

Integrated ctDNA and Multi-omic Profiling Reveal Distinct Immune Landscapes and Predict Outcomes in Extensive-Stage Small Cell Lung Cancer



2026 World Conference
on Lung Cancer

SEPTEMBER 12 - 15, 2026 | SEOUL, REPUBLIC OF KOREA

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Introduction

Extensive-stage small cell lung cancer (ES-SCLC) remains an aggressive malignancy with limited durable benefit from immune checkpoint inhibitors (ICIs), largely driven by an immunologically “cold” tumor microenvironment (TME). Biomarkers that integrate tumor burden with immune heterogeneity are critically needed to refine patient stratification and improve therapeutic outcomes.

Methods

In this multicenter study, 87 treatment-naïve ES-SCLC patients were enrolled. Serial plasma samples underwent ctDNA sequencing and Olink proteomics, alongside PBMC transcriptomic profiling for systemic immunophenotyping.

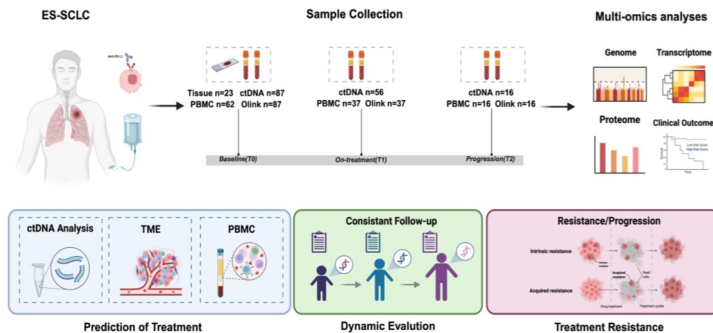


Figure 1 Workflow of the study

Results

Frequent alterations included TP53, RB1, MUC16, ZFX4, and LRP1B. Integrative analysis revealed a high-risk subtype defined by concurrent DNA damage response (DDR) alterations (PARP1, SLX4, PMS1, MSH2), CREBBP mutations, and high MSAF.

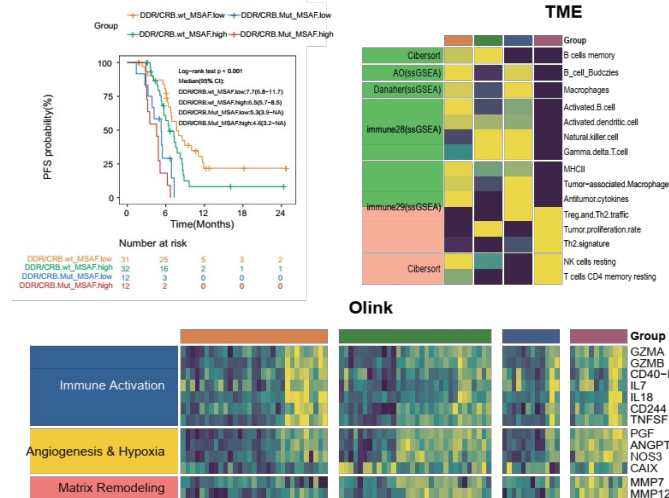


Figure 2 Baseline Stratification by ctDNA

The subtype exhibited an immunosuppressive TME characterized by reduced activated B cells/DCs, impaired MHC-II antigen presentation, and enrichment of Th2/Treg, proliferative, angiogenic, and hypoxia-related programs, including elevated PGF, ANGPT2, CAIX, and MMP7.

Results

Longitudinal ctDNA dynamics stratified outcomes: $\geq 50\%$ MSAF reduction ($n=31$) was associated with significantly improved PFS ($HR=5.05$, $p<0.001$) and marked immune remodeling, including increased DCs, macrophages, NK cells, and CD8+ $\alpha\beta$ T cells with activation of inflammatory and cytotoxic pathways.

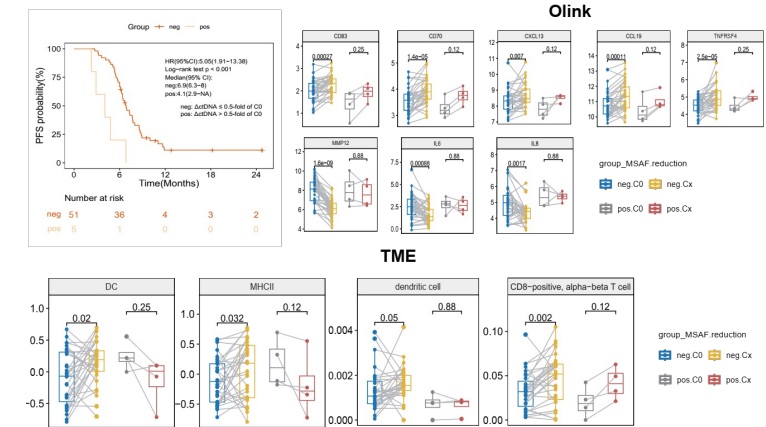


Figure 3 Dynamic Evaluation through RNA and Olink.

Conclusion

Integrated ctDNA and multi-omics profiling identified biologically distinct ES-SCLC subtypes and linked tumor dynamics to TME reprogramming, supporting a scalable framework for real-time patient stratification and adaptive treatment strategies.