Cabozantinib in the treatment of advanced renal cell carcinoma in adults following prior vascular endothelial growth factor targeted therapy: clinical trial evidence and experience

Susanne Osanto and Tom van der Hulle

Abstract: Cabozantinib is an oral multitargeted tyrosine kinase inhibitor (TKI) that potently inhibits MET and AXL, both associated with poor prognosis in renal cell carcinoma (RCC), next to vascular endothelial growth factor receptor 2, KIT, FLT3 and RET. Chronic treatment with vascular endothelial growth factor receptor (VEGFR)-targeting sunitinib upregulates MET and AXL in RCC, indicating that cabozantinib may be particularly effective in patients with advanced RCC whose disease progressed on prior VEGFR-targeted treatment. Cabozantinib (60 mg once daily) has been investigated in comparison to everolimus (10 mg once daily) in a phase III randomized controlled trial (RCT) in 658 patients with advanced RCC of whom 71% had received one prior and 29% had received at least two prior lines of VEGFR-targeted therapy. This study demonstrated highly significant improved progression-free survival of 7.4 months versus 3.9 months with a hazard ratio (HR) of 0.51 [95% confidence interval (CI) 0.41–0.62] in favour of cabozantinib. Cabozantinib also showed a superior overall survival of 21.4 months versus 16.5 months (HR 0.66; 95% CI 0.53–0.83). Objective response rate was higher in cabozantinib-treated patients, 17% versus 3%. Clinical benefit was shown in all subgroups of patients, including in patients with bone or visceral metastases. The safety profile was acceptable with manageable side effects. Based on this study, cabozantinib is a highly effective approved second-line treatment option for patients with advanced RCC with a manageable toxicity profile. Other recently approved second-line agents include checkpoint inhibitor nivolumab and VEGF-targeting agent lenvatinib combined with everolimus. In the absence of predictive markers as well as head-to-head comparisons of these three recently approved treatments, the choice between these drugs in second-line treatment will probably be made based on comorbidities, tolerability of previous treatment and presence of high tumour burden with rapidly progressive disease. Future pretreatment assessment of MET and AXL tumour aberration may aid clinicians to make a rational choice between currently approved second-line treatment options.

Keywords: AXL, cabozantinib, MET, renal cell cancer, targeted therapy, tyrosine kinase inhibitor, vascular endothelial growth factor receptor

Introduction

With an incidence of 338,000 new cases per year in 2012 and a related mortality of 143,000 worldwide, renal cell carcinoma (RCC) is one of the most common urological malignancies.1 RCC refers to a heterogeneous group of cancers originating within the renal cortex and comprising over 90% of malignancies in the kidney. Several
RCC subtypes can be identified based on histologic and molecular variants, with clear cell (70%), papillary (10–15%) and chromophobe (5%) carcinoma as the main histological types. RCC is considered to be insensitive to traditional chemotherapy and until 2005 cytokine treatment with high-dose interleukin (IL)-2 was the only treatment option, although associated with a low response rate and significant toxicity. Advances in understanding the pathogenesis of RCC resulted in new treatment options that changed the management and prognosis dramatically since 2005. Although the approved targeted agents effectively prolong progression-free survival (PFS) and overall survival (OS), inevitably drug resistance develops, emphasizing the need for new therapeutic options. In recent years, the therapeutic options for patients progressing on vascular endothelial growth factor (VEGF)-targeting first-line treatment are rapidly evolving with the introduction of nivolumab, cabozantinib and lenvatinib combined with everolimus. In this review, we will focus on cabozantinib, a recently approved novel agent for second-line treatment after prior VEGF-targeting agents, its safety and toxicity profile and its use in different settings. Furthermore, current treatment alternatives and a second-line treatment algorithm for patients with advanced RCC will be discussed.

**Insight in signalling pathways in RCC**

Increased angiogenesis, one of the hallmarks of cancers, is characteristic for clear cell RCC, the main histological type of renal cell cancers. Molecular biological studies in patients with hereditary and sporadic RCC unravelled signalling pathways involved in the development of RCC, paving the way for new therapeutic options. In the majority of clear cell RCC cases, alterations in the VHL tumour suppressor gene located on chromosome 3p are present resulting in inactivation of the VHL protein. The VHL protein is part of a cellular protein complex that is involved in the ubiquitination and degradation of a hypoxia-inducible factor (HIF). The loss of VHL protein activity results in accumulation of HIF and subsequently increased levels of proangiogenic factors, including VEGF, platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF). These growth factors are involved in signalling pathways stimulating angiogenesis, proliferation and migration, which all support tumour growth. Besides their role in the development of RCC, these proangiogenic factors remain important throughout the whole course of disease. Resistance to first-line treatment targeting proangiogenic factors, particularly VEGF, is related to re-establishment of these proangiogenic pathways. Described underlying mechanisms are a shift to alternative proangiogenic pathways, changes in gene expression patterns and additional genetic mutations.

The other key molecular signalling axis in RCC is the phosphatidylinositol-3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway. This Akt/mTOR pathway is involved in important cellular functions such as protein synthesis, glucose metabolism, cellular migration, and cell survival. It has been implicated in promoting tumour growth and is relevant in multiple cancers, including RCC.

**Targeted therapies and paradigm shift in RCC**

Better understanding of the genetics and molecular biology of RCC and the identification of the pathways involved in the development and progression of RCC have led to the development of several small molecules targeting receptors of VEGF, PDGF and c-KIT. Notably, these targeted therapies, often referred to as multireceptor tyrosine kinase inhibitors (TKIs), inhibit the tumour vasculature and not so much the tumour cells directly. Since December 2005, several targeted agents received US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for treatment of advanced disease based on large international phase III trials, and targeted therapies became standard therapies in both the first- and second-line setting of advanced RCC.

