Editorial

Cabozantinib in advanced renal cell carcinoma: a METEOR impact on clinical practice

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Final results from the randomised phase III METEOR study have been recently published and confirmed the superiority of cabozantinib over everolimus in patients with advanced or metastatic clear-cell renal cell carcinoma (mRCC) who received at least one previous VEGFR tyrosine-kinase inhibitor (TKI) (1). Overall, 658 subjects were randomized 1:1 to receive either cabozantinib or everolimus and the two treatment arms were well balanced for age, sex, race, geographic area, Karnofsky performance status, Memorial Sloan Kettering Cancer Center (MSKCC) criteria, and previous nephrectomy as well as the number of previous antiangiogenic therapies. All the patients received sunitinib or pazopanib as first-line treatment while a few patients received sorafenib, bevacizumab, axitinib, or cytokines before entering the study. The final overall survival (OS) results from the METEOR study reported an improvement in progression-free survival (PFS) (7.4 *vs*. 3.9 months, P<0.0001), OS (21.4 *vs*. 16.5 months, P<0.00026) and ORR (17% *vs*. 3%, P<0.0001) in the cabozantinib arm. The subgroup analysis confirmed both OS and PFS benefit of cabozantinib across all the subgroups analyzed including MSKCC risk groups, number and duration of previous antiangiogenic therapies, previous nephrectomy, number and sites of metastases (bone *vs*. visceral *vs*. visceral and bone). Median duration of treatment exposure was 8.3 and 4.4 months in patients given cabozantinib and everolimus respectively with cabozantinib requiring more dose reduction due to toxicity compared to everolimus (62% *vs*. 25%). Similar proportions of patients received subsequent systemic treatment after study discontinuation in both treatment arms (55% *vs*. 50% respectively). The most common grade 3 or 4 adverse events recorded were hypertension (15% in the cabozantinib group *vs*. 4% in the everolimus group), diarrhea (13% *vs*. 2%), fatigue (11% *vs*. 7%), palmar-plantar erythrodisestesia (8% *vs*. 1%), anemia (6% *vs*. 17%) and hyperglycemia (1% *vs*. 5% respectively). Overall grade 3 or 4 adverse events were recorded in 71% of patients treated with cabozantinib and 60% of patients treated with everolimus.

The second-line treatment scenario has been recently complicated with the approval of nivolumab, an immune-checkpoint inhibitor, that demonstrated superiority over everolimus in terms of OS (25 *vs*. 19.6 months, P=0.002) for mRCC patients after previous antiangiogenic treatment (CheckMate-025 study) (2). Nivolumab has also shown an improvement in ORR (25% *vs*. 5%, P=0.001) without significant differences in terms of PFS (4.6 *vs*. 4.4 months, P=0.11) over everolimus (2).

Considering these results some issues need to be addressed and deserve further discussion:

(I) The overall PFS in the METEOR study and that reported in patients receiving cabozantinib after sunitinib represented the best outcome for a single agent used for mRCC. Besides, the PFS reported in the same study with everolimus was consistent with that reported in the RECORD-1 study (3). This

data support the METEOR study suggesting that the prognostic features of the patients population enrolled into this study may not be more favorable in comparison to previous studies;

(II) In the METEOR study, only 12% of cases experienced progressive disease as best response with cabozantinib as compared with 35% of patients treated with nivolumab. The definition of progressive disease by RECIST criteria may be confounding when applied to immunotherapies. Moreover, a standardized methodology to assess radiological treatment-related pseudoprogression as well as the potential impact of nivolumab treatment beyond progression still represents a major issue. These considerations may indirectly support the concept that cabozantinib may potentially be able to better overcome resistance to VEGF-inhibition;

(III) In the light of the recent announce of positive results from the phase II CABOSUN study (4) comparing cabozantinib to sunitinib as first-line therapy for previously untreated mRCC, cabozantinib may have the potential to become a new option in first-line setting. The final results from CABOSUN will be presented soon;

(IV) The safety profile and tolerability of nivolumab and cabozantinib are very different. In general, nivolumab was associated with less all grades adverse events and showed a good patients' compliance. In contrast, 62% of patients receiving cabozantinib received a dose reduction due to toxicity. As a result, the management of the toxicity of patients receiving cabozantinib may be a potential key driver for treatment choice;

(V) Patients treated with nivolumab appeared to have improved quality of life (QoL) in CheckMate-025, while these data are not reported for cabozantinib (5). Nevertheless this information would be of great relevance because QoL underlines the tolerability associated to the treatment;

(VI) Results from METEOR study suggested that MET expression might not affect outcome with cabozantinib for this patient population as well as PD-L1 expression in the Checkmate study was not predictive of response to nivolumab. Additional studies are thus needed to better define the potential role of MET expression;

(VII) Both studies enrolled patients receiving one or two prior antiangiogenic treatments and they both pushed everolimus over second line. On the other hand, these studies have not clarified which role should be given to different second-line TKIs, such as axitinib, following upfront TKI. Should nivolumab or cabozantinib be considered second-line treatment for all patients or physicians may still consider axitinib as second-line for select cases? Clinical data now available do not seem to be conclusive.

In conclusion, the armamentarium of agents against kidney cancer will be improved with the next introduction of cabozantinib in clinical practice. The right placement of cabozantinib into treatment algorithm is not easy due to difficult cross-trial comparison. A sequential strategy including cabozantinib after nivolumab may be suitable for some patients who had previously received sunitinib or pazopanib. Moreover, a second TKI, such as cabozantinib could be a reasonable option to defer nivolumab in third-line. Due to the lack of validated predictive biomarkers able to drive treatment choice a careful patient-based evaluation of clinical factors and disease features still remain the main criteria for treatment selection.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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