

INTRODUCTION

Exon 19 deletions (Ex19del) and the exon 21 L858R point mutation (L858R) are both classified as classical sensitizing mutations and are targets for EGFR tyrosine kinase inhibitors (TKI). Yet a **significant and persisting survival gap remains between these two subtypes**, with differences in structure and kinetics of the kinase domain having been suggested as an explanation for the superior outcomes of Ex19del. Interestingly, however, L858R has been reported to have better response to immune-checkpoint inhibitors post resistance to EGFR TKIs.

We aimed to **identify potential contributors to the different treatment outcomes by analyzing the TME components across various EGFR mutation subtypes**.

METHODS

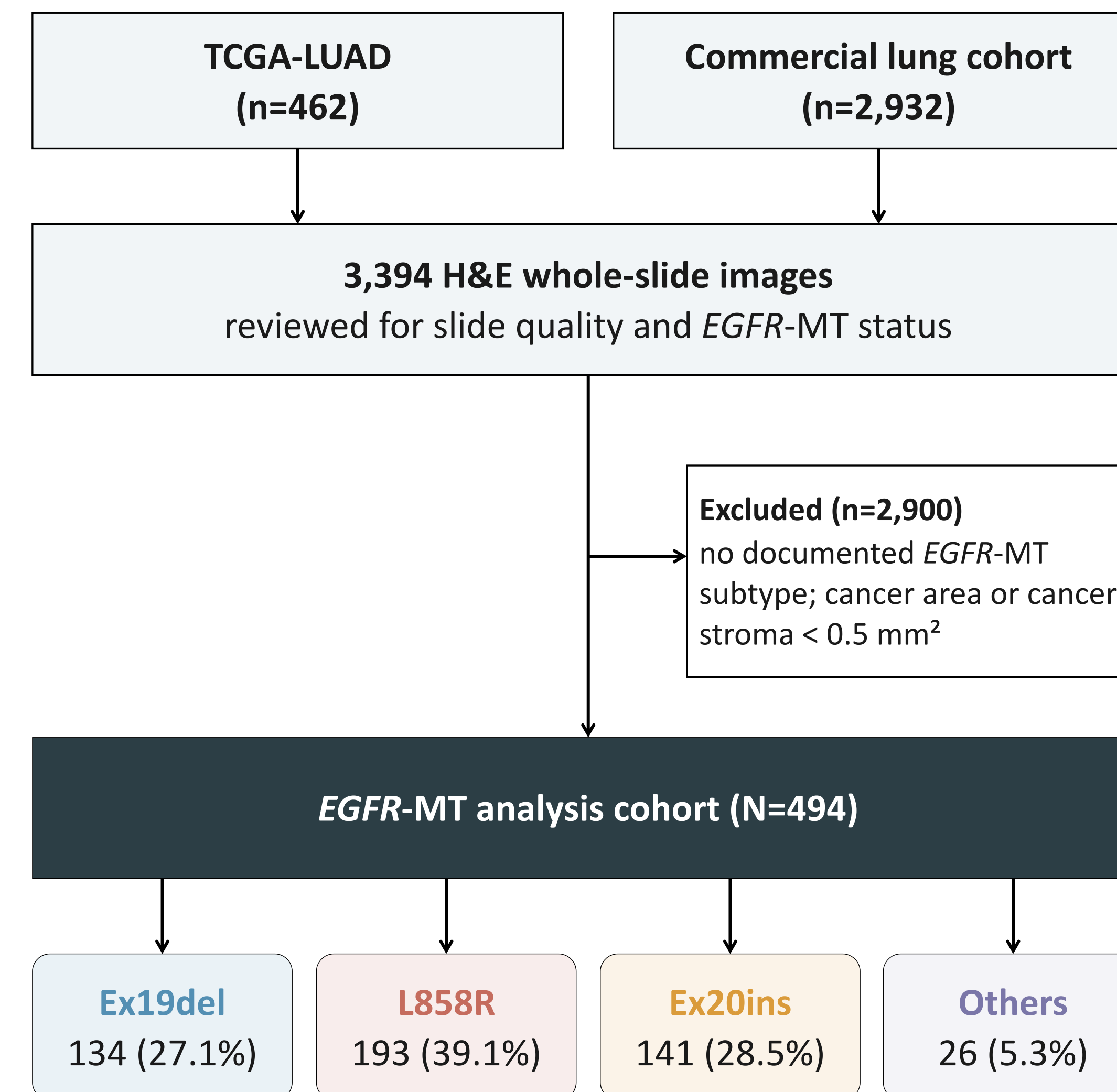
A retrospective cohort of H&E whole-slide images (WSIs) from TCGA-LUAD and a commercial lung cancer cohort was reviewed for slide quality and EGFR-MT status. After removal of slides with cancer or stroma area <0.5mm², a total of 494 H&E WSIs with documented EGFR-MT variant subtype was included [Figure 1].

