

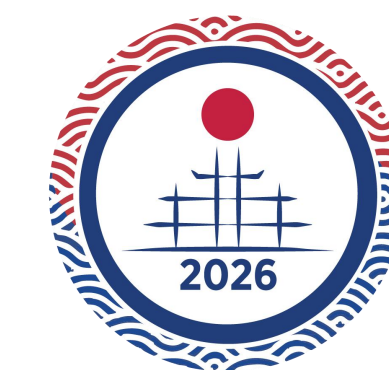


P3.306: TLS Maturity and Spatial Architecture Predict Immunotherapy Outcomes in Extensive-Stage SCLC

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INTRODUCTION

Small cell lung cancer (SCLC) is an aggressive malignancy with poor prognosis. Immune checkpoint inhibitors (ICIs) improve survival but lack reliable biomarkers. Tertiary lymphoid structures (TLSs) predict ICI response in other cancers, yet their role in extensive-stage SCLC (ES-SCLC) is unknown. This multicenter study of 180 ES-SCLC patients evaluates TLS presence, maturation, and spatial proximity to tumor cells as potential predictors of ICI efficacy.

METHODS

Design:

This multicenter retrospective study enrolled 180 treatment-naïve ES-SCLC patients receiving ICI-based therapy. TLSs were assessed on H&E-stained sections by two independent pathologists. Multiplex immunofluorescence (PanCK, CD3, CD8, CD20, CD21, CD23) and HALO-based spatial analysis quantified immune cell densities and nearest-neighbor distances from TLS-resident cells to tumor cells. TLSs were classified as immature or mature based on germinal center organization and CD21/CD23 expression. Kaplan-Meier, log-rank, and Cox regression were used for survival analysis.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- Assess baseline TLS presence and maturation status on routine biopsy; shorter immune-tumor distance correlates with better ICI response. Use TLS as a complementary biomarker to guide ES-SCLC immunotherapy decisions.

Future Direction for Research

- Explore TLS heterogeneity across SCLC molecular subtypes (A/N/P/I) and investigate TLS-inducing strategies to convert immune-cold tumors.

REFERENCES & ACKNOWLEDGEMENTS

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RESULTS

Baseline TLS presence was identified in 22.2% (40/180) of ES-SCLC patients and independently predicted superior overall survival ($p < 0.001$, Fig. 1). TLS maturation status further refined prognosis that patients with mature TLSs-characterized by CD21⁺ follicular dendritic cell networks and organized germinal centers-achieved significantly longer OS than those with immature TLSs ($p = 0.0049$, Fig. 2-3). Unsupervised clustering revealed that ICI responders (CR/PR) exhibited higher TLS counts and denser immune infiltration, particularly CD8⁺ T cells and CD23⁺ germinal center B cells, both of which correlated with favorable survival ($p = 0.045$ and $p = 0.035$, respectively, Fig. 4). Critically, spatial analysis demonstrated that in responders, TLS-resident CD20⁺ B cells, CD3⁺ T cells, and CD8⁺ T cells were positioned significantly closer to tumor cells ($p < 0.05$), with the most pronounced effect for B cells, implicating their role in facilitating local antitumor immunity (Fig. 5). These findings establish that TLS maturation and spatial architecture serve as independent predictors of ICI efficacy in ES-SCLC.

