A CROSS-COHORT EXAMINATION OF FACTORS IMPACTING IMMUNOTHERAPY SURVIVAL IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Background Highly variable responses to immune checkpoint inhibitors (ICI) among NSCLC patients underscore the need for predictive biomarkers to guide therapy selection. In this study, RNA-seq data were used to classify patients into our previously reported TME subtypes, which are prognostic for survival and predictive for immunotherapy response across multiple cancers, including NSCLC.1 Here, we further validated these TME subtypes in ICI-treated NSCLC patients

Methods NSCLC patients from three independent cohorts, GSE135222 (n = 27), SU2C-MARK (n = 152), and a novel retrospective cohort from St. Luke’s Cancer Institute (n = 161), were screened for the following criteria: (1) advanced lung adenocarcinoma (LUAD) or advanced squamous cell carcinoma (LUSC); (2) ICI-naive at the time of biopsy; (3) no EGFR or ALK alterations, resulting in 258 qualified samples. As described by Bagaev et al.1 transcriptomic-based TME subtyping was applied to classify each sample as fibrotic (F), immune-enriched/fibrotic (IE/F), immune-enriched/non-fibrotic (IE), or desert (D). TME cell types were characterized using Kassandra cell deconvolution.2 Logrank tests were used for Kaplan-Meier and Cox proportional hazards models.

Results Overall (OS, p = 0.002) and progression-free (PFS, p = 0.0002) survival were calculated for each TME subtype using ICI-treated NSCLC cohorts (table 1). IE samples had the best prognosis (median OS 38.7 mos., p = 0.009; median PFS 9.0 mos., p = 0.001), and the D samples exhibited statistically significant lower OS (median 14.1 mos, p = 0.002) and PFS (median 3.3 mos, p = 0.002). TME subtypes were further grouped into immune-enriched ‘hot’ (IE + IE/F, median OS 29.6 mos. and PFS 8.9 mos.) and ‘cold’ (D + F, median OS 13.3 and PFS 4.1 mos.) groups, which further improved patient separation by PFS (p = 0.0002) and OS (p = 1e-05). Independent of PD1 status, CD8 T cell infiltration was qualitatively and quantitatively associated with better OS (HR 0.23, p < 0.005) and PFS (HR 0.25, p < 0.005) in LUAD but not in LUSC.

Conclusions Here, transcriptomic-based TME subtypes and cell type deconvolution were applied to an unselected cohort of NSCLC patients receiving ICIs. The TME subtypes and CD8 T cell infiltration were associated with OS and PFS. When samples were grouped into ‘hot’ (IE + IE/F) and ‘cold’ (D + F) TME subtypes, sample stratification further improved. Our results were consistent with previous findings,1 but further investigation is required to validate these TME subtypes as predictive biomarkers.

REFERENCES

Abstract 532 Table 1 Prognostic value of NSCLC tumor microenvironment (TME) subtypes

<table>
<thead>
<tr>
<th>TME subtype</th>
<th>IE</th>
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<th>D</th>
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<td>Median OS, months</td>
<td>38.7</td>
<td>20.2</td>
<td>13.3</td>
<td>14.1</td>
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<tr>
<td>Median PFS, months</td>
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<td>6.3</td>
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</table>

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Ethics Approval The human data analyzed here was collected under IRB protocol at St. Luke’s Cancer Institute.