

P3.13: Survival-informed transcriptomic classification of resected SCLC with improved prognostic and TME discrimination

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Introduction

Small cell lung carcinoma (SCLC) is a highly aggressive lung cancer (15% of cases), with a poor prognosis

↳ Median overall survival is **9.5 months**.^[1]

Recent transcriptomic analyses proposed neuroendocrine (NE) biomarkers **ASCL1**, **NEUROD1**, & non-NE biomarkers **POU2F3**, and **YAP1/inflamed** to classify SCLC.^[2]

However:

- These groups have **inconsistent prognostic utility**, with conflicting results between cohorts.

- Immune profiles **fail to prove** (non-NE) **YAP1/Inflamed** tumors are **consistently more inflamed**.

- **Inflamed** tumors with enhanced MHC-I expression, CD8+ T cell infiltration, & immunotherapeutic response occur in **both NE & non-NE** tumors.^[3]

A robust classification with better prognostic value is urgently needed to improve SCLC tumor stratification.

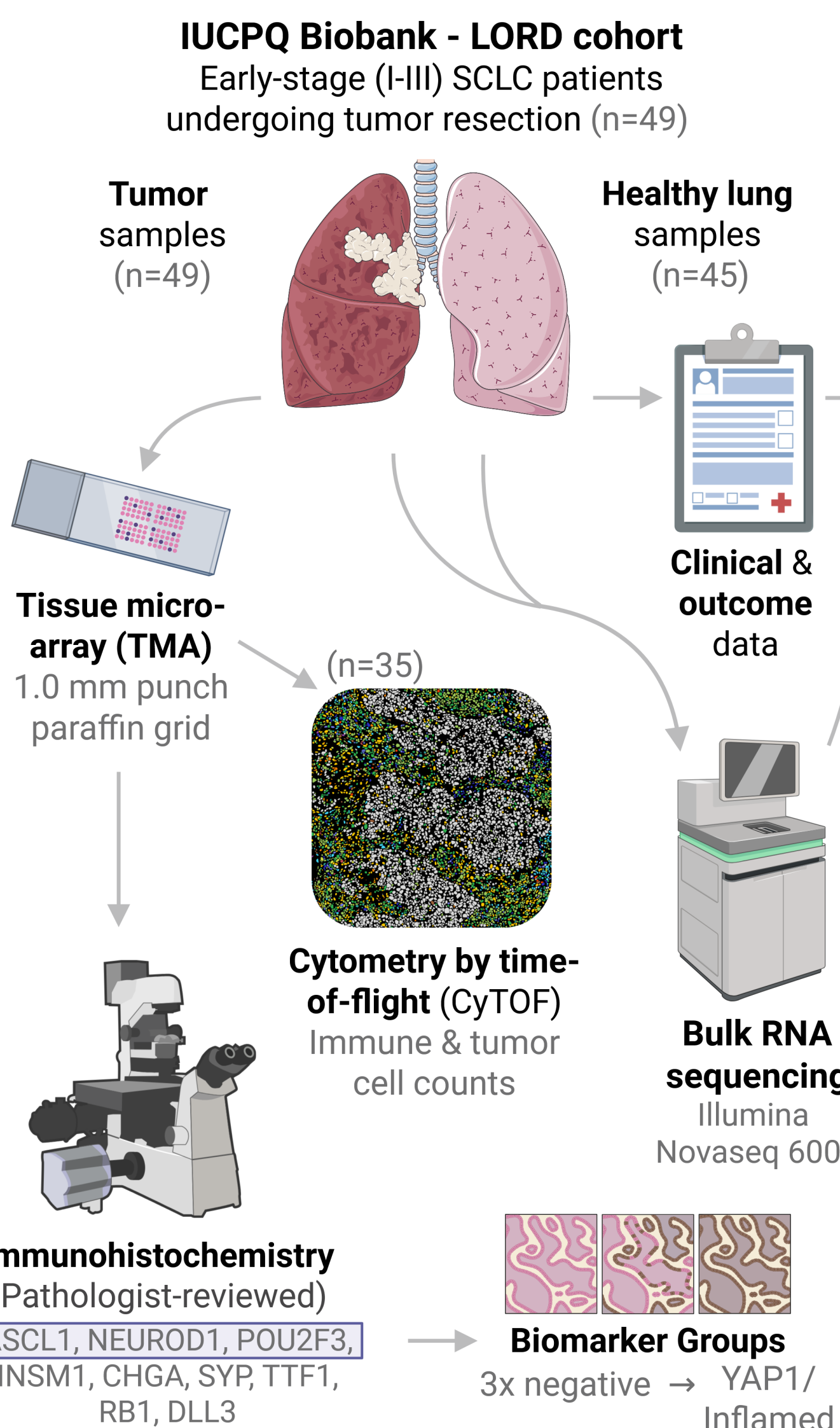
Objectives & Hypothesis

Our main objective is to **identify** and **characterize** a novel SCLC classification with **better prognostic performance**.

