Evaluation of immune-related markers in the circulating proteome and their association with atezolizumab efficacy in patients with 2L+ NSCLC

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Introduction

Anti-PD-L1/PD-1 therapy has become a standard of care in NSCLC. However, understanding of the biological mechanisms of treatment efficacy and resistance is still incomplete. Here we examine the role of the circulating proteome in 2L+ NSCLC patients treated with atezolizumab (anti-PD-L1).

Patients and Methods

Patient Cohorts
• Development Cohort – 77 NSCLC patients treated with atezolizumab (NCT01375842)
• Blinded Validation Cohort – 270 NSCLC patients treated with atezolizumab or docetaxel in the POPLAR study (NCT01903993)

Profiling of Circulating Proteome
• Mass spectra generated from pretreatment serum samples using Deep MALDI® method to obtain expression data with dynamic range of 5 orders of magnitude
• Spectra processed to render them comparable; mass spectral features (peaks) defined
• Methods and parameters locked prior to running validation samples

Test Development
• Test to stratify patients into groups with better (Good) or worse (Poor) outcome on atezolizumab developed using machine learning (ML) platform designed for settings with more samples than molecular attributes
• Reliable results from development cohort generated using cross-validation-like approach
• All parameters fixed using only development cohort samples

Protein Set Enrichment Analysis (PSEA)
• SEA methods applied to an independent set of samples with both mass spectral and protein panel expression data to assess the underlying biology of the test classification groups

Results: Underlying Biology

PSEA indicated trends to association of increased complement activation, acute inflammation and immune response type 2 in the Poor classification phenotype.

Results: Blinded Validation

Predictive and prognostic properties of the test were evaluated in the setting of this randomized study
• 262/270 samples passed QC and could be classified
• 134 patients (51%) were assigned to the good outcome group

Conclusions

The data suggest that a circulating-proteome-defined phenotype characterized by complement activation, acute inflammation and immune response type 2 can provide predictive information on benefit from checkpoint inhibition.