

Cabozantinib in renal cell carcinoma: only a METEOR or a rising star?

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Dear Editor,

the results of the phase III METEOR trial, first published in the *New England Journal of Medicine* (1), and then confirmed with the final evaluation of overall survival (OS) published on *Lancet Oncology* (2), comparing Cabozantinib to Everolimus in second line setting for patients with advanced renal cell carcinoma (RCC), offer the cue for some reflections.

With the uncertain weight of targeting MET and AXL rather than vascular-endothelial growth factor (VEGF) again after progression to previous VEGF-tyrosine kinase inhibitors (TKI), Cabozantinib reaches the primary endpoint progression free survival.

At the first interim analysis, the intersecting curves for estimates OS seemed to suggest an effect of the switch to TKI treatment after progression in the control arm (40% of cases, most with Axitinib, *versus* 16% in the Cabozantinib arm). Despite not being confirmed in the final analysis, more definitely in favour of cabozantinib with clearly separate survival curve, the initial control curve was flattening at a certain delayed time point, with lack of events. On the contrary, the curve of the experimental arm gave its best in the first part; probably corresponding to the TKI-TKI sequence. Those preliminary but interesting findings suggested once again, according to the recent phase II and phase III trials with other therapeutic sequential strategies (3,4), that maintaining or recovering “VEGF pressure” in RCC works.

Of note, three “big issues” have not been touched in this trial:

a) the predictive factors, such as activating RET and RAS mutations, already known from the phase

III pivotal EXAM trial of Cabozantinib in medullary thyroid cancer, and MET mutations/amplification (5);

b) the papillary histology, assuming that this RCC subtype can be an excellent target for a MET inhibitor (6);

c) the bone metastasis, considering the strong clinical and preclinical evidence for this drug in favor of an important improvement of bone scans, pain, analgesic use, measurable soft tissue disease, circulating tumor cells and bone biomarkers through the modification of the bone microenvironment (7).

Despite the positive outcome of Cabozantinib in RCC, its not negligible toxicity deserves careful evaluations: nevertheless, all adverse events (AEs) and not only treatment-related AEs were considered in this trial, overestimating, in fact, also everolimus toxicity in the control arm. With a dose of cabozantinid far lower than the MTD (40 mg versus 175 mg), the rates of diarrhea (74%), nausea (50%), palmar-plantar erythrodysesthesia syndrome (42%) and hypertension (37%) overcome those of phase I trial, in which the median average daily dose was 75 mg. Moreover, a Quality of Life assessment could have been useful as secondary endpoint. Eventually, we curiously noticed the use of the three-parameters Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic criteria, developed in RCC after progression to cytokine treatment, instead of the validated and most used original MSKCC criteria with five parameters or of the International Metastatic Renal Cell Carcinoma Database Consortium prognostic score.

The METEOR trial undoubtedly represents a landmark study, whose data are powerful enough to

modify clinical practice, although it competes with the recently approved immune checkpoint inhibitor Nivolumab and with further emerging new therapies in the same setting (4). Thus, the placement of Cabozantinib in the therapeutic lines sequence for RCC should be considered not obvious despite these positive results and it surely deserves further evaluations.

This issue is intended to become of primary interest in the light of the recent announce of positive results with Cabozantinib compared to Sunitinib for first line treatment of high and intermediate risk RCC. This press release, based on CABOSUN trial's preliminary results, potentially sounds like an earthquake on the consolidated land of first line therapy for renal cancer.

References

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