**First-line treatment trials**

First-line treatment options nowadays include VEGF receptor (VEGFR)-inhibiting small molecules sunitinib, pazopanib and bevacizumab (a monoclonal antibody binding ligand VEGF) combined with interferon (INF)-α, and the mTOR inhibitor temsirolimus (Table 1). Sunitinib was shown to be superior over INF-α, while for pazopanib efficacy was demonstrated in a placebo-controlled trial. In the largest trial ever performed in advanced RCC, pazopanib was compared head to head with sunitinib in 1110 patients and shown to be noninferior to
Table 1. Main outcomes from first-line therapy studies in metastatic renal cell carcinoma approved by the FDA and EMA based on randomized clinical trials.

| Study drug | Control arm | Patients | Risk groups (%)* | Primary endpoint | Median PFS (months) | HR PFS (95% CI) | Median OS (months) | HR OS (95% CI) | ORR (%) |
|------------|-------------|----------|------------------|------------------|---------------------|------------------|-------------------|---------------|---------|
| HD IL-2<sup>3</sup> | IL-2 + INF-α | 192 | F: 13 | 3-year PFS | 3.1 versus 3.1 | NR | 17 versus 13 | NR (p = 0.211) | 23.2 versus 9.9 |
| Sunitinib<sup>15,20</sup> | INF-α | 750 | F: 36 | PFS | 11 versus 5 | 0.42 [0.32–0.54] | 26.4 versus 21.8 | 0.821 [0.673–1.001] | 31 versus 6 |
| Pazopanib<sup>14,21</sup> | Placebo | 435 [46% cytokine pretreated] | F: 39 | PFS | 9.2 versus 4.2 | 0.46 [0.34–0.62] | 22.9 versus 20.5 [pazopanib after progression] | 0.91 [0.71–1.16] | 30 versus 3 |
| Bevacizumab + INF-α<sup>22,23</sup> | AVOREN study | 649 | F: 28 | OS | 10.2 versus 5.4 | 0.61 [0.51–0.73] | 23.3 versus 21.3 (>55% of patients received postprotocol therapy) | 0.86 [0.72–1.04] | 31 versus 13 |
| Bevacizumab + INF-α<sup>24,25</sup> | CALGB 90206 study | 732 | F: 26 | OS | 8.5 versus 5.2 | 0.71 [0.61–0.83] | 18.3 versus 17.4 | 0.86 [0.73–1.01] | 25.5 versus 13.1 |
| Sunitinib<sup>17,26</sup> | COMPARZ study | 1100 | F: 25 | PFS | 9.5 versus 8.4 | 1.05 [0.90–1.22] | 29.1 versus 28.3 | 0.92 [0.79–1.06] | 25 versus 31 |
| Temsirolimus<sup>18</sup> | Global ARCC Trial | 626 | F: 0 | OS | 5.5 versus 4.7 versus 3.1 | 0.66 [0.53–0.81] compared with INF-α | 10.9 versus 8.4 versus 7.3 | 0.73 [0.58–0.92] compared with INF-α | 8.6 versus 8.1 versus 4.8 |

In case updated study outcomes were published these results are reported.

*F, favourable; I, intermediate; P, poor risk groups according to the MSKCC criteria. 27

Forty-six percent of patients received cytokine treatment prior to inclusion.

COMPARZ was a noninferiority study testing whether pazopanib was inferior to sunitinib. Both pazopanib and sunitinib were already approved by regulatory authorities for clinical use in metastatic RCC. 17,26

CI, confidence interval; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HR, hazard ratio; IL-2, interleukin-2; INF-α, interferon-α; MSKCC, Memorial Sloan Kettering Cancer Center; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression free survival; RCC, renal cell carcinoma.
sunitinib.\textsuperscript{17} The intravenously administered mTOR inhibitor temsirolimus has been approved for poor-risk patients with clear cell RCC based on a RCT demonstrating improved OS compared with IFN-\(\alpha\).\textsuperscript{18} To date, antiangiogenesis agents, sunitinib and pazopanib, are currently the most widely prescribed first-line agents.\textsuperscript{19}

**Second-line treatment trials**

Randomized clinical phase III trials were performed in patients who received one or more TKIs or cytokine therapy. Until 2015, approved second-line therapies included VEGFR-targeting agents sorafenib, pazopanib, mTOR-inhibitor everolimus and VEGFR-targeting axitinib (Table 2).

The oral agent mTOR inhibitor, everolimus, was the first drug to be approved for second-line use in metastatic RCC and is used as the comparator in the registration studies of nivolumab, cabozantinib and lenvatinib combined with everolimus. In the RECORD-1 phase III RCT, patients who received at least one prior anti-VEGF treatment were randomized between everolimus 10 mg orally once daily and placebo.\textsuperscript{30} Patients who were included had progressive RCC and were on sunitinib, sorafenib or both, and had even received more than two prior treatments. The study allowed patients on placebo to cross over to everolimus upon progression. Of the patients treated with everolimus, 29% had a favourable prognosis, 56% an intermediate prognosis and only 15% a poor prognosis based on the Memorial Sloan Kettering Cancer Center (MSKCC) prognostic score.\textsuperscript{27} Median PFS was significantly longer in patients treated with everolimus compared with placebo, 4.0 months versus 1.9 months, respectively, with a hazard ratio (HR) for progressive disease of 0.3 [95% confidence interval (CI) 0.22–0.40]. Partial responses (PRs) were observed in only 3 of the 272 patients (1%) who received everolimus and disease stabilization for at least 8 weeks was the best response observed in 63% of patients. Toxicity included pneumonitis, stomatitis and hyperglycaemia. Based on the RECORD-1 study, everolimus became the standard of care in second-line treatment.

Axitinib inhibits VEGFR-1, VEGFR-2 and VEGFR-3, but not MET and AXL, and is another TKI approved for second-line treatment of advanced RCC. Approval was based on the phase III randomized AXIS trial which showed an improved PFS of 8.3 months for axitinib compared with 5.7 months for sorafenib, with a HR for progressive disease of 0.656 (95% CI 0.552–0.779).\textsuperscript{32,33} Only one previous line of treatment was allowed, which was sunitinib in 54% and cytokines in 35% of patients. Clinical benefit was strongest in patients previously treated with cytokines, while the benefit was modest in the subgroup of patients who received sunitinib as first-line treatment with a median PFS of 4.8 months versus 3.4 months.

**Cabozantinib**

**Mechanism of action**

Cabozantinib is a TKI with pronounced activity against multiple tyrosine kinases involved in tumour growth, angiogenesis, abnormal bone remodelling, metastatic spread, and drug resistance of cancer. Using \textit{in vitro} testing, inhibitory activity of cabozantinib has been tested against a variety of approximately 270 human kinases. Important targets of cabozantinib are VEGFR-1, VEGFR-2, VEGFR-3, AXL and MET (hepatocyte growth factor receptor) and RET, the stem cell factor receptor KIT, FLT3, ROS1, MER, TYRO3, TRKB and TIE-2.\textsuperscript{35,36} Kinetic parameters for cabozantinib binding these targets are shown in Table 3. Particularly the inhibition of AXL and MET could be a critically important characteristic which distinguishes cabozantinib from other multireceptor TKIs, such as sunitinib and pazopanib.

