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European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 962–971 of this issue

Subset Analyses from CheckMate 025: A Challenge to Current Clinical Dogma?

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Arguably the most contentious debate in metastatic renal cell carcinoma (mRCC) 5 yr ago was whether axitinib or everolimus represented optimal second-line therapy. In the absence of any randomized trials comparing the two directly, investigators were left to juxtapose efficacy and toxicity across two independent phase 3 trials [1,2]. Subset analyses from each trial were used to invoke comparisons of progression-free survival (PFS) and response rate in VEGF-tyrosine kinase inhibitor (TKI) pretreated patients. Despite differences in eligibility, many attempts were made to infer from the separate phase 3 data sets which drug has the superior safety profile [3,4].

Fast forward to 2017. For the moment, the nature of first-line therapy remains unchanged. Sunitinib and pazopanib remain the agents most commonly used in this setting; although there is no consensus as to which is superior, comparative data do exist to guide the patient and clinician in decision-making [5]. However, second-line therapy has evolved entirely with the reporting of two phase 3 and one phase 2 clinical trial. CheckMate 025 compares the PD-1 inhibitor nivolumab to everolimus in patients with one to three prior lines of treatment [6]. In this issue of *European Urology*, subset analyses from this study are described. METEOR assesses the TKI cabozantinib, which has affinity not only for VEGF but also for MET and AXL, two putative oncogenic drivers [7]. Finally, a randomized phase 2 study compares the multikinase inhibitor lenvatinib to everolimus and to the combination of drugs.

At recent meetings it has been evident that clinicians have aligned primarily with either cabozantinib or nivolumab in the second-line setting. Despite compelling PFS data for lenvatinib, the relatively small phase 2 experience that led to its approval leaves most oncologists desiring further data. A dogma has emerged among many practicing clinicians around the use of nivolumab and cabozantinib as second-line therapy. In general, patients who have rapidly progressive disease who need a "rapid response" are offered cabozantinib, while patients with more indolent disease are offered nivolumab. Similarly, cabozantinib has been reserved for the more robust patient, while nivolumab is offered to older, frailer patients.

The subset analyses from Checkmate 025 presented by Escudier et al [7] offer an opportunity to examine the appropriateness of this framework. Overall, the study met its primary endpoint, demonstrating an improvement in overall survival (OS) relative to everolimus. The response rate was higher with nivolumab, although no difference in PFS was observed. Curiously, according to OS in subsets divided by Motzer risk group, it is patients with poor-risk disease who benefit the most. By contrast, Kaplan-Meier curves outlining OS in patients with good- and intermediate-risk disease show no significant difference. Forest plots in this report show similar benefit in subgroups divided above and below age 65 yr, but the original publication shows a lesser degree of benefit in OS among patients aged $\geq$ 75 yr, with a trend that appears to favor everolimus [6].

With these rather surprising results in mind, one might ask how cabozantinib performs in the same population. Subset analyses from the METEOR trial show an opposite trend among risk groups; specifically, patients with good- and intermediate-risk disease appear to derive the greatest PFS benefit from cabozantinib relative to everolimus, while

DOI of original article: http://dx.doi.org/10.1016/j.eururo.2017.02.010.
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http://dx.doi.org/10.1016/j.eururo.2017.03.006

poor-risk patients benefit the least [8]. No significant differences appear across subgroups divided by age. These data call into question the prevailing dogma highlighted earlier. Rather than reserving cabozantinib for "aggressive" disease (synonymous with poor risk), it might be reasonable to use the drug in populations with good and intermediate risk as well. Similarly, subset analyses in patients divided by age suggest a similar benefit in older adults.

So where do these subset analyses ultimately position nivolumab? The data presented here suggest that it may be best used in patients with poor-risk disease. Paradoxically, however, nivolumab appears to be associated with a much higher rate of primary progressive disease (PD) [6]. PD as a best response in Checkmate 025 was observed in 35% of patients receiving nivolumab. With the caveat of cross-trial comparisons, PD as a best response was only observed in 14% of patients receiving cabozantinib in METEOR [9]. Thus, in a poor-risk patient, one might make the argument that cabozantinib offers the best opportunity for clinical benefit.

One would be remiss to omit toxicity from a discussion of nivolumab versus cabozantinib. Nivolumab has been purported to offer a toxicity profile far superior to targeted therapies, but again no comparative data exist to support this statement. In the first publication of data from Checkmate 025, grade 3/4 adverse events were noted in 19% of patients treated with nivolumab, compared to 37% of patients treated with everolimus [6]. At first glance, this appears to compare favorably to the 68% rate of grade 3/4 adverse events in patients receiving cabozantinib in METEOR [9]. However, the astute investigator will note a subtle but important difference in adverse event reporting: all-cause adverse events were reported for cabozantinib in the METEOR trial, while only treatment-related adverse events were reported for nivolumab in Checkmate 025. The package insert for nivolumab suggests an all-cause grade 3/4 adverse event rate of 56%, which is more balanced with the toxicities observed for other targeted agents [10].

An ideal scenario would be a biomarker that could predict differential benefit with cabozantinib, nivolumab, and lenvatinib/everolimus. There is ongoing work to confirm observations of the mutational load associated with lung cancer and bladder cancer with PD-1 inhibition, with some supportive evidence in mRCC [11–14]. Furthermore, retrospective studies correlating *TSC1*, *TSC2*, and *MTOR* alterations to mTOR-inhibitor response and *MET* alteration with MET-inhibitor response suggest that these biomarkers could be associated with lenvatinib/everolimus and cabozantinib activity, respectively [15,16]. Tremendous investment would be required to validate these findings prospectively. Apart from biomarkers, specific clinical scenarios may also add to clinical decision-making. One example is bone metastasis, for which there is compelling evidence from subgroup analysis of the METEOR trial that cabozantinib has increased activity in this population [17]. Until then, the standard for second-line treatment should remain cabozantinib. Both nivolumab and cabozantinib offer benefits in response rate and OS, and distinct toxicity considerations exist for each. The benefit in PFS and the lower rate of PD as best response should sway clinicians towards cabozantinib.

Conflicts of interest: Sumanta K. Pal is a consultant for Exelixis, BMS, GSK, Novartis, Pfizer, Astellas, and Genentech, and receives honoraria from Genentech. Neeraj Agarwal has been a consultant for Pfizer, Novartis, Exelixis, Merck, Argos, EMD Serono, and Eisai, and has received research funding from Pfizer, EMD Serono, Novartis, Takeda, and Bayer. Manuel C. Maia and Nazli Dizman have nothing to disclose.

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