O09 Preliminary proteomic analysis of F.F.P.E. tumor samples for predicting the response of bladder cancer patients to anti-PD-1/PDL-1 therapy

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Introduction & Objectives: Metastatic Bladder Cancer (BCa) is characterized by poor survival rates and limited therapeutic options. The recent introduction of immunotherapy-based regimens in BCa treatment seems promising but further research is needed to determine responsiveness to the specific drug schemes. Herein we aim to characterize responsiveness to checkpoint inhibitors (anti-PD-1/PDL-1) using proteomic analysis of tissue specimens.

Materials & Methods: In this pilot study, seven patients with muscle invasive BCa with known outcome with respect to response to anti-PD-1/PDL-1 therapy (4 Responders and 3 Non-responders) were included. Patients were treated with Nivolumab or Atezolizumab and response to therapy was evaluated based on radiological criteria (RECIST 1.1). Formalin-Fixed Paraffin-Embedded (FFPE) bladder tumor specimens, acquired through transurethral resection of bladder tumor prior to any treatment for BCa, were processed following an optimized sample preparation protocol. Extracted proteins were analyzed with Liquid Chromatography and tandem mass spectrometry (LC-MS/MS).

Results: Taking into consideration proteins that were identified in at least 50% of samples of at least one group and after omitting high abundance plasma proteins to minimize impact from blood contamination, a total of 1183 proteins were identified. When comparing Responders to Non-responders, 461 proteins were found to differ by at least 2 fold change between the two groups with 19 proteins reaching statistical significance (Mann-Whitney p-value <0.05). Interestingly, Responders presented with significantly higher levels of IL17RC, a membrane receptor that binds to the pro-inflammatory cytokines IL-17A and IL-17F, enhancing inflammation and progression of autoimmune diseases. Additionally, HINT, a protein implicated in natural killer cell-mediated immunosurveillance, was also significantly upregulated in Responders compared to Non-responders. In agreement to these findings, pathway enrichment analysis showed that immune response pathways, including T Cell Receptor and PD-1 signaling, are significantly enriched with proteins upregulated in Responders compared to Non-responders. This suggests the importance of preexisting immunological control of the tumor prior to treatment, in responsiveness.

Conclusions: Although preliminary, our study is the first to show the proteomic changes between Responders and Non-responders to anti-PD-1/PDL-1 therapy for BCa. Our results suggest that an activated immune response, preexisting to immunotherapy, might be the key molecular feature of BCa patients who respond positively to this therapy. Correlation to recently described cross-omics features associated with aggressiveness (Stroggilos et al., Intern J Cancer, in press) as well as an analysis of bigger cohorts are planned to better understand and enhance these first observations.