



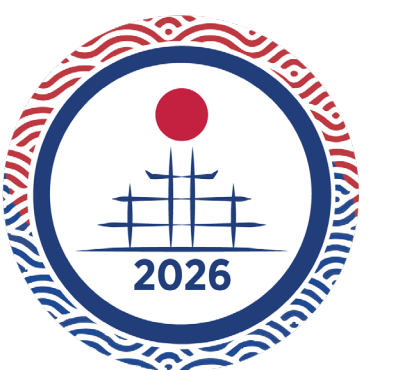
P3.072: Single-Cell Spatial Immune Landscapes of Driver Gene-Positive Lung Adenocarcinomas

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INTRODUCTION

Oncogenic driver mutations remodel the tumor microenvironment (TME) in lung adenocarcinoma (LUAD).

Although tyrosine kinase inhibitors (TKIs) targeting these drivers have demonstrated substantial clinical efficacy, patients invariably encounter primary or acquired resistance, ultimately leading to disease progression.

Elucidating how driver mutations reshape the cellular and spatial architecture of the TME has therefore become urgent research to refine combinatorial therapeutic regimens and overcome drug resistance.

METHODS

We developed a 24-marker IMC panel to profile treatment-naïve tumor biopsies from a cohort of locally advanced or metastatic LUAD patients with different driver genotypes, aiming to systematically delineate the single-cell spatial immune landscape of driver gene-positive LUAD.

By integrating multidimensional information including cell-type composition, spatial distribution, cell-cell interactions, and cellular neighborhood architectures, this study seeks to uncover the spatial heterogeneity of the TME across distinct driver mutation backgrounds, providing novel spatial-dimension insights into how oncogenic driver mutations shape the TME, and informing the rational design of personalized immuno-combination therapeutic strategies.