Overexpression of MET and AXL are observed in a wide range of malignancies and are associated with
Table 2. Main outcomes from second-line and later therapy studies in metastatic renal cell carcinoma approved by the FDA and EMA based on randomized clinical trials.

| Study drug          | Control arm | Patients | Risk groups (%)* | Primary endpoint | Median PFS (months) | HR PFS (95% CI) | Median OS (months) | HR OS (95% CI) | ORR (%) |
|---------------------|-------------|----------|------------------|------------------|---------------------|------------------|-------------------|-----------------|---------|
| Sorafenib**28,29    | Placebo     | 903      | F: 51 I: 49 P: 0 | OS               | 5.5 versus 2.8     | 0.44 (0.35–0.55) | 17.8 versus 15.2 | 0.88 (0.74–1.04) | 10 versus 2 |
| TARGET study        |             |          |                  |                  |                     |                  |                   |                 |         |
| Everolimus**30,31   | Placebo     | 410      | F: 29 I: 56 P: 15| PFS              | 4.9 versus 1.9     | 0.33 (0.25–0.43) | 14.8 versus 14.4 | 0.87 (0.65–1.17) | 1.8 versus 0 |
| RECORD-1 study      |             |          |                  |                  |                     |                  |                   |                 |         |
| Axitinib**32,33     | Sorafenib   | 723      | F: 28 I: 37 P: 33| PFS              | 6.7 versus 4.7     | 0.665 (0.544–0.812) | 20.1 versus 19.2 | 0.969 (0.800–1.174) | 19 versus 9 |
| AXIS study          |             |          |                  |                  |                     |                  |                   |                 |         |
| Nivolumab**4        | Everolimus  | 821      | F: 36 I: 49 P: 15| OS               | 4.6 versus 4.4     | 0.88 (0.75–1.03) | 25.0 versus 19.6 | 0.73 (0.57–0.93) | 25 versus 5 |
| CHECK MATE025 Study |             |          |                  |                  |                     |                  |                   |                 |         |
| Cabozantinib**5,34  | Everolimus  | 658      | F: 46 I: 42 P: 13| PFS              | 7.4 versus 3.9     | 0.51 (0.41–0.62) | 21.4 versus 16.5 | 0.66 (0.53–0.83) | 17 versus 3 |
| METEOR study        |             |          |                  |                  |                     |                  |                   |                 |         |
| Lenvatinib +        | Lenvatinib  | 153      | F: 16 I: 61 P: 22| PFS              | 12.8 versus 9.0    | 0.45 (0.27–0.79)  | 25.5 versus 19.1 | 0.51 (0.30–0.88) | 35 versus 39 |
| Everolimus**6       | Everolimus  |          |                  |                  | (lenvatinib) versus 5.6 (everolimus) |                  |                   |                 |         |
| phase II study      |             |          |                  |                  |                     |                  |                   |                 |         |

In case updated study outcomes were published these results are reported.

*F, favourable; I, intermediate; P, poor according to the MSKCC criteria.27
CI, confidence interval; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HR, hazard ratio; IL-2, interleukin-2; INF-α, interferon α; MSKCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate; OS, overall survival; PFS, progression free survival.
a poor prognosis in patients with advanced RCC.\textsuperscript{37,38} Moreover, in preclinical models sunitinib treatment led to increased MET and AXL signalling, thereby promoting metastatic effects and angiogenesis, whereas MET and AXL signalling were reduced and tumour growth inhibited by cabozantinib in RCC xenografts that had become resistant to sunitinib treatment.\textsuperscript{36,39} Therefore, the MET and AXL pathway seems to play an important role in primary resistance as well as in the development of resistance to VEGF pathway inhibition by sunitinib.\textsuperscript{40} Simultaneous blocking of MET and AXL in addition to the VEGF pathway may offer an advantage in the treatment of advanced RCC. Cabozantinib treatment may thus be suitable for patients whose disease has progressed on prior anti-VEGF treatment, but may also be beneficial in the first-line setting as MET has been shown to be already upregulated in treatment-naïve RCC.\textsuperscript{41–43}

Pharmacokinetics and metabolism

A study in healthy individuals demonstrated a dose-proportional increase of plasma exposure after single doses of 20, 40 and 60 mg of cabozantinib.\textsuperscript{44} The median time to the maximum plasma concentration ($T_{\text{max}}$) is approximately 4 h and the terminal half life after a single oral dose in healthy individuals was approximately 120 h.\textsuperscript{44,45} In a phase I dose-escalating study, accumulation of cabozantinib after repeated doses was demonstrated with a four- to fivefold higher steady-state exposure compared with day 1.\textsuperscript{44} Steady-state plasma levels were reached after 15 days. At steady state, the half life is approximately 55 h. Cabozantinib is highly protein bound \textit{in vitro} in human plasma (\(\geq 99.7\%\)) and a low serum albumin is associated with a lower $C_{\text{max}}$ and a higher free cabozantinib concentration.\textsuperscript{47}

Cabozantinib is metabolized by the liver to less active metabolites which all possess \textit{in vitro} inhibition potencies of up to 10\% of parent cabozantinib against the most relevant target kinases.\textsuperscript{48} The hepatobiliary route is the most important route for cabozantinib clearance. After a single oral dose of radioactive $^{14}$C-cabozantinib in healthy individuals, approximately 81\% of the total administered radioactivity was recovered, mainly in faeces (54\%) and less in urine (27\%).\textsuperscript{48} In a pooled analysis including 289 patients of whom the majority were treated with cabozantinib 140 mg once daily, interindividual variability in oral clearance (CL/F) was 35\%. Only a high body mass index (BMI) (defined as the 95\% percentile BMI relative to the median) and female sex were shown to be associated with a 28\% higher steady state area under the curve (AUC), but this difference is not considered clinically meaningful and does not require dose adjustments.\textsuperscript{49}

### Table 3. \textit{In vitro} kinase inhibition profile of cabozantinib.

| Kinase | \(IC_{50} \pm \text{SD,*} \) nmol/liter | Enzyme concentration, nmol/liter | ATP concentration, \(\mu\)mol/liter |
|--------|-------------------------------------|---------------------------------|----------------------------------|
| VEGFR-2 | 0.035 ± 0.01 | 0.05 | 3 |
| MET | 1.3 ± 1.2 | 10 | 1 |
| KIT | 4.6 ± 0.5 | 1 | 3 |
| RET | 5.2 ± 4.3 | 15 | 2 |
| AXL | 7 | Not determined | Not determined |
| FLT3 | 11.3 ± 1.8 | 0.5 | 1 |
| TIE2 | 14.3 ± 1.1 | 15 | 5 |
| RON | 124 ± 1.2 | 60 | 1 |

*Mean ± SD of at least three independent determinations. Adapted from Yakes \textit{et al.} \textsuperscript{35} ATP, adenosine triphosphate; IC\textsubscript{50}, half maximal inhibitory concentration; SD, standard deviation; VEGFR, vascular endothelial growth factor receptor.
cabozantinib concentrations were higher in subjects with mild and moderate renal impairment, and much higher (81% and 63%) in subjects with mild and moderate hepatic impairment, respectively. In patients with impaired liver or moderate impaired renal function, cabozantinib treatment should be carefully monitored and dose adjustments made if needed. Of note, cabozantinib has not been investigated in patients with severe renal impairment (defined as eGFR < 30 ml/min/1.73 m²).