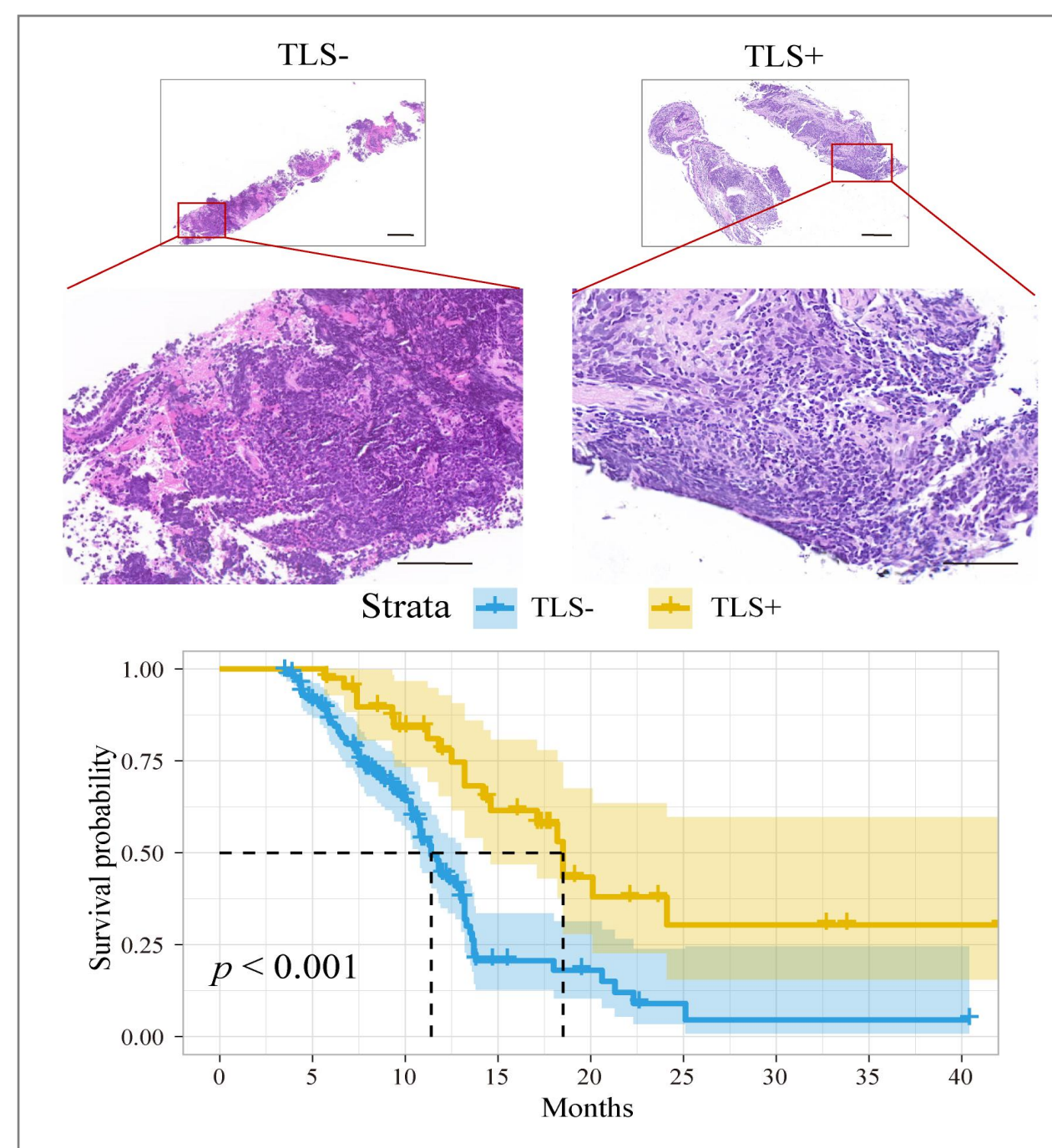


Figure 1. Baseline TLS Presence Predicts Favorable Immunotherapy Outcomes in ES-SCLC.