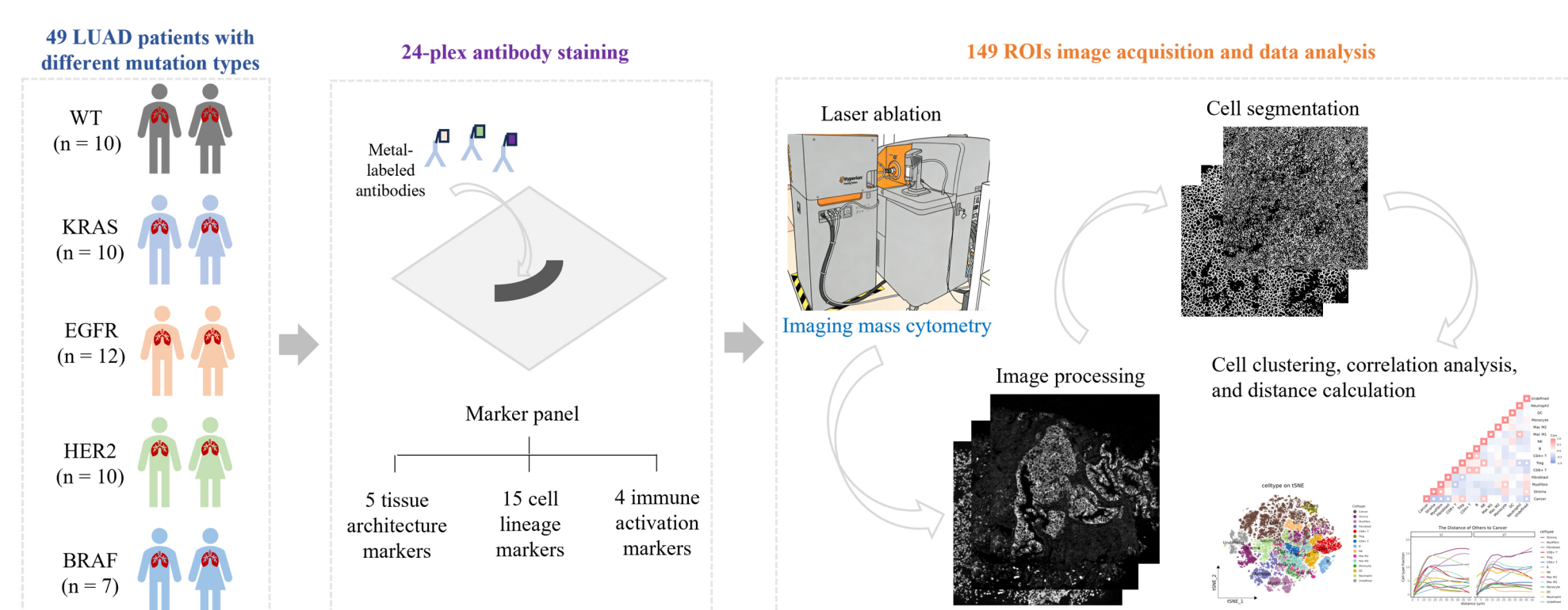


Figure 1 Study design.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- This study provides a comprehensive single-cell spatial atlas of the TME across major driver-mutant lung adenocarcinoma subtypes.
- Our findings demonstrate that distinct oncogenic driver mutations exert profound, genotype-specific effects on TME landscapes, differentially remodeling cellular composition, spatial architecture, intercellular communication, and local niche organization.
- We highlight three core mechanistic features across driver-mutant subtypes: a unique myofibroblast-enriched immune-desert signature dominating EGFR- and HER2-mutant tumors, widespread CD8⁺ T cells functional impairment across genotypes, and highly divergent spatial interaction networks defined by individual mutation status.

Future Direction for Research

- Future studies integrating longitudinal clinical cohorts and functional experimental models will be essential to translate these spatial insights into clinically actionable biomarkers and therapeutic strategies.