Drug–drug interactions and Cytochrome P450 (CYP) metabolism
The absorption of cabozantinib is affected by food intake: a high-fat meal increased C\text{max} and AUC values after a single 140 mg oral cabozantinib dose, by 41% and 57%, respectively, and delayed T\text{max} relative to fasting conditions in healthy volunteers from 4 h to 6 h after administration. It should be noticed that cabozantinib capsules were used in this study, but nowadays tablets are generally used whereas bioequivalence was not demonstrated for both formulations.44 Food fasting is recommended 2 h prior and 1 h after administration of cabozantinib. Another study investigated the effect of proton pump inhibition (esomeprazole) on cabozantinib exposure and did not demonstrate a clinically meaningful change in plasma exposure, suggesting that concomitant use of pH-lowering agents is allowed.45

Cabozantinib is a substrate of CYP3A4 \textit{in vitro} that metabolizes cabozantinib to metabolites of which four are present in plasma at exposures (AUC) over 10% of the parent compound, whereas inhibition of CYP3A4 reduces the formation of one of these metabolites (cabozantinib N-oxide metabolite) by over 80%.48,50

Chronic coadministration of strong inhibitors or inducers of CYP3A4 should thus be avoided when prescribing cabozantinib to reduce the risk of drug–drug interactions, or the dose of cabozantinib should be adjusted.

Clinical phase I, II and III trials with cabozantinib in advanced RCC
Phase I trial in advanced RCC and other tumours
Phase I clinical trials in patients with solid tumours have been conducted to define the maximum tolerated dose/recommended dose for oral administration of cabozantinib. In a phase I study in patients with medullary thyroid cancer a maximum tolerated dose of 140 mg cabozantinib daily was established.46 Subsequently, cabozantinib was investigated in a single-arm, open-label phase I trial [ClinicalTrials.gov identifier: NCT01100619] in 25 patients with advanced RCC whose disease progressed on prior TKI and mTOR therapies.51 Grade 3 and higher adverse events (AEs) included fatigue (20%), diarrhoea (12%), anorexia (4%), hypophosphatemia (40%), hypertension (4%), vomiting (4%) and hand–foot syndrome (4%). Three patients developed grade 3 pulmonary embolism, and one patient had grade 4 mental status changes. Dose reduction because of AEs occurred in 20 (80%) patients. Cabozantinib was highly effective with a median PFS of 12.9 months, a median OS of 15.0 months, and an objective response rate of 28% in this phase I study.

Cabozantinib versus sunitinib in first-line phase II randomized trial in metastatic RCC
The CABOSUN [ClinicalTrials.gov identifier] randomized phase II study evaluated 60 mg of cabozantinib compared with standard of care sunitinib (50 mg once per day; 4 weeks on, 2 weeks off) as first-line therapy in 157 intermediate- or poor-risk patients with metastatic RCC (79 patients received cabozantinib and 78 patients sunitinib).52 Inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and intermediate or poor risk as per International Metastatic Renal Cell Carcinoma Database Consortium (IDMC) criteria.53 PFS was the primary endpoint. Updated results were recently presented at the ESMO 2017 meeting (poster LBA38). Cabozantinib had a significantly longer median PFS of 8.6 months compared with 5.3 months with sunitinib and was associated with a 52% reduction in rate of progression (HR 0.48; 95% CI 0.31–0.74).52 PFS according to IDMC risk group showed PFS advantage for cabozantinib across risk groups, with IDMC intermediate-risk group patients (n = 127) having a median PFS of 11.4 \textit{versus} 6.1 (HR 0.52; 95% CI 0.32–0.82) and in the smaller poor risk group (n = 30) a median PFS of 6.8 \textit{versus} 2.7 (HR 0.31; 95% CI 0.11–0.92). Patients with bone metastases, a poor prognostic factor, seemed to benefit from cabozantinib therapy with a median PFS of 5.5 months \textit{versus} 3.3 months with a HR of 0.51 (95% CI 0.26–0.99).
A PR was observed in 16 of the 79 patients (20%) who received cabozantinib and in 7 of the 78 patients (9%) who received sunitinib. Additionally, stable disease occurred in 43 patients (54%) with cabozantinib versus 30 patients (38%) with sunitinib. After a median follow up of 30.8 months and the occurrence of 90 deaths, the median OS for cabozantinib- and sunitinib-treated patients was 26.6 (95% CI 14.6–not evaluable) versus 21.2 months (95% CI 16.3–27.4) with a HR of 0.79 (95% CI 0.53–1.2). The incidence of grade 3 or 4 AEs seems to be comparable in patients treated with cabozantinib and sunitinib: 68 and 65%, respectively. In Table 4, AEs occurring in over 30% of either treatment arm of the CABOSUN study are shown. Dose reductions were more frequently required in patients who received cabozantinib, 58% of patients versus 49% of patients. The primary endpoint was PFS, secondary endpoints included time to progression (TTP), OS, objective response rate (ORR), disease control rate (DCR) and safety.

The majority of patients (71%) received only one prior VEGFR-targeted TKI (sunitinib in 63% and pazopanib 43% of patients), whereas 29% had more than one prior treatment. Forty-six percent of patients belonged in the favourable, 42%

### Table 4. Adverse events reported in at least 30% of patients in either treatment arm of the CABOSUN study.

| Adverse events               | Cabozantinib (n = 78) | Sunitinib (n = 72) |
|------------------------------|-----------------------|--------------------|
|                              | Any grade %           | Grade 3 or 4 %     | Any grade %           | Grade 3 or 4 %     |
| Any adverse event            | 96                    | 68                 | 99                    | 65                 |
| Fatigue                      | 64                    | 6                  | 68                    | 17                 |
| Hypertension                 | 67                    | 28                 | 44                    | 21                 |
| Diarrhoea                    | 73                    | 10                 | 54                    | 11                 |
| AST increased                | 60                    | 3                  | 31                    | 3                  |
| ALT increased                | 55                    | 5                  | 28                    | 0                  |
| Anorexia                     | 47                    | 5                  | 32                    | 1                  |
| Hand–foot syndrome           | 42                    | 8                  | 33                    | 4                  |
| Dysgeusia                    | 41                    | 0                  | 29                    | 0                  |
| Thrombocytopenia             | 38                    | 1                  | 61                    | 11                 |
| Oral mucositis               | 37                    | 5                  | 29                    | 6                  |
| Anaemia                      | 33                    | 1                  | 46                    | 3                  |
| Nausea                       | 32                    | 3                  | 39                    | 4                  |
| Weight loss                  | 32                    | 4                  | 17                    | 0                  |
| Neutropenia                  | 15                    | 0                  | 35                    | 4                  |
| Leukopenia                   | 12                    | 0                  | 35                    | 3                  |

Patients were counted once at the highest grade for each preferred term. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Adapted from Choueiri et al. and updated at ESMO meeting 2017, poster LBA38. ALT, alanine transaminase; AST, aspartate transaminase; ESMO, European Society for Medical Oncology.

