e16594 **Publication Only**

Urine DNA model to predict response to neoadjuvant immune checkpoint inhibitors combined with chemotherapy in muscle-invasive bladder cancer.

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Background: Neoadjuvant immune checkpoint inhibitors (ICIs) combined with chemotherapy show promise in the treatment of muscle-invasive bladder cancer (MIBC). However, not all patients benefit from the treatment. Urine can overcome shortcomings of tissue-based biomarkers to guide treatment decisions. **Methods:** Thirty-Three patients were recruited in this study and they received three cycles of tislelizumab 200 mg intravenously on day 1 plus nab-paclitaxel 200 mg intravenously on day 2 every three weeks, followed by surgical treatment. Acornmed 808 panel and shallow whole-genome sequencing were performed to predict the efficacy based on the urine DNA. **Results:** The urine ctDNA levels (highest variant allele fraction) were significantly lower in responder (CR and PR) patients than this in non-responder (SD and PD) patients ($p < 0.001$). In addition, a decrease in chromosomal instability number (CIN) occurred in responding tumors ($p = 0.028$). Furthermore, ROC curves were used to compare the sensitivity and specificity of efficacy prediction, including the urine ctDNA level and CIN. In the ROC analysis, urine ctDNA level setting with an area under the ROC curve (AUROC) of 0.781 (95% CI 0.603 - 0.905, $p = 0.005$), achieving 100% sensitivity and 54.6% specificity in efficacy prediction. The ROC curve for CIN achieved a sensitivity of 68.2% and specificity of 72.7% (AUC = 0.731; 95% CI: 0.549-0.870, $p = 0.013$). Combination urine ctDNA level and CIN achieved a sensitivity of 100%, specificity of 63.6% (AUC = 0.806; 95% CI: 0.631-0.922, $p = 0.002$), positive predictive value (PPV) of 0.846, and negative predictive value (NPV) of 1.000. **Conclusions:** The classifier provides a framework for novel biomarker discovery and for optimizing treatment and surveillance in next-generation clinical trials. Research Sponsor: None.