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RESULTS

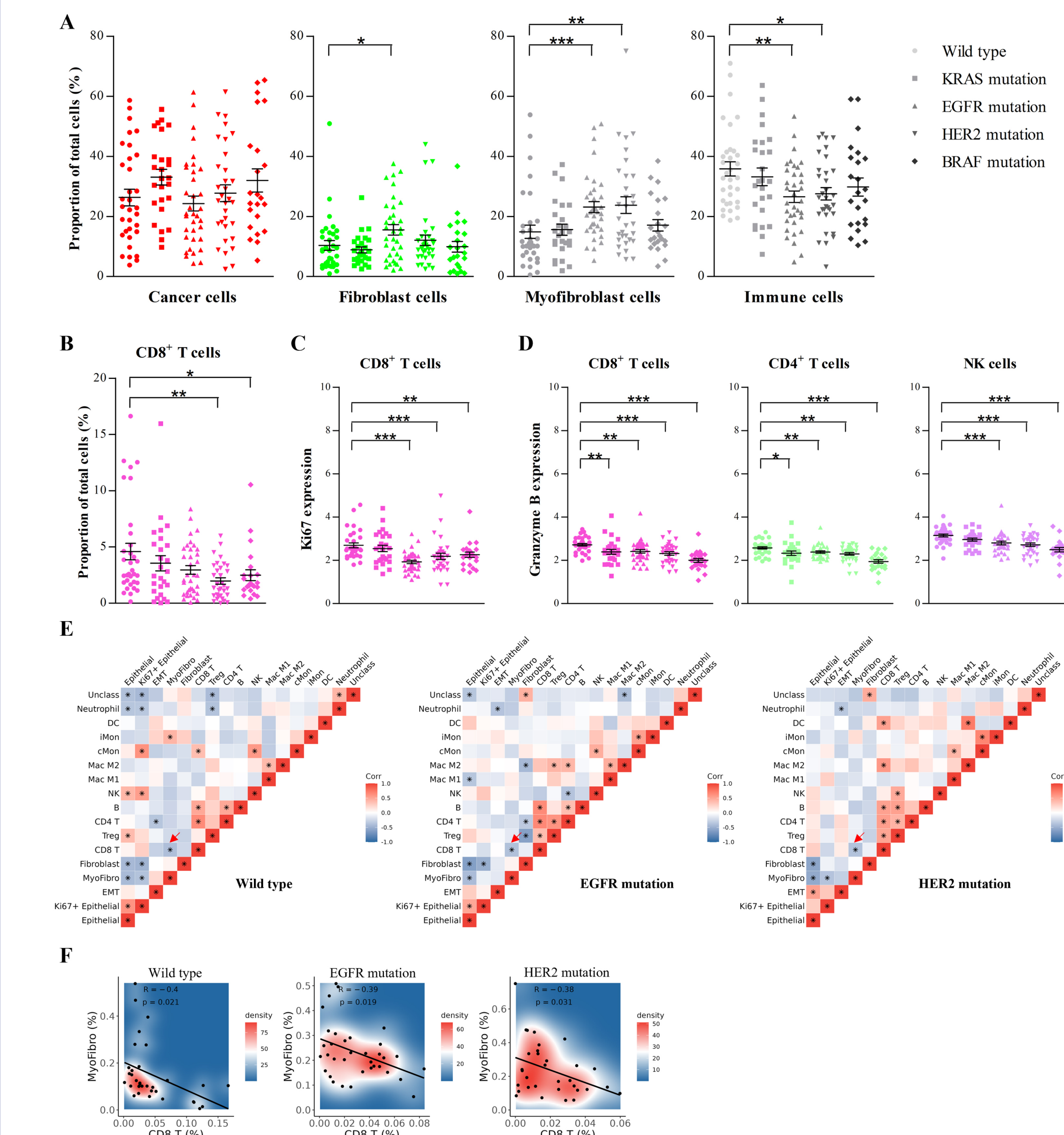


Figure 2 EGFR- and HER2-mutant tumors exhibited a striking enrichment of myofibroblasts accompanied by reduced immune infiltration, diminished CD8⁺ T cell proliferation and cytotoxicity, and a negative correlation between myofibroblast and CD8⁺ T cell abundances.

(A-B) Prevalence of cancer cells, fibroblasts, myofibroblasts, immune cells and CD8⁺ T cells as a proportion of total cells across different oncogenic driver groups.
(C-D) The median expression of Ki67 and Granzyme B among indicated cell types across different oncogenic driver groups.
(E) Heatmap illustrating the Spearman's rank correlation coefficient with high coefficients represented in red and low coefficients in blue across different oncogenic driver groups. The asterisk inside the box indicates that $p < 0.05$.
(F) The interrelationships between CD8⁺ T cells and myofibroblasts (the arrow in E) across different oncogenic driver groups.

