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Words of Wisdom

Re: Comprehensive Molecular Characterization of Muscle Invasive Bladder Cancer

Authors: Robertson AG, Kim J, Al-Ahmadie H, Bellmunt J, Guo G, Cherniack AD, Hinoue T, Laird PW, Hoadley KA, Akbani R, Castro MAA, Gibb EA, Kanchi RS, Gordenin DA, Shukla SA, Sanchez-Vega F, Hansel DE, Czerniak BA, Reuter VE, Su X, de Sa Carvalho B, Chagas VS, Mungall KL, Sadeghi S, Pedamallu CS, Lu Y, Klimczak LJ, Zhang J, Choo C, Ojesina AI, Bullman S, Leraas KM, Lichtenberg TM, Wu CJ, Schultz N, Getz G, Meyerson M, Mills GB, McConkey DJ; TCGA Research Network, Weinstein JN, Kwiatkowski DJ, Lerner SP. Cell. 2017 Oct 19;171(3):540-556.e25. PMID: 28988769

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Expert's summary

The authors present tumour genetics for a panel of 412 chemotherapy-naïve, clinically annotated bladder cancers (BC). This "multi-platform" analysis of muscle invasive BC (MIBC) reports mutational prevalence and survival data and updates work from 2014 on 131 MIBC patients [1]. The frequency of somatic copy number mutations (SCNMs), epigenetic events, mNA expression differences, pathway alterations, and non-coding RNA levels are evaluated using techniques such as Affymetrix arrays, whole genome sequencing, RNA-seq and microbial integration analysis.

Ultimately, Robertson et al identify 5 expression subtypes that may be utilized to stratify patients (disease natural history and predicted treatment response e.g. to neo-adjuvant chemotherapy (NAC)) and inform clinical trials. They include luminal-papillary (commonest; defined by FGFR3 mutations, TACC3 fusions and low progression risks), luminal-infiltrated, (low tumour purity with fibroblastic and immune marker expression), luminal (KRT20 and SNX31 expression), basal-

squamous (female preponderance and immune marker expression including PD-L1) and neuronal (neuroendocrine gene expression and high proliferation signatures). The latter represented the poorest survivors. [2]. Luminal-papillary may respond to FGFR3 inhibitors, and luminal-infiltrated and basal-squamous to anti-PD-L1 drugs, whilst neuronal subtypes should respond to etoposide/cisplatin NAC. Luminal-papillary and luminal-infiltrated are likely to be poor responders to NAC and perhaps should be accelerated towards early cystectomy.

Expert's opinion

Robertson et al provide a wonderfully illustrative manuscript that is larger than previous studies on the topic, providing a step towards *precision medicine* in this high-risk cohort [1].

The importance of identifying clinically relevant genomic alterations (CRGAs) is well known [3]. Cisplatin-based chemotherapy has been the mainstay of non-surgical treatment for advanced MIBC patients but a large proportion are not fit enough or do not respond [4]. Anti-angiogenic and anti-epidermal growth factor (EGFR) targets have shown promise but are not tailored to patient genomics. Targeted therapies aim to overcome these barriers. For example, Atezolizumab, a PD-L1 (checkpoint inhibitor) was given FDA breakthrough status in 2014 (high response/low side effects) and trials are ongoing (NCT02108652) [5]. Prospective trials such as The MATCH-UP trial (Molecular Allocation Trial to CHoose therapy for Urothelial carcinoma following Platinum-based chemotherapy) will evaluate the exploitation of pathways such as PIK3, AKT, mTOR, PTEN and EGFR and are in progress [5]. Innovations such as the COXEN (CO-eXpression ExtrapolatioN) alogorithm will match tumour genomics against drug-sensitivity signatures and will enable clinicians to allocate patients to treatments arms [4].

Robertson et al provide invaluable insight and confidence for predictive and prognostic biomarkers and future treatment targets that will feed such tools.

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BLOG TITLE:

“Unraveling the genomic map of invasive bladder cancer”