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

M. Kowanetz1, N. Leng1, J. Roder2, C. Oliveira2, S. Asmellash2, K. Meyer2, H. Roder2, M. Ballinger3, W. Zou1, D. Shames1
1 Oncology Biomarker Development, Genentech, South San Francisco, CA, USA; 2 Biodesix Inc, Boulder, CO, USA; 3 Product Development Oncology, Genentech, South San Francisco, CA, USA

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 (NCT019375842)
- 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 available to assess the underlying biology of the test classification groups

Results: Development

50 patients (65%) were assigned to the Good group and 27 (35%) to the Poor group

Results: Underlying Biology

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