MEETING SUMMARY

The METEOR trial of cabozantinib versus everolimus in advanced renal cell carcinoma (RCC) was reported by Prof Choueiri at the European Cancer Congress 2015. This presentation follows the publication in the *New England Journal of Medicine* of the METEOR trial back-to-back with the CheckMate 025 trial of nivolumab versus everolimus in the same patient setting. Excitingly, these trials demonstrated, for the first time, significant benefits over the standard of care for heavily pre-treated patients with advanced RCC. Cabozantinib, an oral multi-targeted tyrosine kinase inhibitor (TKI) aims to address the challenge of resistance to targeted therapy with TKIs. While the METEOR trial has not yet reached its final analysis of overall survival (OS), the clear progression-free survival (PFS) benefit, acceptable safety profile, and similar tolerability to other TKIs shown by cabozantinib indicate that this represents a promising new treatment option for second-line or subsequent therapy for patients with advanced RCC.

Cabozantinib Versus Everolimus in Patients with Advanced Renal Cell Carcinoma: Results of a Randomised Phase III Trial (METEOR)

Professor Toni Choueiri

While the 5-year survival rate for early stage RCC is high, it is <10% for patients with advanced or late-stage metastatic RCC, and has not improved significantly despite the availability of targeted agents. Inactivation of the von Hippel–Lindau tumour suppressor protein in clear cell RCC, the predominant subtype in patients with RCC, upregulates vascular endothelial growth factor (VEGF), MET, and AXL tyrosine kinase signalling pathways, and drugs targeting the VEGF pathway are standard therapies in RCC. However, resistance to targeted therapy occurs in most patients and has been associated with increased MET and AXL expression. This represents a major challenge in improving medical outcomes for patients with RCC. While second-line treatment with the mammalian target of rapamycin (mTOR) inhibitor everolimus is associated with longer PFS, no significant OS benefit has been demonstrated. Cabozantinib is an oral, small molecule inhibitor of multiple kinases, including MET, AXL, and VEGF receptors (VEGFR), and has demonstrated clinical activity in heavily pre-treated RCC patients. The international, open-label Phase III METEOR trial was therefore designed to evaluate the efficacy and safety of cabozantinib compared with everolimus in patients with advanced RCC who had progressed after VEGF TKI therapy.
Patients with advanced or metastatic clear cell RCC and measurable disease, who had received prior treatment with at least one VEGFR TKI and had progressed on therapy or within the last 6 months of the most recent dose of VEGFR TKI, were randomised 1:1 to receive 60 mg cabozantinib or 10 mg everolimus orally once daily. There was no limit to the number of prior therapies, which could include cytokines and anti-PD-1/PD-L1 monoclonal antibodies, but not an mTOR inhibitor, and patients with brain metastases were eligible if they were adequately treated and stable. Patients were stratified by Memorial Sloan-Kettering Cancer Center (MSKCC) risk group and number of prior VEGFR TKI therapies. Treatment was continued until loss of clinical benefit or intolerable toxicity. Crossover between treatment groups was not allowed.

The METEOR ‘trial within a trial’ design allowed for appropriate statistical power for both the primary PFS endpoint and the secondary OS endpoint while avoiding over-representation of patients with rapidly progressing disease for the primary endpoint. The first 375 patients enrolled were evaluated for PFS, with 259 events estimated to be needed to provide 90% power to detect a hazard ratio (HR) of 0.667. For the OS endpoint, 408 events among 650 patients were estimated to be required to provide 80% power for detecting an HR of 0.75. An interim analysis of OS at the time of the primary endpoint analysis was planned. PFS and objective response rate (ORR) endpoints were assessed by the independent radiology review committee.

Of the 658 patients who were randomised, 330 received cabozantinib and 328 received everolimus, of whom the first 187 and 188, respectively, formed the PFS analysis population. By the primary endpoint analysis cut-off point, 40% of patients in the cabozantinib arm were still receiving treatment compared with 21% of patients in the everolimus arm. Patient characteristics were balanced between the treatment arms, with the majority of patients having a good performance status (68% of cabozantinib-treated patients and 66% of everolimus-treated patients had an Eastern Cooperative Oncology Group status score of 0) and being in a favourable or intermediate risk group according to MSKCC criteria. The majority of patients had received one prior VEGFR TKI (71% of cabozantinib-treated patients and 70% of everolimus-treated patients), with sunitinib the most common VEGFR TKI received (64% of cabozantinib-treated patients and 62% of everolimus-treated patients).

