

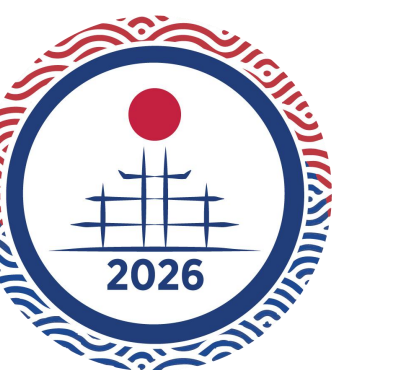


P3.273: Spatial Multi-Omics Reveals TME Remodeling Across Sequential EGFR-TKIs in EGFR-Mutant NSCLC

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IASLC 2026 World
Conference on Lung Cancer

SEPTEMBER 12 - 15, 2026
SEOUL, REPUBLIC OF KOREA

INTRODUCTION

Resistance to epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) remains a main challenge in EGFR-mutant non-small cell lung cancer (NSCLC) patients [1]. The evolution of the tumor microenvironment (TME) within the same patient from baseline to resistance to first- and then third-generation EGFR-TKIs is still largely unknown [2-4]. By leveraging rare consecutive re-biopsies, this research create a longitudinal, compartment-resolved spatial atlas that depicts TME changes during sequential targerd therapy.

METHODS

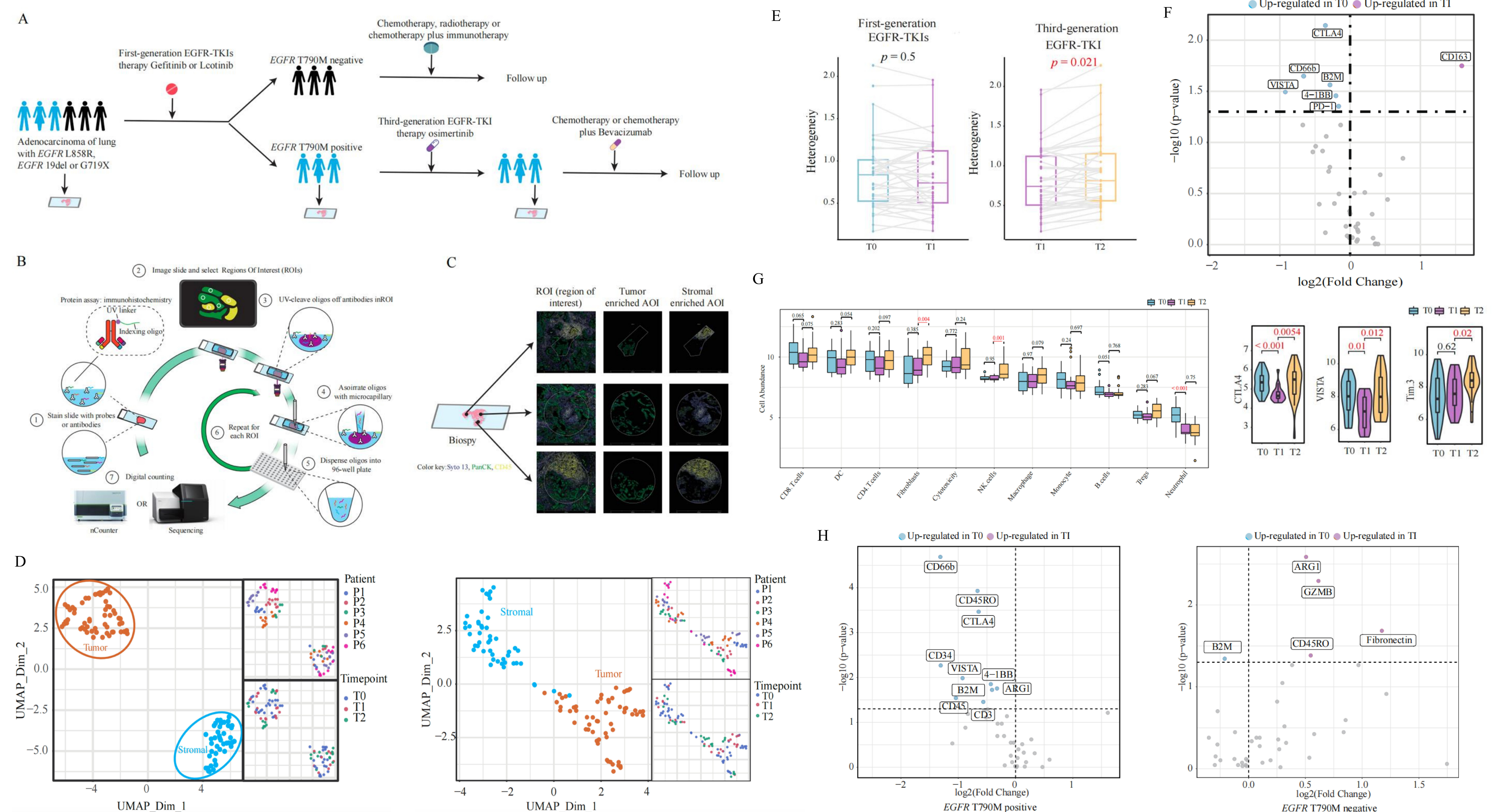
A patient-matched cohort with serial samples for each patient at baseline (T0), after resistance to first-generation EGFR-TKI (T1), and after resistance to third-generation EGFR-TKI (T2) was constructed (Fig A). Tumor-enriched and stroma-enriched areas of interest (AOIs) were segmented by GeoMx Digital Spatial Profiling (DSP) for paired spatial RNA and protein quantification (Fig B,C). Changes over time in compartment-specific heterogeneity and immune remodeling were examined.

CONCLUSION

The study reveals how the spatial TME dynamically changes over time during sequential EGFR-TKI therapy in EGFR-mutant NSCLC. It demonstrates late stroma-driven heterogeneity and biphasic immune remodeling. Early remodeling patterns differ between T790M-positive and negative tumors. These findings offer a longitudinal spatial framework for generating experimentally verifiable hypotheses to overcome acquired resistance of EGFR-TKIs.

RESULTS

We gathered 15 samples from 6 patients. Tumor and stromal compartments were clearly separated and remained so at all time points, both at protein and RNA level (Fig D). Spatial heterogeneity was unchanged between T0 and T1 but became significantly diferent at T2 ($p=0.021$), with this change being mainly attributed to stromal remodeling (Fig E).The earliest changes were characterized by loss of T-cell activation, reduction of neutrophil signatures, increase myeloid remodeling, and impaired antigen presentation (Fig F). Longitudinal immune response analysis revealed a biphasic immune trajectory: myeloid remodeling in the early phase and stromal checkpoint reprogramming in the late phase (Fig G). Notably, early remodeling patterns in tumors that later acquired T790M difered from those in the tumors that did not (Fig H).



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