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KIDNEY CANCER

CheckMate for advanced-stage ccRCC? Nivolumab and cabozantinib aMETEORate poor survival

Results from two new phase III trials, CheckMate 025 and METEOR, show that patients with advanced-stage, pretreated clear cell renal cell carcinoma (ccRCC) derive increased survival benefits from treatment with nivolumab or cabozantinib in comparison with everolimus. The data, which have also been presented at the European Cancer Congress 2015 in Vienna, Austria, have recently been published in two articles in *The New England Journal of Medicine*.

Current first-line therapy for patients with metastatic ccRCC focuses on antiangiogenics that target the VEGF signalling pathway, for example, bevacizumab or sunitinib. However, development of resistance is common and the mTOR inhibitor everolimus is the standard second-line treatment when anti-VEGF therapy has failed. "Patients who progress on first-line antiangiogenics have few therapeutic options and most are associated with a moderate benefit at best," explains Toni Choueiri from the Dana–Farber Cancer Institute who is an investigator in both CheckMate 025 and METEOR, which were initiated to test alternative agents for that patient group. "Both nivolumab and cabozantinib had shown efficacy in earlier smaller studies in heavily pretreated patients with RCC."

In both multicentre studies, patients were randomly assigned to receive either everolimus or one of the two novel targeted agents: nivolumab in CheckMate 025 or cabozantinib in METEOR. Nivolumab is a monoclonal antibody targeted against programmed cell death protein 1 (PD-1), which restores antitumour immune responses. Cabozantinib is a small-molecule tyrosine kinase inhibitor that targets VEGF receptors, as well as the hepatocyte growth factor receptor (MET) and the tyrosine-protein kinase receptor UFO (AXL). Overexpression of MET and AXL have previously been suggested to have a role in the development of resistance to antiangiogenic agents.

"The baseline characteristics of both trials were overall similar, although the METEOR trial did not have a limit on prior lines of therapies," Choueiri summarizes. In CheckMate 025, the primary and secondary end points were overall survival and progression-free survival (PFS), respectively, whereas it was the opposite in the METEOR trial.

Notably, both trials met their primary end points. In CheckMate 025, nivolumab treatment resulted in a median overall survival of 25 months compared with 19.6 months for everolimus; the hazard ratio for death was 0.73 (nivolumab versus everolimus; $P = 0.002$), meeting the prespecified superiority criterion. Interestingly, when overall survival data were compared with PD-L1 tumour expression levels, the investigators did not observe any correlation. In METEOR, cabozantinib treatment resulted in a median PFS of 7.4 months in comparison with 3.8 months for everolimus and the hazard ratio for disease progression or death was 0.58 (cabozantinib versus everolimus; $P < 0.001$). A planned interim analysis demonstrated a trend for longer overall survival for cabozantinib in comparison with everolimus, but the significance cut-off point for this analysis was not reached and follow-up observation is ongoing.

"The differences in survival were not only statistically significant but clinically meaningful," highlights Choueiri. "In addition, the data on quality of life with nivolumab is very interesting and the drug seems to be better tolerated than everolimus." In CheckMate 025, 19% of patients receiving nivolumab, but 37% of patients receiving everolimus, experienced grade 3 or grade 4 treatment-related adverse events. In METEOR, the incidence of grade 3 or grade 4 adverse events (irrespective of causality) was 68% for cabozantinib and 58% for everolimus, which is similar to previous observations. In both trials, the numbers of treatment discontinuation due to adverse events were not substantially different between the experimental arms and everolimus.

The investigators are now planning to conduct further subgroup and biomarker analyses for both trials to find out whether certain patients might respond particularly well to either nivolumab or cabozantinib. In addition, clinical trials that investigate the possible benefits of combining both agents for the treatment of patients with genitourinary cancers, including RCC, are currently underway.

"Both nivolumab and cabozantinib should now be standard options for second-line or later treatment of RCC," concludes Choueiri. "A great time for patients with kidney cancer!"

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This article has also been published in *Nat. Rev. Urol.* (doi:10.1038/nrurol.2015.246)

Original articles Choueiri, T. K. *et al.* Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N. Engl. J. Med.* doi:10.1056/NEJMoa1510016 | Motzer, R. J. *et al.* Nivolumab versus everolimus in advanced renal-cell carcinoma. *N. Engl. J. Med.* doi:10.1056/NEJMoa1510665

CORRECTION

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In the version of this article originally published online and in print, nivolumab was incorrectly stated as targeting programmed cell death 1 ligand 1 (PD-L1), rather than programmed cell death protein 1 (PD-1). This error has now been corrected in the online HTML and PDF versions of the article.