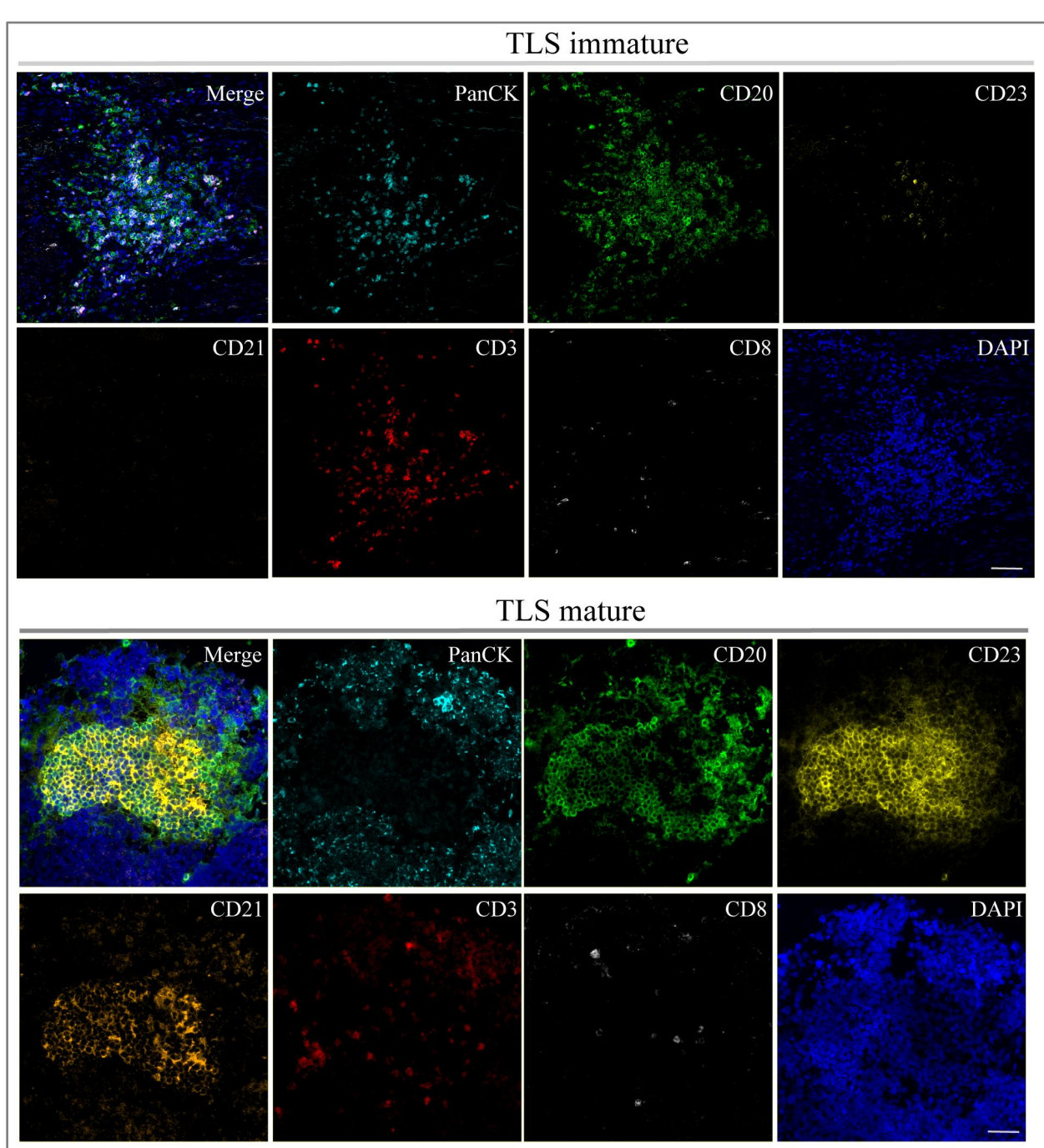


Figure 2. Representative multiplex immunofluorescence (mIF) image of immature TLS.