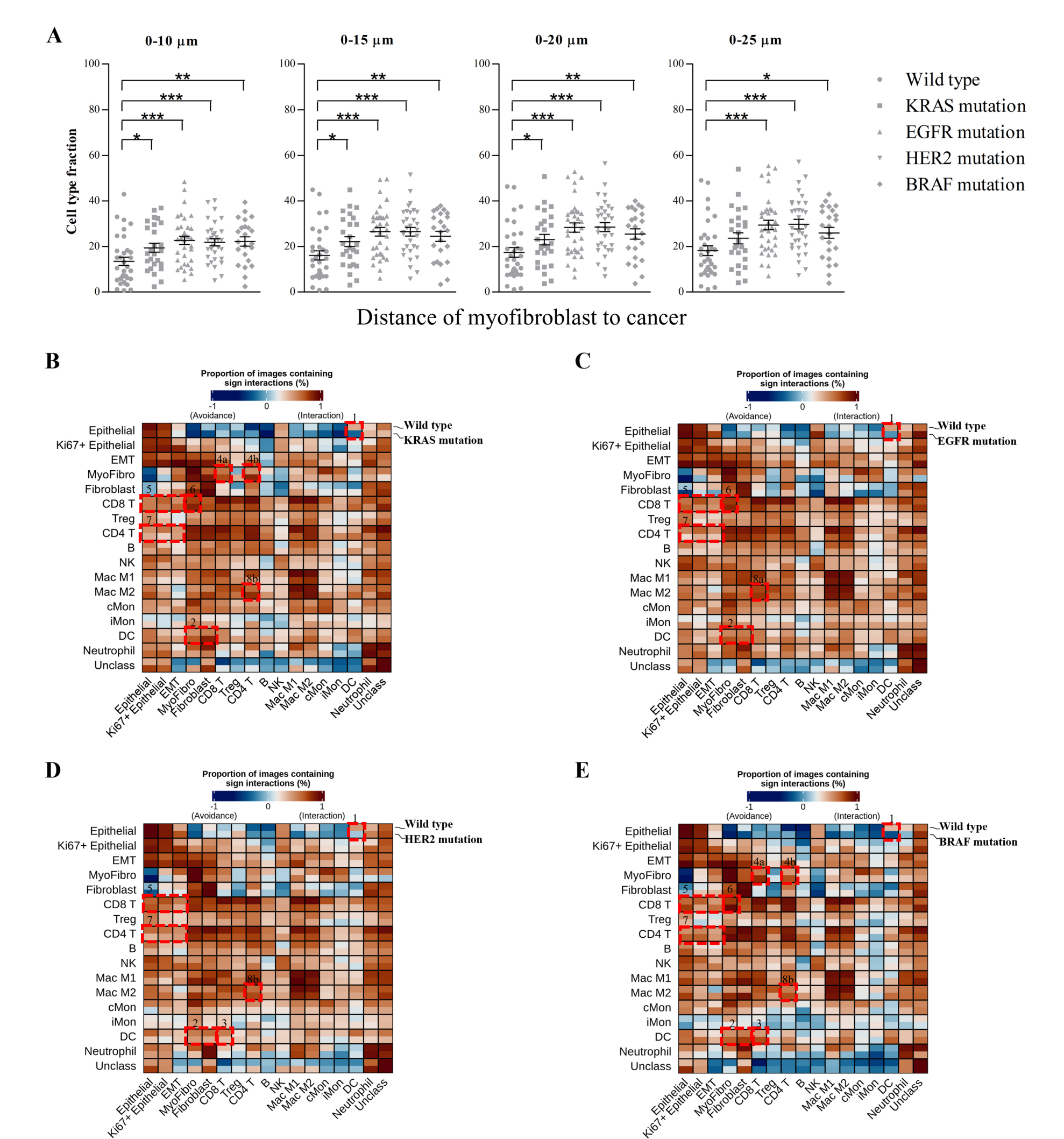
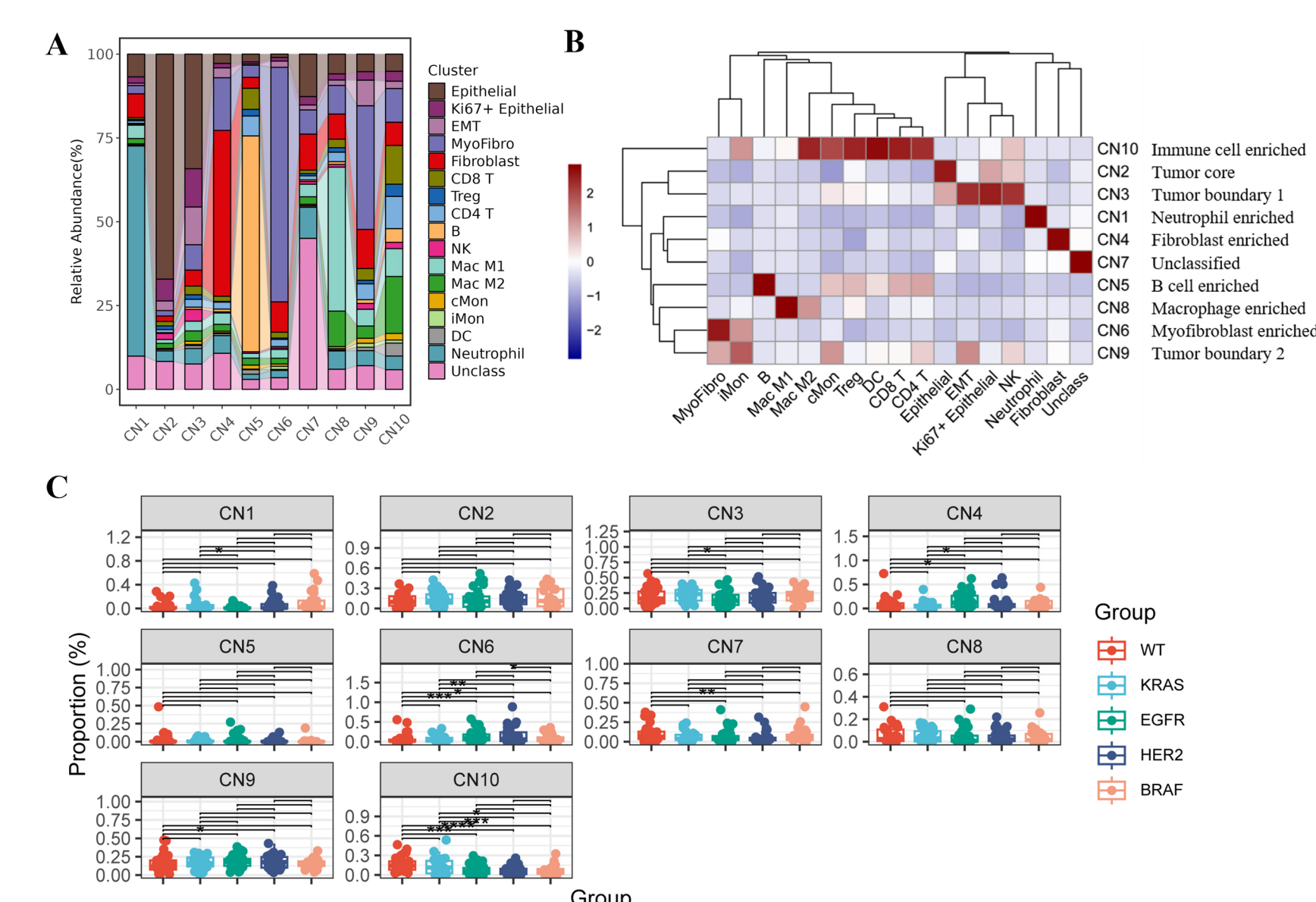


