Belzutifan: enhancing the blockade of angiogenesis in renal cell carcinoma

**Belzutifan: the "new kid on the block"ade of angiongenesis.**

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**Commentary**

Choueiri et al. [1] presented the result of cohort 2 of the phase II trial (NCT03634540) of belzutifan in combination with cabozantinib in patients with RCC previously treated with one prior immune checkpoint inhibitor (ICI) (54% of the 52 patients enrolled) or both prior immunotherapy and an anti-VEGF/VEGFR tyrosine kinase inhibitor (TKI) (46%). The combination showed extremely promising results, with an objective response rate (ORR) of 31% (primary endpoint). The additional effect of belzutifan is highlighted by the indirect comparison with the phase III METEOR trial, in which cabozatinib, in patients pretreated with TKIs, obtained an ORR of 17%. Moreover, it has to be underlined the short median time to response (3.2 months) and change from baseline in target lesions of 87%, two endpoints that confirm the pivotal role of enhancing the blockade of angiogenesis in order to achieve a satisfactory disease control.

This study surely represents a promising and deeply needed treatment strategy in previously treated patients with RCC, considering the current shortage of options at disposal after ICI or TKI.

This trial should also be praised for the high percentage of patients with ECOG PS 1 (56%) enrolled that makes it highly adherent to real-world populations of pretreated patients.

Nonetheless, some issues could be pointed out and different points could be discussed in the study.

It could be interesting to know the responses in patients that received ICI and TKI in combination or in sequence. In fact, the combined or sequential treatment could affect tumor microenvironment composition in a different manner, thus leading to more angiogenetic or immunological profiles. In addition, the results of the phase II trial of the combination of lenvatinib plus everolimus in pretreated patients should be discussed, considering that is currently one of the few options at disposal [2]. This combination uses drugs with different targets with respect to first line TKI included in the immune combinations (with the exception of lenvatinib plus pembrolizumab), even though this study included a different setting of patients that progressed to previous VEGF-targeted therapy.

The results of this trial surely elicit a great interest in a phase III with the same combination, considering its manageable and expected safety profile. Nonetheless, at the current moment, only a phase III trial investigating the combination of belzutifan with lenvatinib versus cabozantinib in pretreated patients is ongoing (NCT04586231).

A further issue to address could be the potential comparator arm of belzutifan plus cabozantinib, considering the limited options available in patients treated with ICI + ICI or ICI + TKI. Nowadays, there is no unanimous standard of care in this setting, even though some limited evidences are arising, suggesting that the best control arm could be cabozantinib (excluding patients treated with first line cabozantinib plus nivolumab, that are still orphan of valid subsequent alternatives). During the recent ASCO Genitourinary Symposium 2023 the interim analysis results of the phase II CaboPoint trial (NCT03945773), investigating the activity of cabozantinib in patients pretreated with nivolumab plus ipilimumab (cohort A) or ICI plus TKI (cohort B), were presented. Even though results are still immature, Cabozantinib seems to be active in these patients, irrespective of first line combination, with on ORR of 31% [3]. Given the lack of predictive factors of response, one of the most interesting studies in this field is the BIONIKK phase II trial [4], that divided patients according to 4 molecular groups (ccrcc1–4). Recently, the results of second line TKIs after nivolumab alone or plus ipilimumab were presented and included 49 patients treated with cabozantinib, 32 with sunitinib/pazopanib, 13 with axitinib 2 with lenvatinib. ORR resulted to be 28.5% in patients previously treated with nivolumab alone and 39% in those that received nivolumab plus ipilimumab, with higher benefit in terms of median PFS for ccrcc2 patients. This group is composed of tumors with an angiogenic-high and immune-high signature.

Furthermore, flourishing retrospective evidences are confirming the activity of cabozantinib as second line treatment [5, 6], making it the most widely treatment strategy used in real-world scenarios. Moreover, it has been recently announced that the phase III trial CONTACT-03, evaluating the combination of cabozantinib plus atezolizumab versus cabozantinib alone in patients progressed

to an ICI and a TKI, did not meet its primary endpoint of PFS, underlying the pivotal role of cabozantinib alone in these patients [7].

The present study of cabozantinib plus belzutifan also underlines the emerging role of the HIF inhibitor belzutifan, that is currently being widely investigated in different stages of RCC, from the adjuvant setting, e.g. in the phase III LITESPARK 022 trial in combination with pembrolizumab, to the metastatic disease, e.g. the phase III MK-6482-005 in pretreated patients compared to everolimus. Moreover, cohort 1 of the commented trial is evaluating the same combination of belzutifan plus cabozatinb in previously untreated patients with metastatic RCC in a phase II trial (LITESPARK-003, NCT03634540), with promising initial results of 57% confirmed ORR [8]. The rationale supporting the investigation of belzutifan in RCC is that it targets one of the first steps of angiogenesis, HIF2α, crucial for RCC development and progression. The role of this drug has been especially pointed out in RCC associated with *VHL* disease [9], in which inactivating mutation on *VHL* lead to accumulation of HIF2α and consequent upregulation of hypoxia-responsive genes, including *VEGFA*, one of the first steps of RCC tumorigenesis. Interestingly, preclinical evidences showed that *VHL* loss is linked to a constitutive activation of MET, that is one of the targets of cabozantinib, thus supporting the combination of belzutifan and cabozantinib [10].

Considering the embarrassment of riches that is flourishing in first line treatment of metastatic RCC, it will be challenging and interesting to discover new therapeutic targets that could open some possibility of an active treatment in subsequent lines of therapy [11]. Given its ambitious target and a plethora of promising preliminary evidences in support, belzutifan is a great candidate to open a new field of treatment. It remains to be investigated the right setting and partner, if needed, and whether the throne of second or further line of therapy of cabozantinib could be stolen or shared.

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