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.