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Platinum Priority – Editorial

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Mutation Analysis of the FGFR3-encoding gene Does Not Predict Response to Checkpoint Inhibitor Treatment in Metastatic Bladder Cancer

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In this issue of *European Urology*, Wang et al [1] present novel and critical results on biomarker analyses of the IMVIGOR 210 and Checkmate 275 metastatic urinary bladder cancer (mUC) phase 2 trial cohorts, and explore the relation between FGFR3 mutational status and resistance to immune checkpoint inhibition. The paper highlights the ongoing search for treatment-predictive biomarkers for immunotherapy and points to the need for a better understanding of resistance mechanisms in immunotherapy and potential ways to overcome such resistance.

UC is a major global health problem, affecting 550 000 new individuals and accounting for almost 200 000 deaths each year [2], so there is a global need for better treatment strategies and better individualization of existing therapies. Localized non–muscle-invasive UC is routinely cured, or at least controlled over the long term, using transurethral resections and intravesical instillations of chemotherapeutics and/or the immune-activating bacillus Calmette-Guérin (BCG) vaccine. For localized muscle-invasive UC, more aggressive approaches are indicated, but cystectomy (potentially following neoadjuvant chemotherapy) or organ-preserving radiotherapy/chemoradiotherapy still provides options for cure [3].

However, the treatment of mUC remains a major clinical challenge. Cisplatinum-based regimens have been the standard of care for decades, and may provide palliation in terms of prolonging survival and alleviating cancer-related symptoms. Unfortunately, the long-term efficacy of cisplatinum is modest, with median overall survival usually in the range of 12–15 mo, and serious adverse effects that could be disabling or even life-threatening are not uncommon [4]. Therapeutic opportunities for patients unfit for cisplatinum and patients with progressive disease following cisplatinum-based chemotherapy have been limited until recently. Second-line chemotherapy, such as vinflunine monotherapy, offers a limited survival benefit for a minority of patients [5].

While "local immunotherapy" via intravesical BCG instillations was established as a well-tolerated and effective means for controlling localized disease in the 1970s, systemic immunomodulatory therapy for metastatic disease remained a purely hypothetical option for a long time. The recent advent of immune checkpoint inhibitors, which target the PD1/PDL1 pathway and thus release the "lock" on the antitumoral T-cell response, was therefore a significant game changer, allowing the use of systemic immune therapy in several forms of metastatic cancer including neoplasias of the bladder [6]. Studies over the past few years have explored several PD1/PDL1 antibodies and found significant clinical activity in patients with mUC progressing on cisplatinum [7–9], of which atezolizumab, nivolumab, and pembrolizumab are now approved by regulatory authorities in Europe. In addition, atezolizumab and pembrolizumab are available for PDL1-positive patients as first-line treatment for individuals considered unfit for cisplatinum combinations [6].

While a subgroup of approximately one-fifth of patients with mUC experience a long-term benefit from anti-PD1/PDL1

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therapy, the vast majority of patients are unfortunately nonresponders and will experience rapid progression and death due to their disease. In the worst-case scenario, a patient will develop severe adverse effects related to immune activation without any positive effects in terms of cancer remission or stabilization. Hence it is crucial to identify patients who are suitable or unsuitable for anti-PD1/PDL1 therapy before commencing treatment.

To date, the reason for primary resistance to PD1/PDL1 inhibitors is poorly known, and treatment-predictive biomarkers remain to be established. The level of PDL1 expression in intratumoral immune cells seems to be a prognostic parameter, but as a guiding tool for clinical decision-making its value is limited and its potential role as a biomarker predicting immunotherapeutic response is yet to be confirmed [6].

It is known that some bladder cancers have lower infiltration of T-cells than others, which could hypothetically explain an endogenous inability to respond to immunotherapy. This UC subgroup is characterized by a luminal papillary phenotype and often harbors mutations in the *FGFR3* gene and enhanced expression of FGFR3 [10]. Wang et al investigated the potential predictive value of mutations in the *FGF3* gene among patients previously treated with atezolizumab in the IMVIG 210 1 and 2 trial cohorts [1,7]. *FGFR3* genotypes were tested using DNA next-generation sequencing for 274 individuals, of whom 49 had mutant *FGFR3*. In addition, genotyping was performed in a separate cohort of patients treated with nivolumab in the Checkmate 275 trial [8]. As expected, mutant *FGFR3* (as well as enhanced FGFR3 expression) was negatively associated with a T-cell gene signature. However, response rates and survival were similar among all patients regardless of *FGFR3* status. Although it is unclear whether the statistical power was sufficient to rule out a limited or modest predictive value, the findings point against a major impact of *FGFR3* mutational status in the development of resistance against checkpoint inhibition, at least in the short-term follow-up setting. The authors provide in vivo and in vitro experimental data from various urothelial cancer cell lines that demonstrate an inverse association between mutant *FGFR3* and a TGF-β–-associated stromal anti-inflammatory and mesenchymal-to-epithelial–transition signature. This represents a potential, albeit causally not proven, mechanism that could possibly counterbalance the potential interaction between mutant *FGFR3* status, absence of T-cell infiltration, and impaired response to checkpoint inhibitors.

On the basis of the results presented by Wang et al, *FGFR3* mutational status should not be used to decide whether or not PD1/PDL1 checkpoint inhibition is suitable for an individual mUC patient. Unfortunately, with the evidence currently available there is still no predictive biomarker ready for use in this setting, so the only way to know whether a patient will respond or not is to treat and then "watch and wait". While presenting crucial albeit mainly negative data, the paper by Wang et al clearly encourages further studies on this topic and underlines the need for intensified efforts to identify clinically useful biomarkers for immunotherapy in mUC. Notably, several trials are now focusing on modalities to overcome resistance mechanisms and improve the potency of checkpoint inhibition in various stages of UC. In malignant melanoma, combined inhibition of both PDL1 and CTLA4 is now an established form of highly potent immunotherapy in stage III–IV disease, and a similar approach is being explored in the DANUBE phase 3 trial, which is evaluating combination PDL1/CTLA4 inhibition with durvalumab and tremelimumab in the first-line mUC setting. Other trials, funded by Merck and Roche, are focusing on chemotherapy and checkpoint inhibition alone or in combination. In addition, currently recruiting studies are exploring the role of immunotherapy in earlier stages of both non–muscle-invasive and muscle-invasive UC as neoadjuvant or adjuvant treatment. With expanding indications for immunotherapy, it is crucial to evaluate both the clinical efficacy and the toxicity of established drugs that are now assessed in earlier disease stages and different patient subgroups, as the immune-mediated toxicity profile may differ between patients with minimal metastatic or measurable disease and those with nodal or visceral metastatic disease. With evolving therapeutic modalities and expanding treatment indications, the results reported by Wang and others underline the need for prognostic and predictive biomarkers to tailor optimal treatment strategies for individual patients.

Conflicts of interest: Syed A. Hussain has received lecture fees from Roche, MSD, AstraZeneca, BMS, Sotio, Janssen, Pierre Fabre, Ipsen, and Pfizer, and advisory board and consultancy fees from Roche, MSD, Astra Zeneca, Astellas, BMS, Pierre Fabre, Janssen, Pfizer, Bayer, GSK, and Eisai. Nils O. Elander has nothing to disclose.

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