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A blind retrospective analysis of a novel predictive marker to immune checkpoint inhibition in lung cancer, calculated from histopathological slides through inferred transcriptomics

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Background: Immune checkpoint inhibitors (ICI) have dramatically improved outcomes in non-small-cell lung cancer (NSCLC). Nevertheless, response to ICI varies widely and commonly used predictive markers have limited predictive value. We present results of a blind retrospective analysis of a novel predictive marker of response to ICI in NSCLC relying solely on scanned Hematoxylin and Eosin (H&E) slides.

Methods: We obtained H&E slide scans from tumor-tissue of 50 cases of metastatic NSCLC treated with first-line ICI. We retrospectively applied ENLIGHT-DP to generate an individual response score to PD-1 inhibition for each slide composed of: (i) predicting mRNA expression from H&E slides using our digital-pathology-based algorithm; and (ii) use these predicted mRNA as input to ENLIGHT, our transcriptome-based precision oncology platform, which generates a response score to targeted and immune therapies. We then unblinded the clinical outcomes and evaluated performance of ENLIGHT- DP in comparison to as programmed death ligand (PD-L)-1 and tumor mutational burden (TMB).

Results: ENLIGHT-DP score is predictive of response with ROC AUC = 0.69 and outperforms PD-L1 (ROC 0.46) and TMB (0.52). Using a predefined threshold for binary classification of response derived from independent data, ENLIGHT-DP achieved 100% PPV and 44% sensitivity. In comparison, response according to PD-L1>50% achieves 65% PPV and 38% sensitivity and high TMB (>10) archives 82% PPV and 26% sensitivity. ENLIGHT-DP was particularly good at stratifying patients in PD-L1<1% outlier group (18 patients, ROC AUC = 0.8). In this cohort ENLIGHT-DP is the only biomarker significantly correlated with progression free survival (HR: 0.45, 95%CI: 0.2- 0.99, p=0.048).

Conclusion: ENLIGHT-DP demonstrates high predictive power for response to ICI in NSCLC relying solely on H&E slides, outperforming commonly used biomarkers. Importantly, our approach does not require training on prior treatment outcomes and can therefore be generalized to drugs for which such data is unavailable or scarce.