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European Association of Urology

Letter to the Editor

Re: Pooja Ghatalia, Matthew Zibelman, Daniel M. Geynisman, Elizabeth Plimack. Approved Checkpoint Inhibitors in Bladder Cancer: Which Drug Should Be Used When? Ther Adv Med Oncol 2018;10:1758835918788310

Knowing PD-L1 Status is Not Enough: Applying a Molecular Subtype Approach to Bladder Cancer is Also Needed

Metastatic urothelial carcinoma (UC) represents a major clinical challenge and the standard treatment for patients with this disease is cisplatin-based combination chemotherapy [1]. Nevertheless, more than half of all patients with metastatic UC are cisplatin-ineligible, although some of them can be treated with carboplatin-based combinations. Immune checkpoint blockade has emerged as a new treatment principle, currently with two indications: for progression during or after platinum-containing chemotherapy and for cisplatin-ineligible patients.

Atezolizumab, nivolumab, pembrolizumab, durvulumab, and avelumab are all approved by the US Food and Drug Administration in the setting of progression during or after platinum-containing chemotherapy. However, regarding this indication, one negative [2] and one positive [3] phase 3 trial for atezolizumab and pembrolizumab, respectively, have been conducted. The negative atezolizumab trial used PD-L1 expression in $\geq$5% of tumour-infiltrating immune cells as a threshold for treatment. This outcome discrepancy for immune checkpoint blockade [2,3], together with a recent European Medicines Agency (EMA) recommendation (report EMA/364553/2018, www.ema.europa.eu/docs/en_GB/document_library/Press_release/2018/05/WC500249798.pdf), complicates the use of immune checkpoint blockade for the second indication (ie, in cisplatin-ineligible patients).

In the setting of cisplatin ineligibility, the evidence today consists of phase 1b and 2 studies, and no head-to-head comparisons with other chemotherapy regimens are available. On the basis of preliminary data from randomised investigations (Keynote 361 and IMvigor130), on June 1, 2018, the EMA limits the use of atezolizumab and pembrolizumab to patients with >5% PD-L1–positive immune cells and a PD-L1 combined positive score of $\geq$10. However, randomised data indicate that such selection yields a more favourable outcome (overall survival and response rates) with both chemotherapy and atezolizumab [2]. Furthermore, restricting immune checkpoint blockade in cisplatin-ineligible patients does not consider the facts that it is well tolerated and offers durable responses in some patients [3], even those who do not fulfil such PD-L1 criteria, because almost 25% of the whole population responds irrespective of PD-L1 status [4].

An alternative to such a treatment restriction would be to apply a more granular assessment to predict treatment response based on, for example, tumour mutational burden (TMB). TMB outperforms PD-L1 expression in predicting nivolumab treatment outcomes for several tumour types [2,5], and the correlation between PD-L1 and TMB is only modest (r = 0.13) [2]. The accumulation of responders in the genomically unstable (GU) UC molecular subtype (50% partial response/complete response) [5] is also intriguing. The GU subtype may serve as a proxy for TMB, because it has the highest average mutation burden among all subtypes [5]. Moreover, the GU subtype can be assessed via immunohistochemistry or RNA profiling, thus circumventing the practical and economic difficulties in evaluating TMB via whole-exome sequencing. Exploring such alternative biomarkers would compensate for the disparities among the various PD-L1 assays used for different drugs.

Applying molecular subtype classification to available studies [3,4], would probably provide useful hypothesis-generating findings in addition to current clinical response predictors (ie, lymph node metastases only and PD-L1 status). Such data could then be formally evaluated via molecular profiling in the awaited Keynote 361 and IMvigor130 investigations.

Conflicts of interest: The authors have nothing to disclose.

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