TME analysis was performed using **Lunit SCOPE IO**, an AI-powered H&E analyzer that quantifies the spatial cell densities (lymphocytes, fibroblasts, endothelial cells) within tumor and stroma [1]. Mann-Whitney U tests were performed between subtypes to reveal relative differences in the density of cells in the TME.

An illustrative example of the H&E analyzer is included in Figure 2.

RESULTS

Figure 1. Study design and cohort selection



Key findings

Ex19del — lowest intratumoral TIL density (95.2 vs 122.0 in L858R, P=0.026; 135.9 in Ex20ins, P=0.002)
L858R — highest intratumoral macrophage density (14.9 vs 6.7 in Ex19del, P=0.006; 6.6 in Ex20ins, P=0.017)
Ex20ins — highest cancer-area endothelial density (11.3 vs 7.7 in Ex19del, P=0.009; 7.9 in L858R, P=0.019)

Figure 3. Cell densities across EGFR mutation subtypes. Mann-Whitney U, *P<0.05, **P<0.01

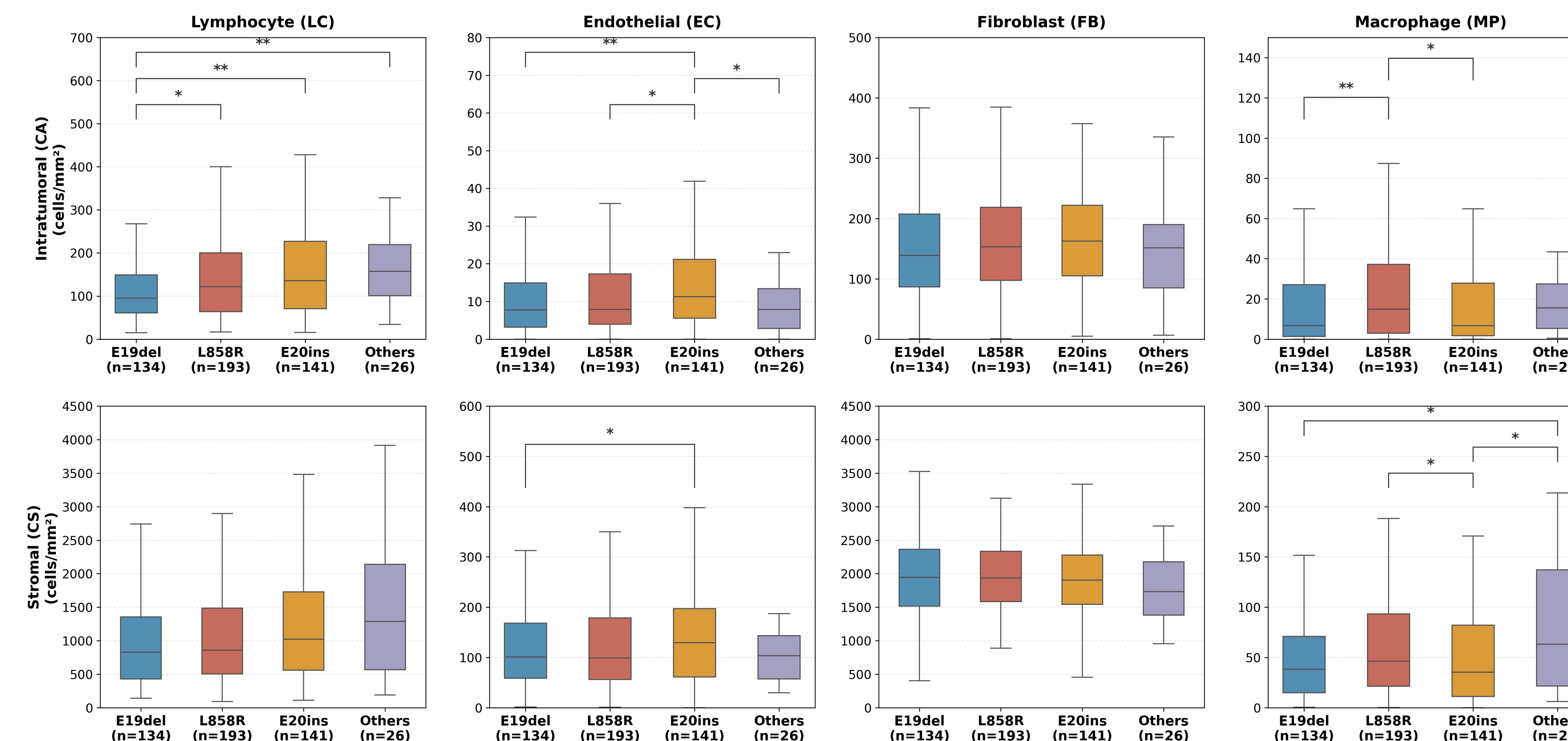
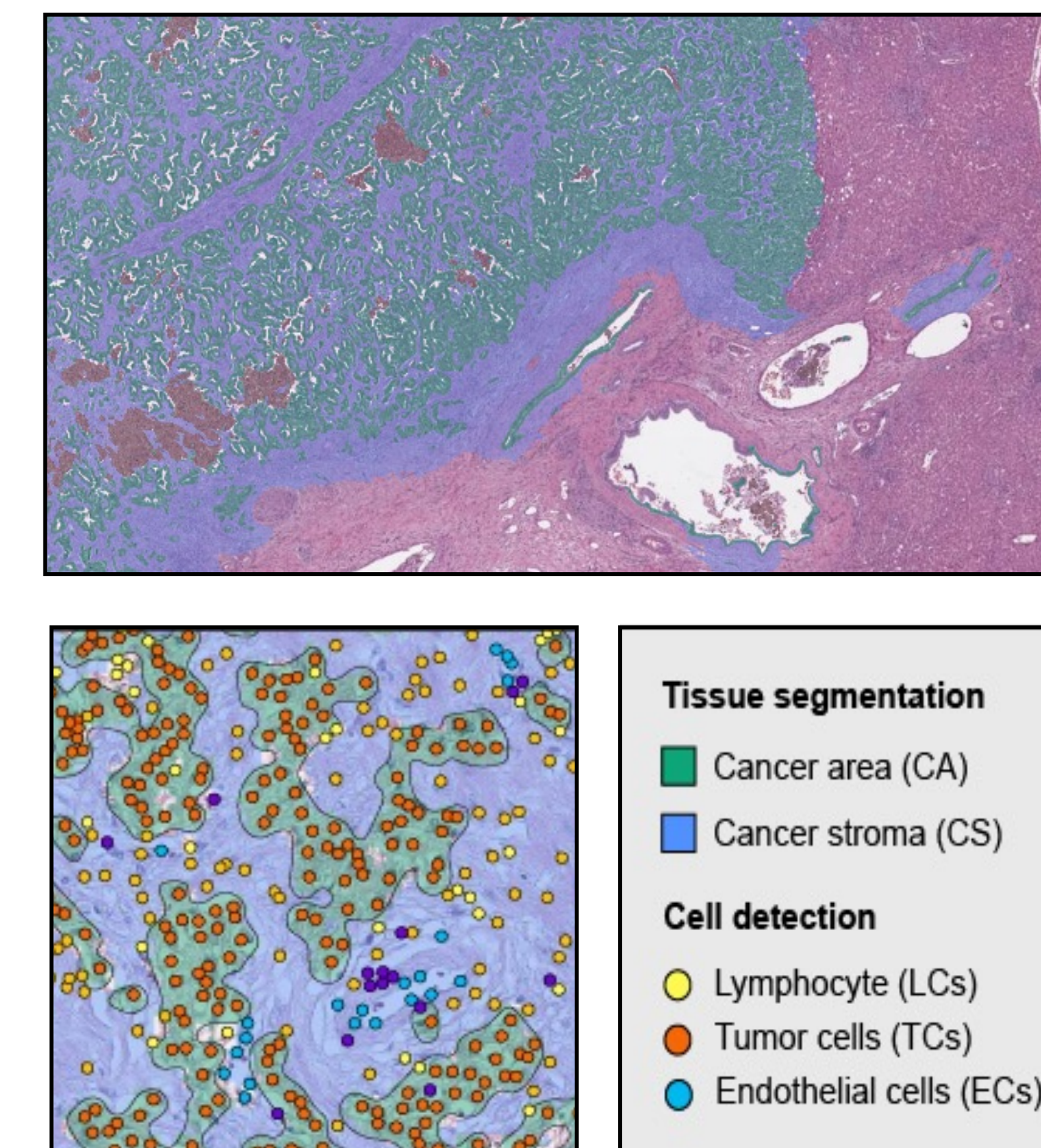