**METEOR phase III randomized trial of cabozantinib versus everolimus**

METEOR, a phase III randomized trial, investigated the efficacy of 60 mg cabozantinib versus 10 mg of everolimus once daily in 658 patients with advanced RCC whose disease progressed on or after one or two lines of VEGFR-targeted therapies. Patients were included between August 2013 and November 2014 and were stratified based on number of prior VEGFR TKIs (one or at least two) and MSKCC risk group. Patients thus had to have progressive disease on at least one VEGFR-targeted therapy, but there was no limit on the number of lines of prior treatment. Multiple types of prior therapies including cytokines, monoclonal antibodies (such as those targeting VEGF or programmed death 1 [PD-1]), and chemotherapies were allowed, while only prior mTOR inhibitor treatment was an exclusion criterion. Patients with treated brain metastases were also allowed.
in the intermediate, and 13% in the poor-risk category as defined by MSKCC criteria.

METEOR reached its primary endpoint of a statistically significant prolongation in median PFS of cabozantinib compared with the standard of care, single-agent everolimus (7.4 months versus 3.9 months), with a highly significant HR of 0.51 (95% CI 0.41–0.62; \( p < 0.001 \)) corresponding to a 49% reduction in the risk of disease progression or death (Table 2). Also, two other efficacy endpoints were reached: cabozantinib showed a benefit in ORR (17% versus 3%; \( p < 0.0001 \)) and there was a significant improvement in OS with a HR of 0.66 (95% CI 0.53–0.83) in favour of cabozantinib.34

Moreover, an increased OS and PFS with cabozantinib compared with everolimus (HR <1) were also observed for all subgroups analysed, including age, sex, race, but also MSKCC risk groups, number of prior VEGFR-targeted TKIs, duration of prior VEGFR-targeted TKI treatment, prior sunitinib or pazopanib therapy, prior treatment with checkpoint inhibitors targeting PD-1 or programmed death-ligand 1 (PD-L1), and MET expression level, as can be seen from the HR for OS and PFS shown in Table 5. Interestingly, improvement of OS and PFS with cabozantinib was irrespective of tumour burden or metastatic site, and even irrespective of presence of bone metastases, known to be associated with poor prognosis.54

Highly relevant for clinicians, the presence of bone metastases or visceral metastases was associated with favourable response to cabozantinib versus everolimus. Moreover, patients with metastases in at least three organs had a higher chance of a clinical response than those with metastases in one or two organs, indicating that patients with high volume disease may particularly benefit from cabozantinib treatment. Longer response to first VEGFR inhibitor and a longer interval between the start of the prior treatment and study enrolment were associated with a higher chance of a favourable response (Table 5).

Toxicity and safety profile
In both treatment arms AEs were observed, namely in 100% of cabozantinib and 99% of everolimus-treated patients. Table 6 shows AEs occurring in over 30% of patients in either treatment group. The toxicity profile of cabozantinib in this trial seems to be similar to what is observed for other TKIs (Table 4). The most common grade 3 or 4 AEs were hypertension (15%), diarrhoea (13%) and fatigue (11%) with cabozantinib, and anaemia (17%), fatigue (7%) and hyperglycaemia (5%) with everolimus. Grade 3 and higher AEs more frequently or exclusively observed in the everolimus-treated group include anaemia (17%), hyperglycaemia (5%) and pneumonia (4%).

Discontinuation of study treatment due to AEs not related to RCC occurred in 9.1% of cabozantinib- and 10% of everolimus-treated patients, indicating a similar overall tolerability. Among patients treated with cabozantinib, 60% had to have their dose decreased during the trial. Importantly, the median daily dose was 43 mg for cabozantinib and 9 mg for everolimus.

Cabozantinib regulatory status
Based on the results of the phase III METEOR study, cabozantinib (Cabometyx; Exelixis, Inc., San Francisco, CA) tablets were approved by the FDA in April 2016 for the treatment of advanced RCC in patients who have received prior antiangiogenic therapy, and by the EMA for the treatment of advanced RCC following VEGF-targeted therapy in September 2016 (Cabometyx; Ipsen, Paris, France). Based on the CABOSUN study, EMA approval for first-line treatment has been requested.

Two other recently approved second-line targeted therapies
In September 2015, three clinical trials including METEOR reported the advantage of novel drug treatment in patients with advanced RCC who have previously received VEGF inhibitors, and all trials compared the new drug or a combination of drugs of interest to everolimus.

Anti-PD checkpoint inhibitor nivolumab in second-line treatment
FDA approved PD-1 checkpoint inhibitor nivolumab (Opdivo, Bristol-Myers Squibb, New York) in November 2015 as a new second-line treatment for advanced RCC based on the results of the phase III trial CHECKMATE-025 [ClinicalTrials.gov identifier: NCT01668784]. Patients with advanced RCC progressive on one or two antiangiogenic therapies were included in the study and randomized between nivolumab (3 mg/
kg intravenously every 2 weeks) or everolimus (10 mg orally once daily). The study reached its primary endpoint of a statistically significant prolongation in OS: 25.0 months in the nivolumab group versus 19.6 months in the everolimus group with a HR of 0.73 (98.5% CI 0.57–0.93) (Table 2), while no improvement in PFS was observed.\(^4\) OS benefit for nivolumab was observed across prespecified subgroups, including subgroups based on the MSKCC prognostic score and the number of previous antiangiogenic therapies. The ORR was higher with nivolumab: 25% \textit{versus} 5% for everolimus with an odds ratio of 5.98 (95% CI 3.68–9.72). Objective responses were mainly a PR (24% out of

