

## EVALUATION OF A COMPOSITE IMMUNOTHERAPY SIGNATURE IN NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH ATEZOLIZUMAB

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**Background** Immune checkpoint inhibitors have transformed the care of NSCLC, however many patients do not respond and current biomarkers have limited predictive value. While current guidelines recommend that patients with advanced NSCLC undergo large panel NGS to guide treatment selection, most of the genomic data generated are rarely utilized for therapeutic decision making in the absence of an actionable driver mutation. In this work, we validated a composite IO biomarker that integrates multiple genomic features readily available on large-panel NGS to predict response to ICI in NSCLC patients.

**Methods** OAK is a phase III trial that randomized 1250 patients with advanced stage NSCLC who progressed on initial platinum therapy to receive atezolizumab (Atezo) or docetaxel until disease progression (1). 239 participants with Foundation Medicine tissue NGS were included and 180 were WT for EGFR, ALK, ROS1, BRAF, MET and RET, of whom 86 received Atezo while 94 received docetaxel. We tested the predictive value of 7 biomarkers that had been trained previously on a subset of squamous lung patients treated with immunotherapy and were part of the Lung-MAP clinical trial, including TMB < 10, 10-19 and  $\geq 20$  Mut/Mb; PD-L1 IHC <1%, 1-49% and  $\geq 50\%$ ; mutations or loss of ARID1A, KEAP1, STK11, CDKN2A; and altered DDR defined as functional loss of one or more of these 7 genes: ATM, BRCA2, BRIP1, MRE11, POLE, MSH2 and PARP1. A nominal system included binning scores based on individual biomarker positivity of 0-2, 3-4 or 5-8 (IO signature low, medium, high). We used a Cox proportional hazards regression model to investigate the effect of individual covariates and three composite bins on OS of the two treatment arms.

**Results** Individual biomarker analysis showed that TMB  $\geq 20$  exerted the greatest effect on OS in Atezo-treated patients (HR= 0.4,  $P = 0.07$ ). Altered DDR, PD-L1 >50% and STK11 loss numerically impacted OS but did not reach statistical significance due to small sample size. High IO signature correlated with improved OS within the Atezo-treated patients, yielding a median OS of 23 months vs. 7 months (HR=0.38; 95% CI, 0.18-0.81) between high vs. low, as well as a median OS of 23 months vs. 10 months between Atezo and docetaxel treated patients within the high IO signature subpopulations (HR=0.68; 95% CI, 0.34-1.3).

**Conclusions** Our data suggest that Composite IO signature might be more accurate and informative than a single biomarker in guiding ICI treatment selection in NSCLC.

**Trial Registration** OAK Trial NCT02008227

### REFERENCE

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**Ethics Approval** All patients signed informed consent prior to publication of the original study manuscript at the Lancet in 2017.

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