Metastatic clear cell renal cell carcinoma (RCC) still has a poor outcome despite the introduction of targeted therapy. This is particularly true in patients who have failed vascular endothelial growth factor (VEGF) receptor-targeted therapy. In 2015, the results of two pivotal trials with nivolumab (a monoclonal antibody that targets the programmed cell death 1 [PD1] immune checkpoint) and cabozantinib (a multi–tyrosine kinase inhibitor [TKI] of MET, AXL, and VEGF) were published in this setting [1,2]. The current European Association of Urology (EAU) guidelines do not take into account these two practice-changing randomised phase 3 trials [1–3], which show that the experimental agents (nivolumab and cabozantinib) are superior to the current standard of care (everolimus) in patients who have failed one line or more of VEGF targeted therapy (level of evidence [LE] 1b). For this reason, the renal cancer guidelines group has amended the EAU guidelines (Fig. 1).

1. **New recommendations for patients who have failed one line or more of previous VEGF targeted therapy**

Nivolumab is superior to everolimus (hazard ratio [HR]: 0.73 [95% CI, 0.57–0.93]; \( p < 0.002 \)) in VEGF-refractory renal cancer, with median overall survival (OS) of 25 mo (95% CI, 21.8–not estimable) for nivolumab and 19.6 mo (95% CI, 17.6–23.1) for everolimus [1] (LE 2a). Patients who had failed multiple lines of VEGF targeted therapy were included in this trial, making the results broadly applicable. PD1 ligand (PD-L1) biomarker expression on tumour cells did not predict outcome with nivolumab, making pretreatment patient selection difficult at this time. Subset analysis did not show that any specific subgroup benefitted with everolimus. Durable responses occurred with nivolumab. It was well tolerated, with a low incidence of grade 3 or 4 adverse events (19% for nivolumab vs 37% for everolimus). There was no progression-free survival (PFS) advantage with nivolumab despite the OS advantage, as seen with immune therapy in other tumour types [4].

Cabozantinib delays progression or death compared with everolimus in VEGF targeted therapy–refractory disease by 42% (HR: 0.58 [95% CI, 0.45–0.75]) [2] (LE 2a). The median PFS for cabozantinib was 7.4 mo (95% CI, 5.6–9.1) versus 3.8 mo (95% CI, 3.7–5.4) for everolimus. The trial recruited 658 patients, although PFS was assessed for the first 375 patients. Interim OS results showed a strong trend favouring cabozantinib (HR: 0.67 [95% CI, 0.51–0.89]; \( p = 0.005 \)); however, this was not significant at the
predefined levels at this interim stage. A final planned mature OS analysis is expected in 2016. Grade 3 or 4 adverse events occurred in 68% of patients who received cabozantinib and 58% who received everolimus. Although 60% of patients required dose reduction of cabozantinib, discontinuation due to toxicity was not significantly different with the two drugs.

Both of these agents should be considered as a new standard of care for patients who have failed VEGF targeted therapy (Fig. 1). Prior to the release of these new data, EAU guidelines recommended the use of axitinib (after one line of VEGF targeted therapy) or everolimus (after one line or more of VEGF targeted therapy) [3]. No trials have compared axitinib and everolimus, and both are widely used.

Axitinib is currently recommended as a second-line agent in VEGF-refractory disease [3]. Axitinib is superior to sorafenib in terms of PFS in patients who have received sunitinib as their only line of VEGF targeted therapy (HR: 0.74 [95% CI, 0.57–0.96]; \( p < 0.01 \); PFS for axitinib: 4.8 mo [95% CI, 4.5–6.4]) [5] (LE 2a). A low proportion of patients in this study had Memorial Sloan Kettering Cancer Center good-risk disease compared with the cabozantinib study, making cross-trial comparison of PFS difficult. There is no survival advantage for axitinib compared with sorafenib in this setting. The OS advantage of nivolumab over everolimus makes it preferable to axitinib in the second-line setting [1]. The impressive PFS and trend towards OS advantage for axitinib compared with sorafenib in this setting makes nivolumab preferable to axitinib, whereas the impressive PFS of cabozantinib makes it an attractive alternative to axitinib. Tolerability is an important consideration when recommendations cannot be made based on efficacy alone. Both everolimus and sorafenib have been outperformed by other agents in VEGF-refractory disease and should not be routine standard of care in pure VEGF-refractory disease. It is not currently possible to determine therapy based on baseline characteristics or biomarker expression for any of the drugs described.

2. New recommendations for patients who have failed VEGF targeted therapy and immune checkpoint inhibitors

There is a lack of data regarding the outcomes of patients who have failed initial VEGF targeted therapy and second-line nivolumab. Cabozantinib was tested in this setting in the randomised phase 3 trial; however, numbers were small [2]. Cabozantinib may be reasonably considered in preference to everolimus due to superior efficacy in VEGF-resistant disease, although everolimus was the most commonly used agent after nivolumab in the pivotal randomised trial [1]. Other agents such as axitinib and sorafenib are also untested in this setting, although both were used after nivolumab in the pivotal trial [1]. Axitinib has not been prospectively tested in patients who have failed multiple lines of therapy but has been used after cytokine therapy with success [5].

3. Conclusions

These two pivotal trials testing nivolumab and cabozantinib have changed treatment paradigms in VEGF targeted therapy–refractory RCC (LE 1a). There is a strong rationale for using both drugs in sequence in the second and third lines following VEGF targeted therapy. This creates a new a
standard for the majority of patients. Nivolumab is particularly compelling because of its survival advantage and adverse event profile. More mature OS data with cabozantinib are expected in 2016 and may further support its use, potentially changing these recommendations further.

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