| Table 5. Hazard ratios for progression-free survival and overall survival for subgroups in the METEOR study. |
|-------------------------------------------------|-------------------------------------------------|
| Total number of patients, \(n\) (%) | Patients on cabozantinib/everolimus, \(N\) | Progression-free survival HR (95% CI) | Overall survival HR (95% CI) |
|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Overall | 658 (100) | 330/328 | 0.51 (0.41–0.62) | 0.66 (0.53–0.83) |
| Age | | | | |
| <65 years | 394 (60) | 196/198 | 0.53 (0.41–0.68) | 0.72 (0.54–0.95) |
| \(\geq65\) years | 264 (40) | 134/130 | 0.50 (0.36–0.69) | 0.62 (0.44–0.88) |
| MSKCC risk group | | | | |
| Favourable | 300 (46) | 150/150 | 0.51 (0.38–0.69) | 0.66 (0.46–0.96) |
| Intermediate | 274 (42) | 139/135 | 0.47 (0.35–0.65) | 0.67 (0.48–0.94) |
| Poor | 84 (13) | 41/43 | 0.70 (0.42–1.16) | 0.65 (0.39–1.07) |
| Previous nephrectomy | | | | |
| No | 96 (15) | 47/49 | 0.51 (0.30–0.86) | 0.75 (0.44–1.27) |
| Yes | 562 (85) | 283/279 | 0.51 (0.41–0.64) | 0.66 (0.52–0.84) |
| ECOG status | | | | |
| 0 | 442 (67) | 226/216 | 0.46 (0.36–0.59) | 0.65 (0.49–0.87) |
| 1 | 216 (33) | 104/112 | 0.44 (0.33–0.57) | 0.64 (0.51–0.80) |
| Diagnosis to randomization | | | | |
| <1 year | 135 (21) | 59/76 | 0.55 (0.36–0.84) | 0.89 (0.58–1.37) |
| \(\geq1\) year | 522 (79) | 271/251 | 0.51 (0.41–0.65) | 0.66 (0.51–0.85) |
| Tumour MET status | | | | |
| High | 101 (15) | 51/50 | 0.41 (0.24–0.68) | 0.55 (0.31–0.99) |
| Low | 312 (47) | 150/162 | 0.58 (0.43–0.79) | 0.72 (0.52–1.00) |
| Unknown | 245 (37) | 129/116 | 0.50 (0.36–0.68) | 0.67 (0.47–0.95) |
| Number of organs with metastases | | | | |
| 1 | 115 (17) | 59/56 | 0.84 (0.52–1.17) | 0.72 (0.39–1.34) |
| 2 | 178 (27) | 101/77 | 0.60 (0.40–0.89) | 0.73 (0.47–1.16) |
| \(\geq3\) | 358 (54) | 168/190 | 0.38 (0.29–0.50) | 0.65 (0.49–0.86) |
| Bone metastases | | | | |
| No | 516 (78) | 253/263 | 0.57 (0.45–0.71) | 0.71 (0.55–0.91) |
| Yes | 140 (21) | 77/65 | 0.33 (0.21–0.51) | 0.55 (0.34–0.86) |
| Visceral metastases | | | | |
| No | 172 (26) | 89/83 | 0.64 (0.42–0.97) | 0.70 (0.44–1.12) |
| Yes | 486 (74) | 241/245 | 0.48 (0.38–0.60) | 0.66 (0.52–0.86) |
| Visceral and bone metastases | | | | |
| No | 546 (83) | 270/276 | 0.56 (0.45–0.70) | 0.73 (0.57–0.93) |
| Yes | 112 (17) | 60/52 | 0.26 (0.16–0.43) | 0.45 (0.28–0.72) |
| Number of previous VEGFR TKIs | | | | |
| 1 | 464 (71) | 235/229 | 0.52 (0.41–0.66) | 0.65 (0.50–0.85) |
| \(\geq2\) | 194 (29) | 95/99 | 0.51 (0.35–0.74) | 0.73 (0.48–1.10) |
| Duration of first VEGFR TKI | | | | |
| \(\leq6\) months | 190 (29) | 88/102 | 0.62 (0.44–0.89) | 0.69 (0.47–1.01) |
| \(>6\) months | 466 (71) | 242/224 | 0.48 (0.38–0.62) | 0.69 (0.52–0.90) |
| Progression after start of most recent VEGFR TKI | | | | |
| \(\leq3\) months | 112 (17) | 44/68 | 0.67 (0.42–1.07) | 0.76 (0.47–1.24) |
| \(\geq3\) months | 542 (82) | 283/259 | 0.50 (0.40–0.62) | 0.68 (0.53–0.88) |
| Previous PD-1 or PD-L1 treatment | | | | |
| No | 626 (95) | 312/314 | 0.54 (0.44–0.66) | 0.68 (0.54–0.85) |
| Yes | 32 (5) | 18/14 | 0.22 (0.07–0.65) | 0.56 (0.21–1.52) |
| Only previous VEGFR TKI | | | | |
| Sunitinib | 267 (41) | 135/132 | 0.43 (0.32–0.59) | 0.66 (0.47–0.93) |
| Pazopanib | 171 (26) | 88/83 | 0.67 (0.45–0.99) | 0.66 (0.42–1.04) |

Adapted from Choueiri et al.\(^3\)\(^4\)

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.
25%) in the nivolumab group and 5% in the everolimus group, whereas complete remissions were rarely observed (1% in the nivolumab group versus <1% in the everolimus group). Side effects were in general modest and treatment well tolerated. PD-L1 expression was not shown to be a predictive marker for a response to nivolumab.

Combination of lenvatinib plus everolimus

In May 2016, the FDA approved the two-drug regimen lenvatinib (Lenvima, Eisai, Tokyo, Japan) in combination with everolimus (Afinitor, Novartis, Basel, Switzerland) as a treatment for patients with advanced RCC following prior antiangiogenic therapy based on the results of a three-arm randomized phase II study in approximately 150 patients (Table 2). Patients were randomized between three arms: lenvatinib (18 mg once daily) in combination with everolimus (5 mg once daily) \( (n = 51) \); lenvatinib alone (at a higher dose of 24 mg) \( (n = 52) \); and everolimus alone (10 mg once daily) \( (n = 50) \). Patients with metastatic RCC progressive on one line of antiangiogenic therapy were included.

This combination inhibits two critical independent VEGF and mTOR pathways simultaneously. Lenvatinib, in addition to VEGFRs, also targets MET (similar to cabozantinib, but unlike cabozantinib not AXL) and the FGF pathway. The pivotal phase II trial demonstrated that lenvatinib plus everolimus reduced the risk of progression or death by 63% versus everolimus alone. Median PFS with lenvatinib plus everolimus was 12.8 months versus 5.6 months with everolimus (HR 0.45; 95% CI 0.22–0.79). Common side effects of lenvatinib included fatigue, nausea, hypertension, and a considerable proportion of patients with high-grade diarrhoea (20%). Two deaths were reported to be related to study treatment: one cerebral haemorrhage in the combination arm and one myocardial infarction in the lenvatinib alone arm.

