Editorial Commentary

Molecular subtypes and response to immunotherapy in bladder cancer patients

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The introduction of immunotherapy for the treatment of patients with advanced urothelial carcinoma has led to a significant interest in markers predicting therapy response. As in other tumor entities, approximately 20% of patients show objective response to single drug checkpoint inhibition. The identification of these patients is of great interest in order to avoid ineffective and expensive treatment. The only marker currently used in daily clinical practice for treatment selection is protein expression of PD-L1 based on immunohistochemistry in cisplatin-ineligible patients. This practice is based on unpublished data from two phase III randomized trials comparing chemotherapy, immunotherapy and the combination of both in this setting (NCT02853305, NCT02302807). The drug approval agencies FDA and EMA have limited their approval of immunotherapy as first-line drug for cisplatin ineligible patients to patients who have PD-L1 positive tumors.

A further marker that has been discussed extensively as potential predictor of treatment response is the mutational burden of tumors (TMB) (1). Data from the Cancer Genome Atlas project (TCGA) show that urothelial carcinomas exhibit a relatively high mutational burden compared to other cancer types (2). In the IMvigor 210 trial investigating Atezolizumab in cisplatin ineligible patients or patients with cisplatin-refractory disease, the mean TMB in patients with objective response was significantly higher (12.4 mutations per megabase pair) compared to non-responders (6.4 mutations per megabase pair) (3).

In a recent publication, Kim *et al.* have analyzed the publicly available dataset from the molecular characterization of tumors from the IMvigor trial 210 to investigate potential associations between molecular subtypes and response to Atezolizumab (4). The introduction of molecular subtypes has led to a significant improvement of the understanding of molecular characterizations of urothelial cancer (5). Several groups have worked on the identification of different subtypes (6-10) that showed strong overlaps, especially regarding the existence of a basal and luminal subtype of tumors. It was the Lund group, that discovered the existence of a neuroendocrine-like (NE-like) subtype in urothelial cancers that did not have histopathologic features suggestive for neuroendocrine origin (11). The TCGA suggests the existence of five subtypes (luminal-papillary, luminal-infiltrated, luminal, neuronal and basal-squamous), thus identified a class of tumors what is similar to the NE-like tumors, identified by the Lund group (2). These tumors show high expression of genes involved in neuronal and neuroendocrine differentiation. These tumors exhibited worst prognosis in the TCGA which was confirmed by other groups using whole transcriptome analysis in other datasets (12).

Kim *et al.* developed a single patient classifier using expression data from urothelial cancers of the bladder to enable the assignment of molecular subtypes of specimens

whose RNA profile has been analyzed in the framework of the IMvigor 210 trial. They used both the TCGA and Lund classification for subtype assignment. Eleven tumors in the cohort were assigned to the neuronal subtype. Association of subtypes with response to Atezolizumab was assessed. The authors showed that the patients with a neuronal subtype defined by the TCGA classifier have a considerably high objective response rate (complete response rate: 25%, partial response rate: 75%). Moreover, in this cohort of patients treated with atezolizumab, the group of patients with neuronal subtypes exhibited the best overall survival. In other cohorts with patients not treated by immunotherapy, these tumors exhibited worst prognosis. Of note, none of these tumors showed characteristics of immune-inflammation (13), which has been identified previously as potential feature predicting response to immunotherapy. Moreover, the neuronal tumors identified by the study did not have a TMB above the average.

The study addresses an important need in the current landscape of advanced urothelial carcinoma. There is high demand of a marker that allows reliable prediction of responders based on a method that allows high reproducibility and validity. However, there are some important limitations of this study that have to be discussed. The IMvigor 210 cohort includes different tissue types (bladder, kidney, liver, lung, lymph node, 'other', ureter). Importantly, the TCGA and other classifiers have been discovered in transcriptomic data of urothelial cancer of the bladder. It's validity in other tissue types has not yet been confirmed. Therefore, the subtype calls in these tissue types should be interpreted with caution. In the subset of patients with bladder tissue analyzed (n=195), 53 were collected after cisplatin-based treatment and 100 before. Previous studies have shown that established molecular subtyping models proved to be inconsistent in their classification of post-NAC samples (6,14). The use of previously defined subtypes that are mainly based on samples from bladder tumors before neoadjuvant chemotherapy. The performance of this classifiers in post-NAC samples is not confirmed yet. The numbers are limited. In the Imvigor210 dataset, only 11 samples with a neuronal subtype were identified and information on response was available in 8 of these 11 samples. Finally, the expression of PD-L1 in NE-like tumors has been shown to be rather low (11,12). However, the neuronal tumors identified by the TCGA classifier in the IMvigor 210 dataset show a broad range in PD-L1 expression. This might be due to the limited "purity" in terms of being NE-like of this group of tumors.

Consequently, before using molecular subtypes of bladder as standard approach for identifying candidates for immunotherapy, proof is needed that these classifiers show robust performance both in primary tumor tissue and tissue from metastases. Moreover, the impact of previous treatments on the performance of classifiers for molecular subtyping in this context needs clarification. The collection of pre- and post-treatment tissue in currently ongoing trials in the neoadjuvant setting may provide important information on the evolution of molecular subtypes in the course of treatment with various agents. These data will be valuable for the future implementation of molecular subtypes as marker for therapy response. It is likely that the combination of various markers (e.g., molecular subtypes, PD-L1 expression, TMB and DNA repair gene status) may improve the performance compared to a single marker.

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None.

Footnote

Conflicts of Interest: The authors have no 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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