months versus 1.8 months (HR, 0.32; $P < 0.001$) [13]. Although this might suggest that everolimus is more active when given in second-line than in third-line, it more strongly demonstrates that everolimus is still active when given after two TKIs.

4. Future of treatment beyond second-line in mRCC

TKIs as well as mTOR inhibitors have been shown to be active in third-line treatment, depending on the previous sequence, as discussed above. In the future, several other options might be available.

Dovitinib, which is currently in phase III, might become a new standard if the ongoing GOLD study turns out to be positive. Interestingly, this study will also demonstrate whether sorafenib is active in a randomised study after the sequence TKI–mTOR.

There is a lot of enthusiasm for targeted immunotherapy, such as anti-PD1 and/or anti-PDL1, in mRCC [14,15]. There is an going phase III evaluating the efficacy of nivolumab (BMS-936558), a T-cell checkpoint (PD-1) inhibitor, after one or two TKIs, in comparison to everolimus (http://clinicaltrials.gov/ct2/show/NCT01668784). Overall survival is the primary endpoint of this study, and this trial will eventually change the standard of care of mRCC treatment if the outcome is positive.

Cabozantinib, a Met and VEGF receptor-2 inhibitor, has shown promising activity in mRCC [16]. The activity of this new TKI will be shortly evaluated in a large phase III trial, in comparison to everolimus, after one or two TKIs. Obviously, this treatment might in the future become a very attractive strategy to overcome resistance.

5. Conclusion

There is evidence that treatment beyond the second line is active in mRCC. Depending on the previous sequence used, both mTOR inhibitors have shown efficacy. New strategies are emerging and might change the landscape, dovitinib being the first drug expected to be incorporated in future guidelines.

Conflict of interest statement

None declared.

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