**Background** Despite immune checkpoint inhibitor (ICI) monotherapy approvals in NSCLC, SOC predominately utilizes combinations of ICI with non-targeted chemotherapy or precision therapies targeting oncogenic drivers. Biomarkers guiding these clinical decisions rely on tumor genotyping to identify actionable mutations, tumor mutational burden (TMB) and on immunohistochemistry for PD-L1 expression. Currently, neither PD-L1 nor TMB perform adequately for ICI patient selection. Emerging evidence indicates a more complete profile of the tumor microenvironment (TME) may improve selection of patients likely to respond to ICI. The Xerna machine learning-based RNA sequencing biomarker assay classifies tumors into four TME subtypes; Immune Active (IA), Immune Suppressed (IS), Immune Desert (ID) and Angiogenic (A). This classification identifies tumors likely to benefit from ICI (IA and IS) or anti-angiogenic agents (ID and A). We examined the distribution of actionable oncogenic driver mutations across Xerna TME subtypes to investigate the potential use for therapy selection.

**Methods** Biomarker prevalence, and Xerna TME subtype classification, were determined for 104 metastatic lung cancer cases previously analyzed using the Oncomap™ ExTra test, tumor-normal whole-exome and whole-transcriptome sequencing. DNA variants and high TMB (>10 mut/Mb) were identified from DNA sequencing, and RNA expression levels were used to assign tumors to Xerna subtypes. Biomarker and associations were compared using Fisher’s Exact Test. The study was approved by WCG IRB Ethics Board, approval number 20181863.

**Results** In total, 53% of cases had high (IA+IS) vs. low (ID+A) Xerna immune subtypes and 60% harbored targetable oncogenic driver mutations (table 1). Actionable EGFR and KRAS mutations were detected in 31% and 20% of cases respectively, while high TMB was detected in 27% of cases. High TMB was significantly higher in IA (62%) vs. IS (14%) or A (13%) categories (p<0.05). Although no significant associations between Xerna subtype and oncogenic drivers were observed, EGFR mutations were least frequent in IA tumors (15%) while 33% of the IS subtype contained KRAS mutations (10% G12C).

**Conclusions** The Xerna TME panel identified a high prevalence of patients who may benefit from ICI (IA+IS) and harbored actionable oncogenic drivers. Within this group, the prevalence of targetable oncogenic drivers within the IS phenotype, such as KRAS G12C, may represent the potential for novel ICI combination therapies. These findings further highlight the importance of adding TME analysis to comprehensive biomarker testing in NSCLC.

**REFERENCES**