

## Abstract EMT

Epithelial-to-mesenchymal signature as independent predicting factor of survival in surgically resected non-small cell lung cancer.

Julien Ancel<sup>1,2</sup>, Maxime Dewolf<sup>2</sup>, Anne Durlach<sup>1,3</sup>, Béatrice Nawrocki-Raby<sup>1</sup>, Véronique Daslstein<sup>1</sup>, Gaëtan Deslée<sup>1,2</sup>, Christine Gilles<sup>4</sup>, Myriam Polette<sup>1,3</sup>.

<sup>1</sup>Inserm, Université de Reims Champagne Ardenne, P3Cell UMR-S1250, SFR CAP-SANTE, 51097 Reims, France.

<sup>2</sup>Service de pneumologie, Hôpital Maison Blanche, CHU de Reims, 51092 Reims, France.

<sup>3</sup>Laboratoire de biopathologie, Hôpital Maison Blanche, CHU de Reims, 51092 Reims, France.

<sup>4</sup>Laboratory of Tumor and Development Biology, GIGA-Cancer, University of Liège, 4000 Liège, Belgium.

Despite recent advances, non-small cell lung cancer (NSCLC) remains the first cause of cancer-related deaths worldwide, including common relapse and high burden for non-metastatic stages. Immune checkpoint inhibitors (ICI) such as anti-PD(L)1 are now daily used in clinical practice, restricted to advanced and metastatic stages. Many studies are now ongoing broadly based on PD-L1 expression to predict tumor response with ICI in early stages. Thus, interests are growing for ICI use (alone or in combination with chemotherapy in early stage) in adjuvant and even in neo-adjuvant condition, aiming to enhance clinical outcomes after surgery. However, all these trials reported many patients experiencing tumor resistance to ICI, despite high PD-L1 expression. On another hand, epithelial-mesenchymal transition (EMT), has been extensively reported to be associated to tumor resistance. Considering PD-L1 as a marker associated with ICI response and vimentin as marker of tumor resistance, we hypothesized that both vimentin and PD-L1 could be of interest to predict clinical outcomes in non-metastatic NSCLC after surgery. In 564 Tumor Cancer Genome Atlas Lung Adenocarcinoma (AC), PD-L1 positively correlated with vimentin ( $r=0.41$ ,  $p<0.0001$ ). A 75-gene EMT expression signature confirmed this correlation with PD-L1 and others EMT markers such as FN1 ( $r=0.4$ ,  $p<0.0001$ ) and ZEB1 ( $r=0.34$ ,  $p<0.0001$ ), with similar observation for lung squamous carcinoma (SqC). In both AC and SqC databases, PD-L1 or VIM were not sufficient to predict overall survival (OS). Interestingly, vimentin and PD-L1 co-characterization significantly predicted OS, with worse outcome for tumors with both high PD-L1 and vimentin expression (Log-rank=11,  $p<0.0001$ ). In multivariate analysis, vimentin and PD-L1 co-statuses remained an independent predictor for OS in non-metastatic NSCLC (HR=1.749 (1.030-2.967),  $p<0.05$ ). All these observations support EMT as a useful biomarker to improve clinical NSCLC personalized management. In surgically resected NSCLC, the detection of mesenchymal polarization could help defining patients with worse outcomes and guide clinicians towards an adaptation of adjuvant strategies and clinical surveillance.

