Editorial Commentary

Validity and utility of switch-maintenance therapy with nivolumab in tyrosine kinase inhibitor-sensitive patients with metastatic renal cell carcinoma: learning from NIVOSWITCH

Taigo Kato^, Norio Nonomura

Department of Urology, Osaka University Graduate School of Medicine, Osaka, Japan

Correspondence to: Taigo Kato, MD, PhD. Department of Urology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan. Email: kato@uro.med.oaska-u.ac.jp.

Comment on: Grünwald V, Ivanyi P, Zschäbitz S, *et al.* Nivolumab Switch Maintenance Therapy After Tyrosine Kinase Inhibitor Induction in Metastatic Renal Cell Carcinoma: A Randomized Clinical Trial by the Interdisciplinary Working Group on Renal Tumors of the German Cancer Society (NIVOSWITCH; AIO-NZK-0116ass). Eur Urol 2023;84:571-8.

Keywords: Renal cell carcinoma (RCC); nivolumab; tyrosine kinase inhibitor (TKI)

Submitted Jan 07, 2024. Accepted for publication April 17, 2024. Published online Jul 16, 2024.
doi: 10.21037/tau-24-14
View this article at: https://dx.doi.org/10.21037/tau-24-14

The incidence of renal cell carcinoma (RCC) is increasing, and approximately 15% of patients with RCC present with distant metastases at the time of diagnosis (1,2). Moreover, distant metastases occur in 20% of patients undergoing surgical resection of primary RCC, necessitating subsequent therapeutic interventions such as administration of tyrosine kinase inhibitors (TKIs) and programmed cell death-1 (PD-1) inhibitors (3,4).

Recently, combination therapy of immune checkpoint inhibitors (ICIs) with axitinib, cabozantinib, or lenvatinib has been introduced to enhance clinical outcomes in patients with metastatic RCC (mRCC) based on the promising results in various clinical trials (5-8). However, combination therapies of ICIs with first-generation TKIs, such as sunitinib and pazopanib, failed owing to the high incidence of grade ≥3 adverse effects (AEs) in patients with untreated mRCC (9,10). Therefore, Grünwald *et al.* conducted the NIVOSWITCH trial to confirm whether switch maintenance therapy using nivolumab improves clinical outcomes in patients with mRCC with sensitivity to first-generation TKIs (11). In this study, patients with mRCC who experienced disease control after a short period (10–12 weeks) of first-generation TKI administration were randomized to either TKIs or nivolumab switch maintenance. The results showed that patients who continued their original TKIs achieved better responses (52% *vs.* 20%; P=0.013) and a longer duration without disease progression (hazard ratio, 2.57; 95% confidence interval: 1.36–4.89; P=0.003) compared to those with switch therapy to nivolumab. These results do not support the usefulness of the switch-maintenance approach for mRCC. However, the study presented some evidence on the TKI treatment strategies.

First, this study reconfirmed that TKIs play an pivotal role in mRCC, especially as the first-line treatment. Till date, the significance of angiogenesis in the pathophysiology of clear-cell RCC (ccRCC) has been extensively reported (12,13). Importantly, most ccRCC cases are associated with genetic deletions and mutations, or epigenetic silencing of the von Hippel-Lindau gene, which results in an accumulation of hypoxia-inducible factors (HIF1 and HIF2) that enhance vascular endothelial growth factor (VEGF) expression resulting in dysregulated angiogenesis (14). Increased VEGF expression is closely related to the hypervascularity of ccRCC, which explains the efficacy of TKIs in ccRCC. The present study does

^ ORCID: 0000-0002-8681-1407.

not indicate a role for nivolumab switch maintenance in untreated mRCC. Therefore, combination therapy of ICIs with next-generation TKIs, and not the sequential use of first-generation TKIs and ICIs, should be the first-line treatment.

Moreover, the results of this study should be interpreted in the context of TKI resistance. Several reports have described the molecular mechanisms for TKI resistance, including involvement of angiogenesis, non-angiogenesis, epithelial-mesenchymal transition, epigenetic modifications, and tumor microenvironment factors (15-17). Further studies are required to clarify the factors associated with TKI resistance and the population who might benefit from switching to nivolumab.

Second, this study emphasized the importance of elucidating predictive biomarkers of responses to ICIs that allow "early" decision making regarding switching to nivolumab. ccRCC is associated with several secondary mutations, including Polybromo-1 (PBRM1) or BAF180, SET domain-containing 2 (SETD2), and BRCA1 associated protein 1 (BAP1), whose roles in immune modulation remain unclear (18,19). Recently, *PBRM1* mutations were reported to be associated with clinical benefit from anti-PD-1 therapy in patients with ccRCC who received prior antiangiogenic therapy (20). Further studies are required to clarify the influence of specific gene mutations on IFNγ-STAT1 signaling and tumor microenvironment (21), and elucidate the potential subset of mRCC that might benefit from switch maintenance using nivolumab.

As a limitation, the reasons for high incidence of grade ≥3 AEs and treatment discontinuation in patients with mRCC receiving a combination of PD-1 inhibitor with first-generation TKIs remain largely unclear. Further studies are needed to validate the subset of patients who benefit from these combination therapies.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Andrology and Urology*. The article has undergone external peer review.

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-14/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-14/coif). T.K. reports lecture fee from MSD. N.N. reports lecture fee from Takeda Pharmaceutical Company. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Kato T, Nonomura N. Validity and utility of switch-maintenance therapy with nivolumab in tyrosine kinase inhibitor-sensitive patients with metastatic renal cell carcinoma: learning from NIVOSWITCH. Transl Androl Urol 2024;13(7):1333-1335. doi: 10.21037/tau-24-14

