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Platinum Priority – Editorial

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Personalised Medicine for Advanced Urothelial Cancer: What is the Right Way to Identify the Right Patient for the Right Treatment?

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Advanced urothelial cancer remains a challenging disease with poor outcomes. This is despite the introduction of checkpoint inhibitor immunotherapy targeting PD-1, or its ligand PD-L1, which overall provides a modest benefit in unselected patients but tantalising durable responses in a minority [1]. There is a pressing need for validated predictive biomarkers to facilitate a precision medicine approach. There has been evolution in our understanding of how transcriptomic profiling can divide urothelial cancer into clinically meaningful subtypes that appear to indicate altered sensitivity to both chemotherapy and immunotherapy [2,3]. These subtypes also indicate enrichment in key genomic alterations, including those relevant to emerging experimental approaches such as FGFR3 inhibition [2]. However, the data on which these assertions are based are mostly from retrospective and nonrandomised sets with a significant risk of bias and challenges for differentiating prognostic versus predictive value (or both).

In this issue of *European Urology*, Kim et al. [4] provide data suggesting that a subtype classifier based on The Cancer Genome Atlas (TCGA 2017) approach to transcriptomic subtyping [2] indicates responsiveness to immunotherapy. This included an exceptionally high response rate in the relatively uncommon neuronal subtype. The study used gene expression data from the prospective phase 2 IMvigor210 single-arm trials of atezolizumab, PD-L1-directed, immunotherapy in two cohorts of cisplatin-ineligible first-line cases ($n = 119$) and second-line, post-platinum cases ($n = 310$) of urothelial cancer [5,6], with 76 and 272 patients, respectively, available for analysis, of whom 298 had response data available. A classifier was developed (the methodology for which is being prepared for publication) that reduced 3347 genes used for unsupervised clustering in TCGA 2017 to 354. This recapitulated the subtype classifications described in TCGA 2017, and with reasonable correlation to other prior classification approaches.

Genomic enrichment within transcriptomic-based subtypes was also consistent with prior data, including more frequent *FGFR3* alterations and low carcinoma in situ scores in the luminal-papillary subtype, high *p53*-like and EMT signature expression profiles in the luminal-infiltrated subtype, high uroplakin expression and *TP53* mutations in the luminal subtype, and enrichment of $CD8^+$ effector T cell and immune checkpoint genes in the basal-squamous subtype. The authors also confirmed detection of a small neuronal subtype ($n = 11$), as previously described in TCGA 2017 in 5% of cases. Neuronal subtype cancers exhibited loss of wild-type *TP53* and *RB1*, high expression of neuroendocrine and neuronal linked genes, and the lowest *TGFB1* and *TGFBR1* expression.

The subtype classification produced by this novel classifier approach was then applied to efficacy data taken from the IMvigor210 trials as a combined group. Most strikingly, this indicated an exceptionally high objective response rate to atezolizumab in neuronal subtype cancers. In 11 neuronal subtype cancers, there were two complete and six partial confirmed responses, and three unconfirmed responses. The luminal subtype had a confirmed overall response rate of 38%, compared to 18–20% for other

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subtypes. In addition, the neuronal subtype in this atezolizumab-treated cohort had the longest overall survival, in stark contrast to the poorest survival outcome in the non-immunotherapy-exposed TCGA 2017 cohort [2].

The authors acknowledge the limitations of their data. Response and survival assessments for a subset of 11 patients are inevitably at risk of low statistical power and the lack of treatment randomisation limits distinction of subtype allocation as a predictive biomarker for immunotherapy benefit as opposed to a prognostic factor. To the best of my knowledge, we also lack prospective data on the value of chemotherapy in this group. The analysis conflates first-line, cisplatin-ineligible metastatic disease (IMvigor210 cohort 1) with progression after platinum-based chemotherapy (IMvigor210 cohort 2). Isolation of cohort 2 indicated a consistent trend for better survival but was not statistically significant (six neuronal cancers from 272). This work used archival tumour samples, presumably mostly taken before systemic treatments in both cohorts. There are various emerging data suggesting that gene expression subtype allocation may differ with sampling either side of chemotherapy, potentially because of either tumour heterogeneity or clonal evolution [7].

Why would a neuronal subtype cancer be sensitive to immunotherapy? These cancers appeared to lack some features linked to immunotherapy response. They were not "immune-inflamed", eight of the 11 were "immune excluded", and they exhibited only average tumour mutation and tumour neoantigen burden. The authors propose that potentially low TGFB1 and TGFBR2 expression, consistent with prior data, and expression of neuronal or neuroendocrine proteins, as potential tissue-restricted antigens, may be relevant to responsiveness [8]. This seems plausible and warrants further investigation. In addition to transcriptional subtype classification, response to immunotherapy has been correlated with other measurable parameters. Potential candidates include tumour or infiltrating immune-cell PD-L1 expression, $CD8^+$ T-cell infiltration, tumour mutational burden, an interferon-γ gene expression signature, and DNA damage response and repair gene alterations [1,5,6,9,10]. To date, the only practical application in the clinic has been to use low PD-L1 expression to indicate less favourable outcome for immunotherapy (atezolizumab or pembrolizumab) compared to chemotherapy for first-line treatment in cisplatin-ineligible patients. Somewhat unusually, at the time of writing this is based on currently unreported phase 3 trials (www.ema.europa.eu/documents/press-release/ema-restricts-use-keytruda-tecentriq-bladder-cancer_en.pdf). Immediate questions surround the relative value of current (PD-L1 expression) versus potential (gene expression subtype and others listed above) predictive biomarkers. Could neuronal subtype designation override low PD-L1 expression status, for example, or will we need to create a composite approach?

To the best of my knowledge, this is a unique analysis of treatment outcomes among patients with neuronal subtype urothelial cancer. From these and other data around subtype classification and the emergence of FGFR3-directed therapy, it is becoming increasingly clear that we will have to view urothelial cancer as a group of diseases and not one. Further therapeutic advances will probably require prospective integration of these distinctions into clinical trials. We may even not be far from having to address this in routine practice as well. However, this work will need to be validated in other prospective trials of immune checkpoint inhibitors, and for other therapies. Larger randomised data sets will mature in the medium term and should provide a significant opportunity to test these hypotheses. Kim et al. [4] have provided a tantalising view of one direction in which these approaches might develop.

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