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Conventional genomic predictive markers to immune checkpoint inhibitors are deteriorated in metastatic clear cell renal cell carcinoma

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Immune checkpoint inhibitors (ICIs) have been one of the most effective cancer therapeutic options in first-line to advanced cancers, but demand effective biomarkers to complement the low responsiveness. Many genomic- and transcriptomic-level predictive markers to ICIs have been identified, including high tumor mutation (TMB) and copy-number variation (CNV) burdens, expression of immune checkpoint genes, and activated immunity measured in tumor microenvironment (TME), some to all of which are correlated with a better response in many different kinds of cancers, whereas no evidences were known in metastatic clear cell renal cell carcinoma (ccRCC). To test the applicability of conventional markers and ccRCC specific markers, we conducted DNA (targeted, 377 genes) - and RNA-sequencing of 60 metastatic ccRCC patients of two groups (26 responders; R and 34 non-responders; NR) in response to ICI therapy. The number of mutations (TMB) and the number of predicted neoantigens on HLA-A showed no significant differences between the two groups (R vs. NR; p=0.37, p=0.051). In addition to the ccRCC-specific markers, such as frameshift Indels (fsINDELs) burden and PBRM1 loss of function mutation, there were no significant differences in the expression levels of 24 tumor microenvironment (TME)-related immune activity markers between the groups. However, among the 13 co-stimulatory molecules, PD-L1 expression was significantly higher in the R group (p=0.02).

Instead, we observed that the only two features distinguishing patient responses were the Nonsense mutation burden (R vs. NR = 0.12 vs. 0.5%; p=0.011) and a machine learning-based classifier using 33 features selected based on Differentially Expressed Genes (DEGs) (n=844; FDR < 0.01; log2FoldChange < |1|, accuracy=0.9). Our findings suggest that the immune environments and immunoediting mechanisms in metastatic ccRCC may differ from those in other cancers, highlighting the need for the development of novel markers specific to metastatic ccRCC to achieve accurate predictions of ICI response.