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European Association of Urology

Letter to the Editor

Re: Roger Li, Philippe E. Spiess, Scott M. Gilbert, Andrea Necchi. Towards Personalized Neoadjuvant Therapy for Muscle-invasive Bladder Cancer. Eur Urol 2019;76:4–6

We read with great interest the Platinum Opinion by Li et al. [1] on neoadjuvant therapy for muscle-invasive bladder cancer (MIBC). This concise commentary uncovered a new indication for immune checkpoint blockade (ICB) for bladder cancer beyond the management of advanced or metastatic BC. We hope that the ongoing clinical trials listed in the manuscript may result in inspiring findings. Nevertheless, there are some aspects of ICB that deserve further attention.

First, several studies have reported fatal myocarditis caused by ICB therapy. Johnson et al. [2] found that nivolumab monotherapy led to a myocarditis incidence of 0.06% (10 cases in 17 620), and one of the ten cases was fatal. The combination of nivolumab and ipilimumab resulted in a much higher incidence of 0.27% (8/2974), and five of the eight myocarditis cases were fatal. It is evident that combination therapy comprising a PD-1 inhibitor and a CTLA-4 inhibitor increases the incidence of myocarditis, especially fatal myocarditis. Another study reviewed the history of 101 patients who had severe myocarditis from 2014 to 2017 following ICB, of whom 46 died of myocarditis (mortality 46%) [3]. However, three-quarters of the 101 patients were not taking concomitant cardiovascular or diabetic medications, so it is not possible to attribute the high incidence of myocarditis to ICB, as it is unclear whether these patients had cardiovascular disease. Raschi et al. [4] found that among 21 034 patients who received at least one type of ICB as of December 2016, 88 developed myocarditis after ICB treatment, which was higher than for any other antitumor drug. Clinicians should be alert to the risk of myocarditis in patients on ICB, especially those receiving immune combination therapy, such as NCT03387761 mentioned in Table 1 of Li et al. [1], because ICB-associated myocarditis could result in high mortality due to myocarditis.

Second, the US Food and Drug Administration and the European Medicines Agency both limited the use of pembrolizumab and of atezolizumab for some patients with urothelial cancer in June 2018. The main reason was a lack of survival for patients with advanced or metastatic urothelial carcinoma receiving ICB compared with platinum-based chemotherapy. The efficacy of ICB heavily depends on the expression of PD-L1. We also believe that cost-effectiveness outcomes should be investigated too.

Overall, there is no doubt that ICB offers a novel option for cisplatin-ineligible patients with advanced or metastatic BC and for MIBC cases in which neoadjuvant therapy is planned. However, ICB may be not suitable as a first-line management approach. Studies are needed to identify the risk factors for myocarditis following ICB, especially among patients without a history of heart disease. Future clinical trials and decision-making should take various factors into account, in line with the notion of personalized (neoadjuvant) therapy.

Conflicts of interest: The authors have nothing to disclose.

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