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# Despite an Abundance of Active Treatment Options for Renal Cell Carcinoma, Shadows Still Obscure the Light

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In this issue of *European Urology*, a group of well-known experts in renal cell carcinoma (RCC) provide a comprehensive overview of first- and second-line treatments for this disease [1]. Several years ago, the late Nicholas Vogelzang used the term "embarrassment of riches" [2] to describe the abundance of agents then available for the treatment of a malignancy that, until a few years before, was considered almost an orphan disease. Despite the fact that our treatment options have multiplied since then, we are left with more unanswered questions than clear-cut answers.

A first key question, possibly the most relevant, relates to what to do when a patient experiences disease progression after adjuvant treatment. We now know that 1 yr of immunotherapy may reduce the risk of relapse and, more importantly, prolong survival for patients with metastatic RCC (mRCC) who have undergone radical resection of a neoplasm at high risk of relapse [3], including those already metastatic patients therapeutically rendered disease free. Despite this undoubted success, a number of patients will still experience recurrence despite adjuvant therapy, and subsequent treatment for these patients remains an open issue. Although a small retrospective series suggested that these patients may benefit from a wide range of treatments, including VEGFR-targeted tyrosine kinase inhibitors (TKIs) (especially for good risk patients) and immune checkpoint inhibitor (ICI)-containing regimens [4], two large, prospective, randomized controlled trials (CONTACT-03 and TiNivo-2) have provided clear-cut evidence that administration of another ICI after failure of a previous one has no impact on patient survival [5,6].

This issue has dramatically re-emerged in the metastatic setting, for which the current first-line standard is an immune-based combination, making any VEGFR TKI not used in the first-line combination the only realistic subsequent treatment option [7], although in many cases this will be suboptimal, at least in terms of progression-free survival. However, it is not known if ICI rechallenge at a relevant time interval after first exposure to this class of agents (several months? years?) could restore an antitumor immune response.

Although decisions on a treatment strategy in the first line are somewhat easier (to date, it has been demonstrated that four immune-based combinations significantly prolong survival), the choice between these combinations remains a matter of both indirect comparisons and a combination of the physician's experience and attitude and the patient's values and preferences (often in terms of toxicities). A further factor is underestimation of the risks of making comparisons between studies that are very different in terms of agents used, patient characteristics, and follow-up duration.

Another unsolved issue is related to the optimal duration of each component in a first-line combination regimen; should we really stop immunotherapy after 2 yr of treatment? The latest survival updates for ICI and VEGFR TKI combinations available suggest the risk of some loss of activity over time, with the separation between the curves starting to reduce after immunotherapy withdrawal, albeit to different extents, depending on the combination considered. What about long-term administration of VEGFR TKIs,

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which are responsible for the most severe treatment-related toxicities? On the basis of strong preclinical data [8], it was believed that tumor vascularization and thus growth restarts a few days after cessation of antiangiogenic agents, leading to the notion that long-term angiogenesis inhibition must be continued. However, results from an elegant hypothesis-generating study suggest that VEGFR TKI cessation while continuing the ICI in patients with a response after 36 wk of therapy did not hamper treatment efficacy and actually greatly improved the safety profile of the combination [9].

It is also unknown if continuous ICI stimulation of the immune system can maintain an effective antitumor immune response or lead to its exhaustion. For the immune doublet ipilimumab + nivolumab, it is unknown if reinduction with ipilimumab, an anti-CTLA4 antibody that primes immune effector cells, could be useful in restoring the immune response in cases with disease progression.

Regulatory or insurance restrictions in many countries also greatly limit treatment options in the second and further lines. Against this background, we should reconsider the role of older agents that are still active despite having been replaced by more recent and potent treatment options. A case in point is the HIF-2a inhibitor belzutifan. Results from the Litespark-005 trial [10] supported the use of belzutifan as a standard treatment for patients who had previously received ICI and antiangiogenic therapies. Given its efficacy and favorable safety profile, belzutifan was subsequently evaluated in earlier treatment lines in combination with other agents. With results from these trials expected soon, the position of belzutifan in the treatment algorithm could radically change in the near future. Of course, all the above is further complicated by the lack of biological biomarkers to help in the therapeutic decision-making process.

Finally, we should acknowledge that we have only scratched the surface of the complex relationships between metabolism and RCC development, growth, and spread, which, in our opinion, remain a key therapeutic target to explore. We should continue to explore the biology of this malignancy and conduct studies aimed at answering key questions that are often not as immediately relevant from a commercial viewpoint. Therefore, beyond continuing valuable collaborations with pharmaceutical companies, academic-driven international collaborative studies aimed at answering some of the above practical questions are warranted to finally shed light on issues clouded by uncertainty and doubt.

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