# CheckpointPx, an interpretable radiology AI tool, predicts immune checkpoint blockade benefit independent of PDL1 status in non-small cell lung cancer (NSCLC): A multi-institutional validation study

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**Background**

Immune Checkpoint Inhibitors (ICIs) are a cornerstone in the treatment of cancers such as Non-Small Cell Lung Cancer (NSCLC). Despite the standard use of biomarkers such as PD-L1 expression for selecting ICI regimens, recent studies suggest missed opportunities for benefit in PD-L1 low/negative patients. Therefore, there is an urgent need for new biomarker strategies capable of guiding the use of ICIs in NSCLC. We introduce and validate an AI-powered radiology tool for ICI patient selection that provides interpretable predictions by quantifying aspects of tumor biology on baseline CT scans directly associated with ICI efficacy, such as tumor heterogeneity and twistedness of the tumor-associated vasculature.

**Methods**

We analyzed CT scans of 439 patients treated with ICI at 4 institutions (D1-D4) using the Picture Health Px platform. Experienced radiologists and physicians across institutions delineated target lesions on baseline CT scans. A deep learning model was used to segment pulmonary vessels. CheckpointPx v1.11, an interpretable neural network incorporating quantitative features extracted from within the tumor and its vasculature, was trained to predict ICI response (defined as disease control per RECIST best overall response) on n=247 patients (D1-D3). It was assessed with respect to response and progression free-survival (PFS) on 192 patients (D2-D4), with D4 (n=105) being an external validation set. CheckpointPx was also evaluated within PDL1 subsets among testing set patients where available (n=138).

**Results**

The cohort was predominantly late stage (>85%) and was mixed with respect to ICI line of treatment (1st-4th). 122 of 247 (49%) and 119 of 192 (62%) were responders in training and test cohorts respectively. CheckpointPx included 16 features, such as entropy-based heterogeneity and quantitative vessel tortuosity (twistedness). The model predicted response to ICI with an AUC=0.65 on the test set. The CheckpointPx High Risk group significantly stratified patients by PFS (HR=1.67 [1.22-2.28], p=0.001). This separation remained significant within the subset of PDL1-negative (HR=2.71 [1.35-5.44], p=0.005) and PDL1-positive patients (HR=2.05 [1.22-3.46], p=0.007).

**Conclusions:**

From baseline radiology, CheckpointPx was shown to strongly predict ICI outcomes across multiple institutions, NSCLC stages, and lines of ICI. Furthermore, the tool stratified patients by ICI benefit within both PDL1-positive and negative subsets - suggesting the potential of CheckpointPx to address critical gaps in the NSCLC biomarker landscape. CheckpointPx is driven by interpretable imaging biomarkers, and thus its predictions are tied to specific and quantifiable phenotypic attributes of the tumor and its microenvironment.