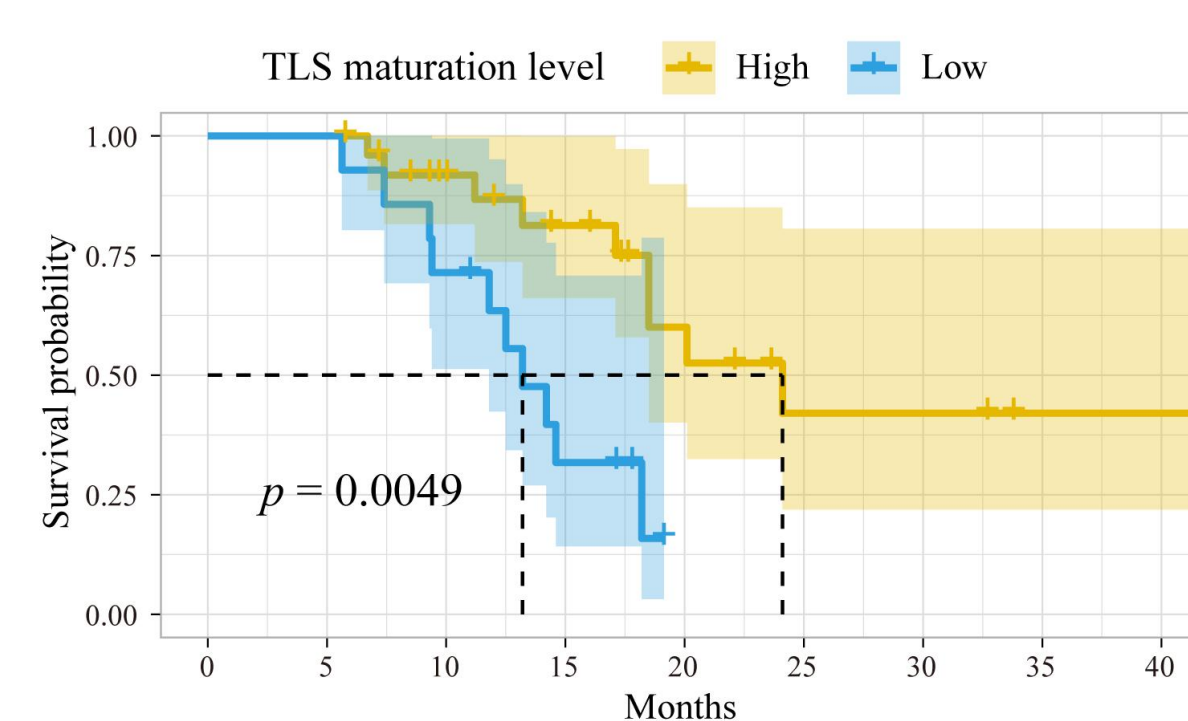


Figure 3. TLS Maturation Status Determines Prognostic Impact in ES-SCLC.

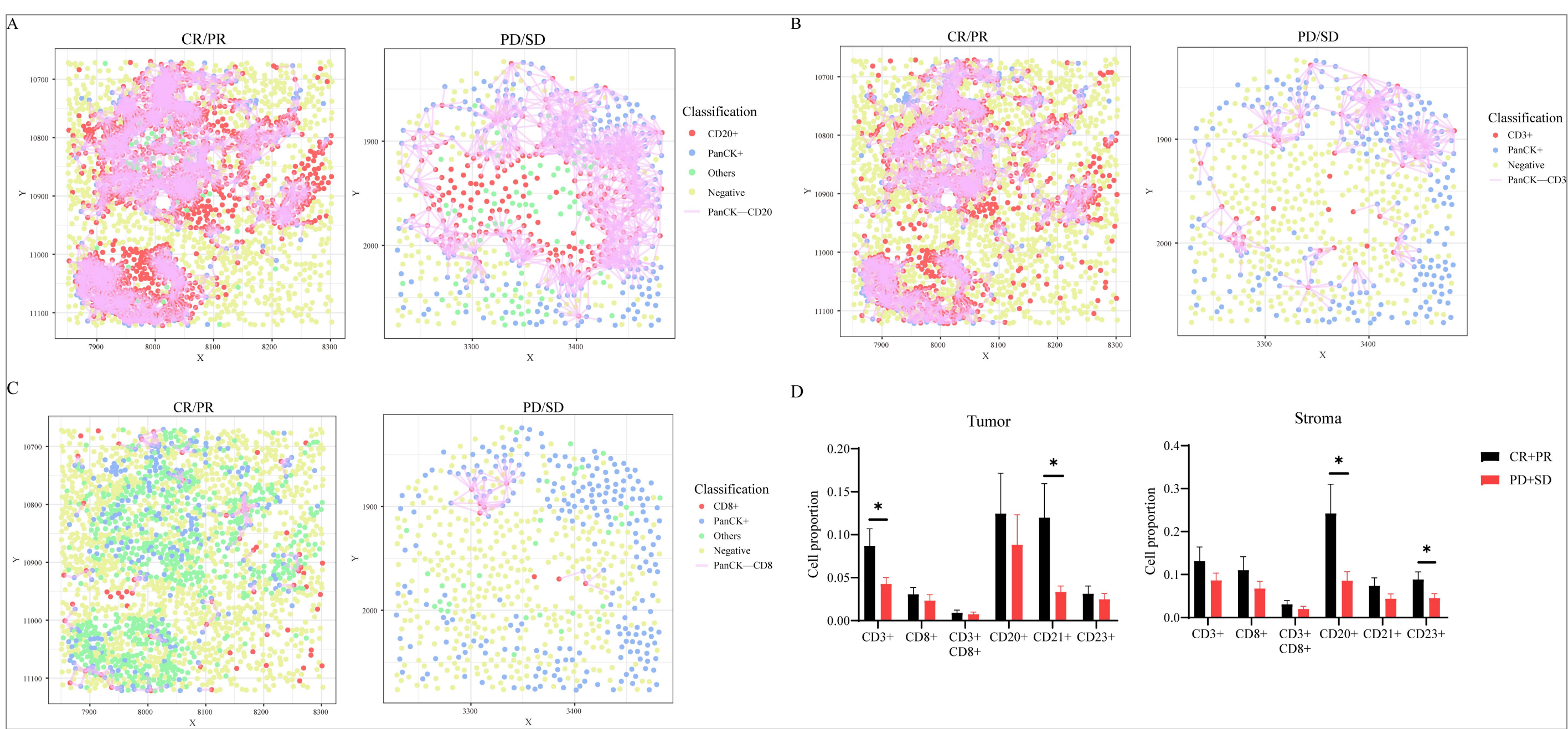


Figure 5. Spatial Architecture of TLS-Associated Immune Cells Discriminates ICI Responders.

