

MASS SPECTROMETRY-BASED PROTEIN BIOMARKER ANALYSIS IN CHEMOIMMUNOTHERAPY COMBINATIONS IDENTIFIES UNIQUE IMMUNE SIGNATURES IN PANCREATIC CANCER

Marco Tognetti, Nigel Beaton*, Kamil Sklodowski, Roland Bruderer, Lukas Reiter. *Biognosys, Schlieren, Switzerland*

Background Although the combination of chemotherapy with immunotherapy has led to significant improvements in the treatment of some solid tumors, metastatic pancreatic ductal adenocarcinoma (mPDAC) prognosis has remained largely unaffected by such approaches. Recently, PRINCE, a randomized phase 2 clinical study, reported significantly improved 1-year overall survival (OS) for mPDAC patients treated with nivolumab (nivo)/chemo compared to historical control¹ but not for sotigalimab (sotiga)/chemo or the sotiga/nivo/chemo combination. However, the study identified potential improvement to treatment outcome with patient stratification.² Here, we report an unbiased mass spectrometry (MS)-based proteomics profiling of a subset of plasma samples from the PRINCE trial.

Methods Plasma proteomic profiling was conducted on PRINCE nivo/chemo and sotiga/chemo longitudinal samples (n = 211, 62 individuals) using Biognosys ultradeep plasma workflow. Briefly, plasma samples were depleted, digested to tryptic peptides, measured by MS/MS and quantified using Spectronaut (Biognosys). Data was investigated for both protein and peptide biomarker with an emphasis on baseline biomarkers associated with clinical outcomes.

Results Plasma profiling identified 1,662 proteins and 17,451 modified peptides across the cohorts. First, we developed a model that identified the pharmacodynamic effects of treatment in individual patients. In accordance with the PRINCE study and among the major model contributors, sotiga/chemo increased proteins associated with innate immunity and chemokines (including CCL15) while proteins aiding in T cell activation and immune cell migration increased with nivo/chemo (including CXCL7 and CD115). Second, we looked for markers in the pretreatment plasma samples that could predict OS. Overall, we found 25 predictive markers (p < 0.05), with only six shared among the two arms, including Attractin and CD58. Among the seven predictive biomarkers specific to nivo/chemo, we found MEGF10 and GALNT1, which are suggested to play a role in neoantigen generation.[3] For sotiga/chemo, we found 12 predictive biomarkers including IGF2, CD304, and periostin (known to support immune responses). Third, we expanded our predictive biomarker search to the identified peptides, an analysis that is currently only possible using an unbiased mass spectrometry-based approach. Using such an approach we were able to identify predictive peptides, likely cleavage products, as well as predictive post-translational modifications.

Conclusions Herein we demonstrate the value of both an unbiased approach, as well as the use of peptide level data for novel biomarker identification. We identify numerous proteins and peptides that have the potential to be used for better patient treatment stratification in the case of mPDAC and immunotherapy.

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