The primary endpoint of the trial was met, with a significant PFS benefit for cabozantinib compared with everolimus (Figure 1). The estimated median PFS was 7.4 months (95% confidence interval [CI]: 5.6–9.1) for cabozantinib-treated patients and 3.8 months (95% CI: 3.7–5.4) for everolimus-treated patients. The rate of disease progression or death was 42% lower with cabozantinib than with everolimus (HR for progression or death: 0.58, 95% CI: 0.45–0.75; p<0.001).

Analysis of the prespecified subgroups showed a PFS benefit regardless of the number of prior VEGF TKI treatments or MSKCC risk group. In a post hoc analysis of patients who had received sunitinib as their only prior VEGF TKI, the benefit of cabozantinib was even greater, with an estimated median PFS of 9.1 months (95% CI: 5.6–11.2) compared with 3.7 months (95% CI: 1.9–4.2) for everolimus (HR: 0.41, 95% CI: 0.28–0.61).

ORR, as assessed by the independent radiology review committee, was significantly higher with cabozantinib than with everolimus (21% versus 5%, respectively; p<0.001; Table 1). Although no complete responses were seen, more patients showed a partial response with cabozantinib than with everolimus, and fewer patients treated with cabozantinib had progressive disease as best response (14% versus 27% of those treated with everolimus). This highlights a low rate of patients with disease that is primarily refractory to this agent. The high level of disease control is also shown by the greater number of patients treated with cabozantinib who experienced tumour reduction as their best target lesion change from baseline (84% versus 59% of those treated with everolimus).

At the prespecified interim analysis, with a minimum follow-up of only 6 months after the last patient was enrolled, 49.5% of the events required for final analysis had occurred in the OS population. While a trend towards longer OS with cabozantinib was observed (HR: 0.67, 95% CI: 0.51–0.89; p=0.005), the interim boundary to reach significance (p≤0.0019) was not reached (Figure 2). Survival follow-up is continuing to the planned final analysis after 408 deaths occur.

Patients had a longer median exposure to cabozantinib (7.6 months, range: 0.3–20.5) than to everolimus (4.4 months, range: 0.21–18.9).
Dose reductions to adjust to an individual patient’s tolerance occurred more frequently with cabozantinib (60% of patients compared with 25% of everolimus-treated patients), similar to other VEGFR TKIs. The rates of discontinuation due to adverse events were similar for cabozantinib and everolimus (9% and 10%, respectively). The safety profile of cabozantinib in this trial was similar to that observed for other TKIs in this patient population, and distinct from that of everolimus (Table 2). Diarrhoea, fatigue, palmar-plantar erythrodysesthesia, and hypertension were the most common Grade 3/4 adverse events with cabozantinib, compared with fatigue, anaemia, and hyperglycaemia with everolimus. The rate of serious adverse events was similar in both groups (40% for cabozantinib and 43% for everolimus).

Table 1: Tumour response in the progression-free survival population.

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<tr>
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<th>Cabozantinib (n=187)</th>
<th>Everolimus (n=188)</th>
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<tbody>
<tr>
<td>Objective response rate, %</td>
<td>21</td>
<td>5</td>
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<tr>
<td>95% confidence interval</td>
<td>16–28</td>
<td>2–9</td>
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<tr>
<td>p value</td>
<td>&lt;0.001*</td>
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<td>Best overall response, %</td>
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</tr>
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<td>Not evaluable/missing</td>
<td>3</td>
<td>6</td>
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*Cochran–Mantel–Haenszel test.
The objective response rate was consistent in patients who received sunitinib as their only prior vascular endothelial growth factor tyrosine kinase inhibitor.
Figure 2: Kaplan-Meier estimate of overall survival at interim analysis. CI: confidence interval.

Table 2: All-cause adverse events. *Events reported in at least 25% of patients in either study group. PPE: palmar-plantar erythrodysesthesia.
In conclusion, METEOR met its primary endpoint, with cabozantinib nearly doubling median PFS compared with everolimus in patients with advanced RCC previously treated with VEGFR TKI therapy, which is a significant improvement over the current standard of care. Cabozantinib improved ORR, and the interim analysis showed a strong trend for OS favouring cabozantinib. The safety profile of cabozantinib is similar to previous experience in this patient population, and tolerability is similar to that of other TKIs in this patient population. Cabozantinib represents a potential new treatment option for second-line or subsequent therapy for advanced RCC.

REFERENCES


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