EXAMINING ELEVATED TMB AND CLINICAL BENEFIT OF 1L IMMUNE CHECKPOINT INHIBITOR IN ADVANCED NSCLC

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**Background** For patients with advanced non-small cell lung carcinoma (NSCLC), immune check point inhibitor (ICPI) and chemotherapy (chemo)-ICPI represent 2 distinct first-line standard-of-care regimens without clear and established biomarkers to inform the optimal choice for individual patients. Here, we examined the complementary roles of tumor mutational burden (TMB) and PD-L1 immunohistochemistry (IHC) to inform first-line therapy using a large real-world (rw) data set.

**Methods** The study included patients with NSCLC from the Flatiron Health (FH)-Foundation Medicine (FMI) de-identified clinico-genomic database (CGDB). All patients underwent genomic testing using FMI’s tissue comprehensive genomic profiling (CGP) assay and PD-L1 IHC assay scored for tumor cell staining (TS).

**Results** Of 2,165 patients included in the analysis, 150 exhibited durable benefit from first line ICPI regimens (these patients were enriched for PD-L1 TS ≥50, non-squamous histology, and TMB ≥20 mutations/Megabase [muts/Mb]). Comparing low TMB (<10 muts/Mb), high TMB (10–19 muts/Mb), and very high TMB (≥20 muts/Mb) receiving ICPI alone, we observed a stepwise increase in median rwPFS (real world-progression free survival) (6.5, 7.5, 17.2 months) and rwOS (real world-overall survival) (10.1, 11.8, 26.9 months) as TMB increased. In the low PD-L1 (TS <50%) cohort, TMB <10 muts/Mb (HR: 0.70 [0.54–0.92]) and 10–19 muts/Mb (HR: 0.48 [0.32–0.72]) showed a more favorable rwPFS on chemoICPI when compared to ICPI alone while no significant additional increases in rwPFS is observed when adding chemo onto ICPI in the TMB ≥20 muts/Mb (HR: 1.18 [0.56–2.48]) cohort.

**Conclusions** This study provides evidence that higher TMB cut-offs, such as 20 muts/Mb, can identify patients with prolonged benefit. TMB ≥20 muts/Mb may identify patients in whom an ICPI without chemo could be considered, even in the setting of lower PD-L1 levels. Prospective validation of these findings could increase access to chemo-sparing regimens for the first-line treatment of advanced NSCLC.

**Ethics Approval** Institutional Review Board approval of the study protocol was obtained prior to study conduct and included a waiver of informed consent.