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Identification of a proteomic signature for predicting immunotherapy response in patients with metastatic non-small cell lung cancer

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Introduction: Immunotherapy have improved patient outcomes in comparison with chemotherapy in metastatic non-small cell lung cancer (NSCLC) patients [1–3]. For years, the selection of patients who received immunotherapy was based on the PD-L1 expression on tumour tissue, however the lack of potential value of PD-L1 expression to predict the response to this therapy has been reported in the last years [4,5]. Thus, find new biomarkers to select those patients who will benefit to immunotherapy is a real clinical challenge. Plasma circulating proteins is an emerged and promising investigated liquid biopsy tool, that can provide information about the physical condition and status of patients. Nowadays, improvements in proteomic technologies allows to identify and quantify nearly all expressed proteins in liquid biopsy samples, emerging as a potential tool to detect new predictive therapy biomarkers[6].

Objectives: In the present study, we hypothesized that differential proteomic quantitative analysis based on SWATH–MS technology, can allow us to identify a blood-based proteomic signature to select and predict the response to first-line of immunotherapy in new diagnosed NSCLC patients.

Methodology: We included 64 newly diagnosed advanced NSCLC patients treated with pembrolizumab as first-line therapy at the Medical Oncology Service of Complexo Hospitalario Universitario de Santiago de Compostela. Blood samples were collected from each patient prior to the treatment onset. After plasma isolation, we performed a differential proteomic quantitative analysis based on SWATH–MS technology to analyse the proteome.

Results: Proteomic analyses by SWATH-MS strategy allow us to identified 324 differentially-expressed proteins (DEPs) between responder and non-responder patients (Student's t tests, *p-value*<0.01)
. The signature provided an optimal separation between both groups according to the first component in the principal component analysis (PCA) and the receiver operating characteristics (ROCs) curves showed high sensitivity and specificity of prediction.

Conclusions: Proteomic analyses from circulating proteins allowed to discover and quantified a high number of proteins in plasma samples, showing their potential value as a screening tool to find new prognostic and predictive biomarkers to immunotherapy field.

In addition, we developed a predictive model and found a combination of seven proteins, including ATG9A, DCDC2, HPS5, FIL1L, LZTL1, PGTA, and SPTN2, with stronger predictive value than PD-L1 expression alone. Additionally, survival analyses showed that low levels of ATG9A, DCDC2, and HPS5 were associated with longer

progression-free survival (PFS) and overall survival (OS), while low levels of SPTN2 were associated with worse OS