

## LUNG-MAP COMPOSITE SIGNATURE FOR IMMUNE CHECKPOINT INHIBITOR (ICI) EFFICACY IN ADVANCED SQUAMOUS CELL LUNG CANCER (SCC)

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**Background** Predictive biomarkers for ICI regimens in NSCLC, namely PD-L1 and tumor mutational burden (TMB), remain suboptimal, leaving oncologists with limited decision-making tools. We sought to develop a more comprehensive solution, integrating genomic alterations detected by comprehensive genomic profiling (CGP), to enrich for association with progression-free survival (PFS) and overall survival (OS).

**Methods** Lung Master Protocol (Lung-MAP) is an NCI-sponsored public-private partnership evaluating new therapies for previously-treated advanced stage NSCLC. In this analysis, 320 SCC patients from sub-studies S1400A (n=68; durvalumab) and S1400I (n=252; nivolumab ± ipilimumab) had tissue CGP data by Foundation Medicine. 204 patients from S1400A (n=43; SP263) and S1400I (n=161; 28–8 pharmDX) had PD-L1 IHC. We evaluated TMB (0–9, 10–20, >20 mut/Mb), PD-L1 IHC, HLA loss of heterozygosity (LOH) of  $\geq 1$  gene (evaluable for n=206), mutations in KEAP1/NFE2L2, DNA damage response genes, ARID1A, and loss of CDKN2A as potential ICI biomarkers. Wilcoxon and Fisher's exact tests assessed association between continuous TMB/PDL1 IHC (<1%, 1–49%,  $\geq 50\%$ ) and each binary biomarker, and between pairs of binary markers. Cox proportional hazards model evaluated the association between each biomarker and OS/PFS, adjusting for age, sex, smoking status, and stage. Based on significance (at the nominal 0.1 level without correction for multiplicity) from univariate analysis, multiple combination signatures were analyzed using a predetermined scoring system. Biomarkers in the most significant combination signature was further examined by adjusting for TMB and PD-L1, to demonstrate if they provided additional value.

**Results** Despite associations between TMB and ARID1A mutations ( $P = 0.009$ ), PD-L1 and KEAP1/NFE2L2 mutations ( $P = 0.007$ ) and ARID1A mutations and KEAP1/NFE2L2 mutations ( $OR = 2.89$ ; 95% CI, 1.43 – 5.91,  $P = 0.0016$ ), the magnitude of correlation was modest, thus representing complementary predictors. Higher TMB (>20 vs. 10–20 vs. 0–9) was the most significant positive predictor of OS ( $HR=0.79$ ; 95% CI, 0.65–0.95,  $p=0.01$ ). A composite combinatorial signature (ICIsig) inclusive of TMB, PD-L1, HLA LOH, ARID1A, and KEAP1/NFE2L2 mutations was associated with better OS ( $HR=0.76$ ; 95% CI, 0.63–0.92,  $p=0.005$ ) and PFS ( $HR=0.84$ ; 95% CI, 0.70–0.99,  $p=0.048$ ). Landmark 3-year OS rates were 29% vs. 6% in ICIsig high vs. low. ICIsig high represented 39% of the evaluable population.

**Conclusions** We show that a composite ICIsig extending beyond TMB and PD-L1 captures NSCLC patients benefiting from ICI therapy more effectively than single biomarkers. ICIsig could inform treatment selection in today's rapidly expanding therapeutic landscape. Validation from a large randomized Phase III trial is ongoing.

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