Rational choice for second and further line treatment in advanced RCC

Currently, an amazing number of seven regulatory approved drugs are available for second-line treatment of patients with advanced RCC (Table 2). Novel approved agents, cabozantinib, nivolumab and lenvatinib, in combination with everolimus, now result in a paradigm shift in treatment of patients who received one prior VEGF-targeted therapy. All three novel treatment options showed superiority compared with everolimus. Moreover, PFS obtained with cabozantinib and the combination of lenvatinib and everolimus was longer, whereas OS obtained with all three novel treatments was longer than the

### Table 6. Adverse events reported in at least 30% of patients in either treatment arm of the METEOR study.

| Adverse event               | Cabozantinib \( n = 331 \) | Everolimus \( n = 322 \) |
|-----------------------------|------------------------------|--------------------------|
| Any adverse event           | Any grade, \( n (\%) \)       | Any grade, \( n (\%) \)   |
|                             | Grade 3 or 4, \( n (\%) \)    | Grade 3 or 4, \( n (\%) \) |
| Any adverse event           | 305 (92)                     | 296 (89)                 |
| Diarrhoea                   | 235 (71)                     | 193 (58)                 |
| Fatigue                     | 195 (59)                     | 154 (48)                 |
| Nausea                      | 173 (52)                     | 93 (29)                  |
| Decreased appetite          | 156 (47)                     | 114 (35)                 |
| Hand-foot syndrome          | 142 (43)                     | 19 (6)                   |
| Vomiting                    | 113 (34)                     | 47 (15)                  |
| Weight decreased            | 114 (34)                     | 42 (13)                  |
| Hypertension                | 122 (37)                     | 26 (8)                   |
| Cough                       | 68 (21)                      | 110 (34)                 |
| Rash                        | 54 (16)                      | 94 (29)                  |
| Anaemia                     | 61 (18)                      | 126 (39)                 |

Events reported irrespective of whether the event was considered by the investigator to be related to the study treatment. One treatment-related death occurred in the cabozantinib group (death not otherwise specified) and two occurred in the everolimus group (one aspergillus infection and one pneumonia aspiration). The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Adapted from Choueiri et al.34
OS demonstrated for previous second-line treatments. However, it should be noted that distribution in prognostic risk groups, number of prior lines of treatment, type of prior treatment, presence of unfavourable risk factors (e.g. presence of bone and liver metastases) and availability of subsequent treatment options, may contribute to observed differences in PFS and OS between studies.

The choice between nivolumab, cabozantinib or the lenvatinib with everolimus combination as a second-line therapeutic approach poses a true challenge for clinicians since head-to-head comparisons and predictive markers are lacking. In the absence of regulatory or financial restrictions, the following considerations should be taken into account when choosing between these three treatment options for a patient.

First, important limitations of the study investigating the combination of lenvatinib with everolimus are the small sample size, the unblinded study design, and it remains unclear whether the combination of lenvatinib with everolimus is superior over single agent lenvatinib. In view of the frequency of AEs, a careful risk–benefit assessment should be done when considering the combination of lenvatinib with everolimus.

Secondly, comorbidity and experienced toxicity to first-line VEGF-targeted therapy should be considered carefully before choosing the second-line treatment. For instance, patients who experienced severe toxicity to first-line VEGF-targeted therapy seem more likely to also tolerate cabozantinib less well. Furthermore, pre-existing autoimmune disease and inflammatory disease are (relative) contraindications for checkpoint inhibitors.

Third, the rate of disease progression and the volume of disease might be considered. It is a general belief that time to response is usually longer for checkpoint inhibitors compared with VEGF-targeted therapy, and this could translate into physician’s preference for cabozantinib over nivolumab in patients with rapidly progressive disease or high volume of disease. The median time to response for nivolumab was 3.5 months, which may translate into a relatively long period of time before the clinician can decide whether the disease does not respond to nivolumab, more so since treatment beyond progression may be followed by a remission in a low percentage of patients on checkpoint inhibitors. Of note, the median time to response was only reported for nivolumab (and everolimus) in the CHECKMATE study. The potential advantage of nivolumab is the prolonged responses in a minority of patients. This consideration is supported by a network meta-analysis comparing the OS results for nivolumab with cabozantinib, indicating that the HR for OS favoured cabozantinib during the first 5 months, whereas the HR for OS became increasingly in favour of nivolumab thereafter. Another network meta-analysis including all available second-line treatment options, except the lenvatinib with everolimus combination, demonstrated no difference in OS (HR 0.9; 95% CI 0.69–1.19) despite the superior PFS for cabozantinib over nivolumab with a HR of 0.58 (95% CI 0.45–0.74).

As both METEOR and CHECKMATE included patients who had already received two lines of treatment, in daily practice the alternative agent (nivolumab or cabozantinib) will most likely be used upon progression of disease as a third-line agent.

Conclusion
Cabozantinib is a novel multitargeted MET-, AXL- and VEGFR-2-targeting TKI that improved PFS, OS and ORR compared with everolimus in patients with advanced RCC whose disease progressed after one or more prior VEGFR-targeted therapies. The safety profile of cabozantinib was acceptable, AEs manageable and similar to those of other VEGFR TKIs. The recommended dose of cabozantinib in metastatic RCC is 60 mg orally daily.

The recent introduction of two other treatment options, nivolumab and lenvatinib combined with everolimus, will now translate into a new treatment paradigm of preferred treatment options in the second-line treatment of patients with advanced RCC whose disease has progressed on one or more prior VEGFR-targeted therapies.

Efforts to assess the efficacy of cabozantinib and other MET inhibitors in the papillary type subset of RCC are ongoing.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement
Susanne Osanto, Leiden University Medical Center, has taken part in an advisory board and a
satellite symposium organized by Ipsen. Tom van der Hulle has no conflicts of interest.

References

1. Ferlay J, Soerjomataram I, Ervik M, et al. Globocan 2012 V1.0, cancer incidence and mortality worldwide: IARC Cancerbase No. 11. Lyon, France: International Agency for Research on Cancer, 2013.

2. Chow WH, Dong LM and Devesa SS. Epidemiology and risk factors for kidney cancer. Nat Rev Urol 2010; 7: 245–257.

3. Mcdermott DF, Regan MM, Clark JI, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. J Clin Oncol 2005; 23: 133–141.

4. Motzer RJ, Escudier B, Mcdermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015; 373: 1803–1813.

5. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015; 373: 1814–1823.

6. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol 2015; 16: 1473–1482.

7. Hanahan D and Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144: 646–674.

8. Duan DR, Humphrey JS, Chen DY, et al. Characterization of the VHL tumor suppressor gene product: localization, complex formation, and the effect of natural inactivating mutations. Proc Natl Acad Sci USA 1995; 92: 6459–6463.

9. Kim WY and Kaelin WG. Role of VHL gene mutation in human cancer. J Clin Oncol 2004; 22: 4991–5004.

10. Kaelin WG Jr. The von Hippel-Lindau tumor suppressor protein and clear cell renal carcinoma. Clin Cancer Res 2007; 13: 680s–684s.

