8543 **Poster Session**

Association of nuclear shape in the tumor epithelium with response to atezolizumab in NSCLC.

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Background: Anti-PD-(L)1 treatment is the standard of care for advanced non-small cell lung cancer (NSCLC). However, additional biomarkers are needed to identify patients who will benefit from these therapies. In this study, we demonstrate the atezolizumab response score (ARS), which uses digital pathology features of the shape and size of nuclei in the tumor epithelium to predict response to the anti-PD-L1 antibody atezolizumab in NSCLC. **Methods:** Patients were drawn from two trials comparing atezolizumab to docetaxel in second-line advanced NSCLC. A single digitized slide stained for the epithelial cell marker pan-cytokeratin (CK) and CD8 was selected for each patient. OAK, a phase III trial, had 819 patients with images available and was used for training the ARS model. POPLAR, the phase II trial preceding OAK, had 168 evaluable patient images for validating ARS. Color deconvolution was used to identify the CK-positive regions in each image. Nuclei were segmented using the hematoxylin channel. The area, perimeter, eccentricity, solidity, and minor/major axis lengths were extracted from each nucleus in the CK-positive compartment of the pathologist-annotated tumor lesion, excluding necrosis and artifacts. Each measure's mean, median, standard deviation, skewness, and kurtosis across the slide was calculated, for a total of 30 features. Features with an interaction $p < 0.35$ with trial arm in a Cox model were used to fit an elastic-net regularized Cox model on the atezolizumab-treated training set patients, producing ARS. The ARS threshold maximizing atezolizumab overall survival (OS) benefit in the ARS-high group was identified in OAK and applied to POPLAR (the validation set). ARS performance was assessed in the validation set by OS concordance index (c-index) and by atezolizumab benefit in the high- vs. low-ARS groups by hazard ratio (HR) [95% confidence interval]. **Results:** ARS employs five features. Lower nuclear median and standard deviation of major axis length, higher perimeter mean and standard deviation, and higher area were associated with better atezolizumab response. In the validation set, high-ARS (prevalence = 42%) patients had longer OS on atezolizumab vs. docetaxel (HR = 0.42 [0.24-0.72]) while low-ARS patients did not (HR = 0.95 [0.62-1.47]). ARS was positively associated with OS in the validation set atezolizumab arm (c-index = 0.60 [0.54-0.66]), but not the docetaxel arm (c-index = 0.47 [0.41-0.54]). **Conclusions:** We validated a nuclear morphology-based biomarker for atezolizumab response in advanced NSCLC. This demonstrates the utility of digital pathology for biomarker development and motivates study into the identified responder phenotype. Combination of ARS with additional markers, such as PD-L1 expression, might further improve stratification. Research Sponsor: Roche.

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