Figure 3 Spatial analysis revealed that myofibroblasts were preferentially localized within 25 μm of tumor cells in all driver-positive groups, and pairwise spatial interaction analysis further uncovered widespread rewiring of cell-cell contacts across driver genotypes (red boxes), including reduced CD8⁺ T cell-proliferating cancer cell interactions and genotype-specific patterns involving dendritic cells, M2-like macrophages, and T cells.

(A) Analysis of the distance from myofibroblasts to cancer cells across different oncogenic driver groups, with a sliding interval of 1 micrometer in total of 25 micrometers.
(B-E) Heatmap depicting cell-cell communication patterns scaled from interaction (red) or avoidance (blue) based on the proportion of images exhibiting significant interactions, across different oncogenic driver groups. Each cell in the heatmap is divided horizontally; the upper half represents interactions originating from wild type group, while the lower half corresponds to interactions from oncogenic driver group.

Figure 4 cellular neighborhood (CN) profiling identified a myofibroblast-enriched niche (CN6) that was significantly increased in EGFR- and HER2-mutant tumors, alongside a corresponding decrease in immune cell-enriched neighborhoods (CN10).

(A) Cellular composition of the ten distinct cellular neighborhoods. The stacked bar chart depicts the relative abundance of each cell type within individual CNs (CN1-CN10).
(B) Heatmap displaying cell type composition of each CN. The TME was resolved into ten distinct neighborhood subtypes: neutrophil enriched (CN1), tumor core (CN2), tumor boundary 1 (CN3), fibroblast enriched (CN4), B cell enriched (CN5), macrophage enriched (CN6), myofibroblast enriched (CN7), unclassified (CN8), tumor boundary 2 (CN9), and immune cell enriched (CN10).
(C) Frequency of CN1-CN10 as a percentage of all CNs across different oncogenic driver groups.