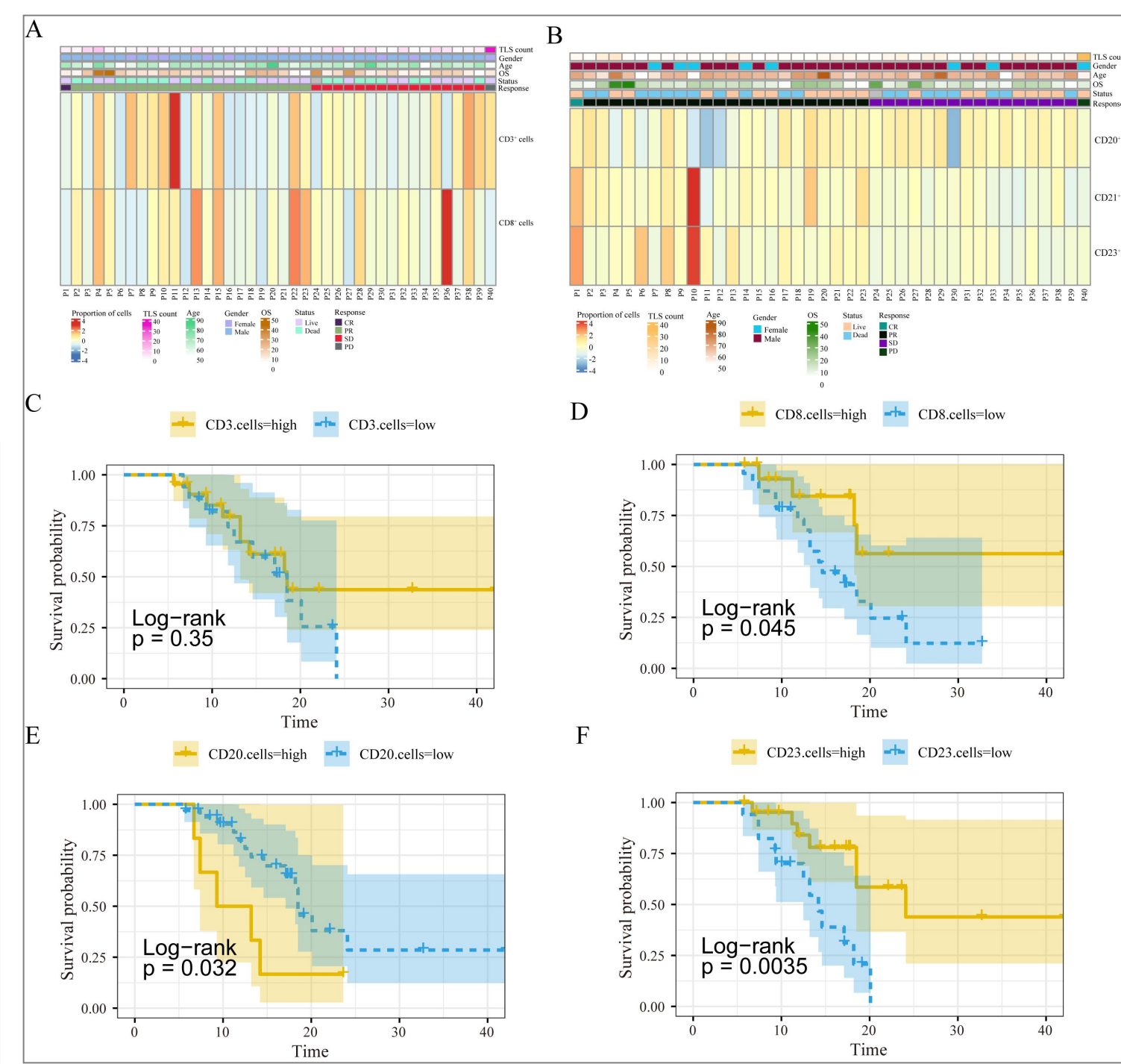


Figure 4. TLS-Associated Immune Cell Composition Distinguishes Responders from Non-Responders and Predicts Survival.