Figure 2. The H&E WSI analyzer (Lunit SCOPE IO) segments the tissue into cancer epithelium, stroma, and background. Detected cells are classified into lymphocytes, tumor cells, endothelial cells, fibroblasts, or other cells. Cell densities are used in downstream analysis.



DISCUSSION AND CONCLUSION

Among EGFR-mutation variants, **Ex19del** was associated with lower intratumoral infiltration of TILs, whereas **L858R** exhibited concurrent relative enrichment of TIL and macrophage infiltration compared to Ex19del.

Interestingly **Ex20ins** showed a significantly higher density of intratumoral endothelial cells compared to all other variants.

These subtype specific findings suggest that **overcoming differential benefits to EGFR TKIs may require tailored combination strategies** that address both kinase kinetics and the TME.

Further validation in independent data cohorts and paired treatment response analysis is warranted.

REFERENCES & ACKNOWLEDGEMENTS

Acknowledgement

The authors gratefully acknowledge the generous contributions of the patients, families, and investigators whose participation made the generation of data within The Cancer Genome Atlas (TCGA) possible.

References

[1] Park S, Ock CY, Kim H, et al. Artificial intelligence–powered spatial analysis of tumor-infiltrating lymphocytes as complementary biomarker for immune checkpoint inhibition in non–small-cell lung cancer. J Clin Oncol. 2022;40(17):1916-1928. doi:10.1200/JCO.21.02010