11. Porta C, Paglino C, Iamariello I, et al. Changes in circulating pro-angiogenic cytokines, other than VEGF, before progression to sunitinib therapy in advanced renal cell carcinoma patients. Oncology 2013; 84: 115–122.

12. Zhang L, Bhasin M, Schor-Bardach R, et al. Resistance of renal cell carcinoma to sorafenib is mediated by potentially reversible gene expression. PLoS One 2011; 6: e19144.

13. Pal SK, Sonpavde G, Agarwal N, et al. Evolution of circulating tumor DNA profile from first-line to subsequent therapy in metastatic renal cell carcinoma. Eur Urol 2017; 72: 557–564.

14. Vivanco I and Sawyers CL. The phosphatidylinositol 3-kinase AKT pathway in human cancer. Nat Rev Cancer 2000; 2: 489–501.

15. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007; 356: 115–124.

16. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010; 28: 1061–1068.

17. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013; 369: 722–731.

18. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007; 356: 2271–2281.

19. Hackshaw MD, Holmes M, Lankford M, et al. Prescribing preferences in the first-line treatment for patients with metastatic renal cell carcinoma in the United States. Clin Genitourin Cancer 2016; 14: e479–e487.

20. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009; 27: 3584–3590.

21. Sternberg CN, Hawkins RE, Wagstaff J, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Eur J Cancer 2013; 49: 1287–1296.

22. Escudier B, Pluzanska A, Kralawski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007; 370: 2103–2111.

23. Escudier B, Bellmunt J, Negrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol 2010; 28: 2144–2150.

24. Rini BI, Halabi S, Rosenberg JE, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with
25. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *J Clin Oncol* 2010; 28: 2137–2143.

26. Motzer RJ, Hutson TE, Mccann L, et al. Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. *N Engl J Med* 2014; 370: 1769–1770.

27. Motzer RJ, Mazumdar M, Back J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol* 1999; 17: 2530–2540.

28. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007; 356: 125–134.

29. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III trial in metastatic renal cell carcinoma. *J Clin Oncol* 2009; 27: 3312–3318.

30. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008; 372: 449–456.

31. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. *Cancer* 2010; 116: 4256–4265.

32. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 2011; 378: 1931–1939.

33. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol* 2013; 14: 552–562.

34. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncol* 2016; 17: 917–927.

35. Yakes FM, Chen J, Tan J, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. *Mol Cancer Ther* 2011; 10: 2298–2308.

36. Katayama R, Kobayashi Y, Friboulet L, et al. Cabozantinib overcomes crizotinib resistance in ROS1 fusion-positive cancer. *Clin Cancer Res* 2015; 21: 166–174.

37. Peltola KJ, Penttula P, Rautila J, et al. Correlation of c-Met expression and outcome in patients with renal cell carcinoma treated with sunitinib. *Clin Genitourin Cancer* 2017; 15: 487–494.

38. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature* 2013; 499: 43–49.

39. Zhou L, Liu XD, Sun M, et al. Targeting MET and AXL overcomes resistance to sunitinib therapy in renal cell carcinoma. *Oncogene* 2016; 35: 2687–2697.

40. Shojaei F, Lee JH, Simmons BH, et al. HGF/c-Met acts as an alternative angiogenic pathway in sunitinib-resistant tumors. *Cancer Res* 2010; 70: 10090–10100.

41. Gibney GT, Aziz SA, Camp RL, et al. C-Met is a prognostic marker and potential therapeutic target in clear cell renal cell carcinoma. *Ann Oncol* 2013; 24: 343–349.

42. Choi JS, Kim MK, Seo JW, et al. MET expression in sporadic renal cell carcinomas. *J Korean Med Sci* 2006; 21: 672–677.

43. Shuch B, Falbo R, Parisi F, et al. MET expression in primary and metastatic clear cell renal cell carcinoma: implications of correlative biomarker assessment to MET pathway inhibitors. *Biomed Res Int* 2015; 2015: 192406.

44. Nguyen L, Benrimoh N, Xie Y, et al. Pharmacokinetics of cabozantinib tablet and capsule formulations in healthy adults. *Anticancer Drugs* 2016; 27: 669–678.

45. Nguyen L, Holland J, Mamlok R, et al. Evaluation of the effect of food and gastric pH on the single-dose pharmacokinetics of cabozantinib in healthy adult subjects. *J Clin Pharmacol* 2015; 55: 1293–1302.

46. Kurzrock R, Sherman SI, Ball DW, et al. Activity of XL184 (cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. *J Clin Oncol* 2011; 29: 2660–2666.

47. Nguyen L, Holland J, Ramies D, et al. Effect of renal and hepatic impairment on the pharmacokinetics of cabozantinib. *J Clin Pharmacol* 2016; 56: 1130–1140.

48. Lacy S, Hsu B, Miles D, et al. Metabolism and disposition of cabozantinib in healthy male volunteers and pharmacologic characterization of...
its major metabolites. *Drug Metab Dispos* 2015; 43: 1190–1207.

49. Miles D, Jumbe NL, Lacy S, *et al.* Population pharmacokinetic model of cabozantinib in patients with medullary thyroid carcinoma and its application to an exposure-response analysis. *Clin Pharmacokin* 2016; 55: 93–105.

50. Nguyen L, Holland J, Miles D, *et al.* Pharmacokinetic (PK) drug interaction studies of cabozantinib: effect of CYP3A inducer rifampin and inhibitor ketoconazole on cabozantinib plasma PK and effect of cabozantinib on CYP2C8 probe substrate rosiglitazone plasma PK. *J Clin Pharmacol* 2015; 55: 1012–1023.

51. Choueiri TK, Pal SK, Mcdermott DF, *et al.* A phase I study of cabozantinib (XL184) in patients with renal cell cancer. *Ann Oncol* 2014; 25: 1603–1608.

52. Choueiri TK, Halabi S, Sanford BL, *et al.* Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the alliance A031203 CABOSUN trial. *J Clin Oncol* 2017; 35: 591–597.

53. Heng DY, Xie W, Regan MM, *et al.* Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol* 2009; 27: 5794–5799.

54. Mckay RR, Kroeger N, Xie W, *et al.* Impact of bone and liver metastases on patients with renal cell carcinoma treated with targeted therapy. *Eur Urol* 2014; 65: 577–584.

55. Wiecek W and Karcher H. Nivolumab versus cabozantinib: comparing overall survival in metastatic renal cell carcinoma. *PLoS One* 2016; 11: e0155389.

56. Amzal B, Fu S, Meng J, *et al.* Cabozantinib versus everolimus, nivolumab, axitinib, sorafenib and best supportive care: a network meta-analysis of progression-free survival and overall survival in second line treatment of advanced renal cell carcinoma. *PLoS One* 2017; 12: e0184423.