

A NOVEL, HIGHLY ACCURATE LIQUID BIOPSY-BASED GLYCOPROTEOMIC PREDICTOR OF CHECKPOINT INHIBITOR TREATMENT BENEFIT IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background Protein glycosylation is the most abundant and complex form of post-translational protein modification. Glycosylation profoundly affects protein structure, conformation, and function. The elucidation of the potential role of differential protein glycosylation as biomarkers has been limited by the technical complexity of generating and interpreting this information. We have recently established a novel, powerful platform that combines liquid chromatography-mass spectrometry with a proprietary artificial-intelligence-based data processing engine that allows, for the first time, highly scalable interrogation of the glycoproteome. Here we report the performance of this platform to predict likely benefit from immune-checkpoint inhibitor (ICI) therapy in advanced non-small cell lung cancer (NSCLC).

Methods Our platform was utilized to assess 532 glycopeptide (GP) and peptide signatures representing 75 serum proteins in pretreatment blood samples from a cohort of 125 individuals (54 females, 71 males, age range 60 to 75 years). Inclusion criteria were as follows: a diagnosis of unresectable stage 3 or 4 NSCLC, treatment with pembrolizumab monotherapy (27 patients), or treatment with combination pembrolizumab-chemotherapy (98 patients). Overall survival (OS) data were available for all patients. Samples and de-identified clinical data were obtained from Tempus Labs (Chicago, IL).

Results A multivariable-model-based classifier for OS was created utilizing 70% of the cohort as a training set and seven glycopeptide and non-glycosylated peptide biomarker features selected from a generalized additive model. The classifier yielded a hazard ratio (HR) for prediction of likely ICI benefit of 3.96 at $p < 0.0001$. Additionally, the classifier was validated using a test set comprised of the withheld 30% of patients, yielding a HR of 3.86 at $p < 0.01$ which separated patients likely benefiting from ICI therapy from those likely not benefiting from ICI therapy (median OS of 23.2 vs. 5.9 months, respectively, based on classifier score above/below cutoff).

Conclusions The glycoproteomic classifier described here predicts with high sensitivity which patients are likely to benefit from ICI therapy. In addition to potentially reducing the use of ICIs in a safe manner in patients who would be unnecessarily subjected to possible adverse drug reactions, our classifier simultaneously has the potential of reducing the burden of health care expenditures. Our results indicate that glycoproteomics holds a strong promise as a predictor for ICI treatment benefit which appears to significantly outperform other currently pursued biomarker approaches.

Ethics Approval The study was conducted under IRB approval obtained by Tempus Labs, with all patients involved providing informed consent for the use of their blood samples for biomarker research.

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