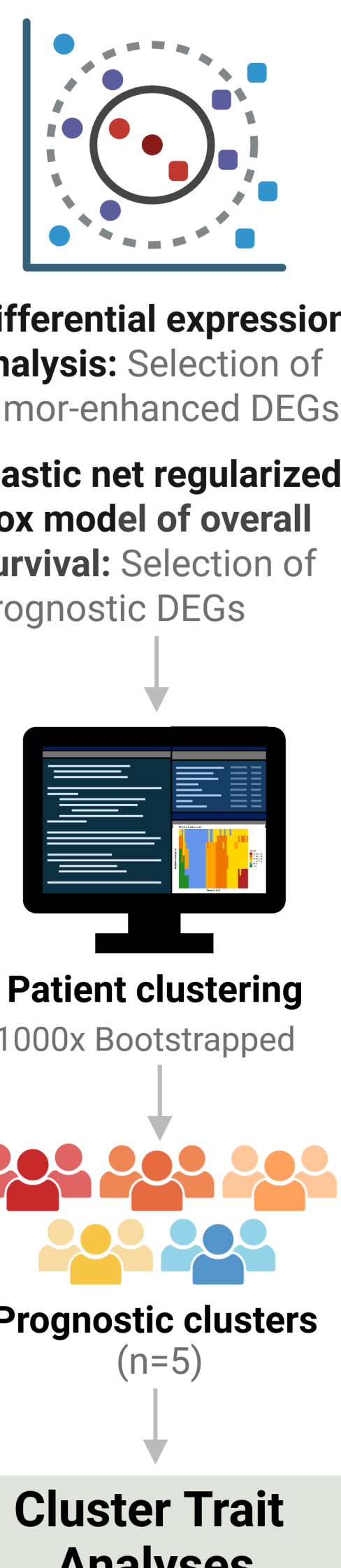
We hypothesize that **integrated survival** and **transcriptomic** data within a clustering framework will reveal molecular subgroups that more accurately **stratify prognosis** in early-stage tumors.

Methods

Cohort Construction & Data Collection

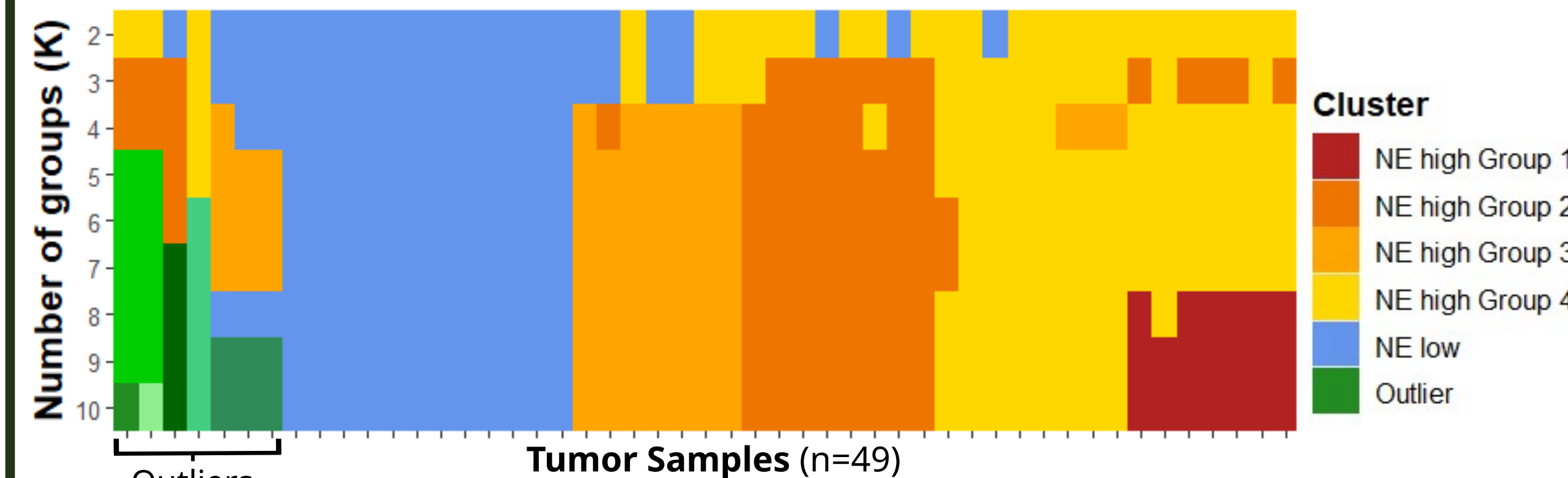


Clustering



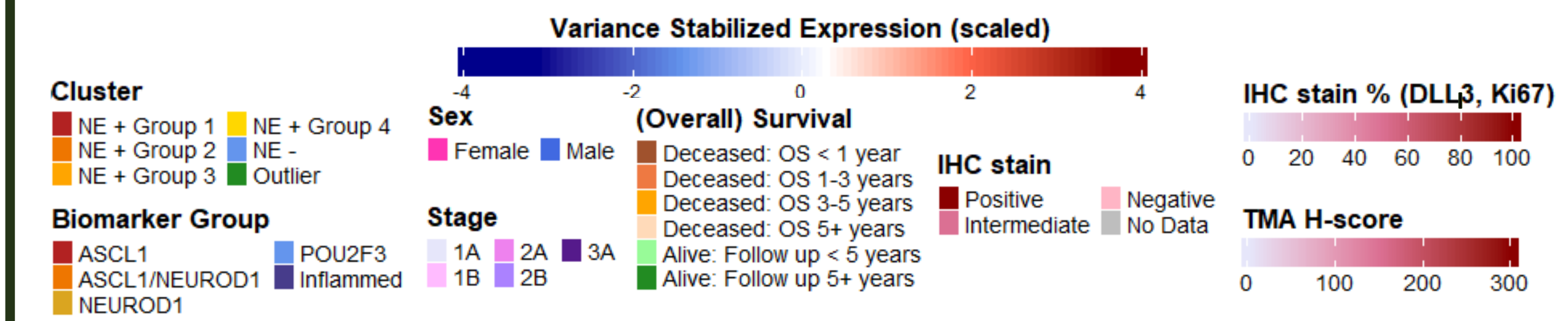
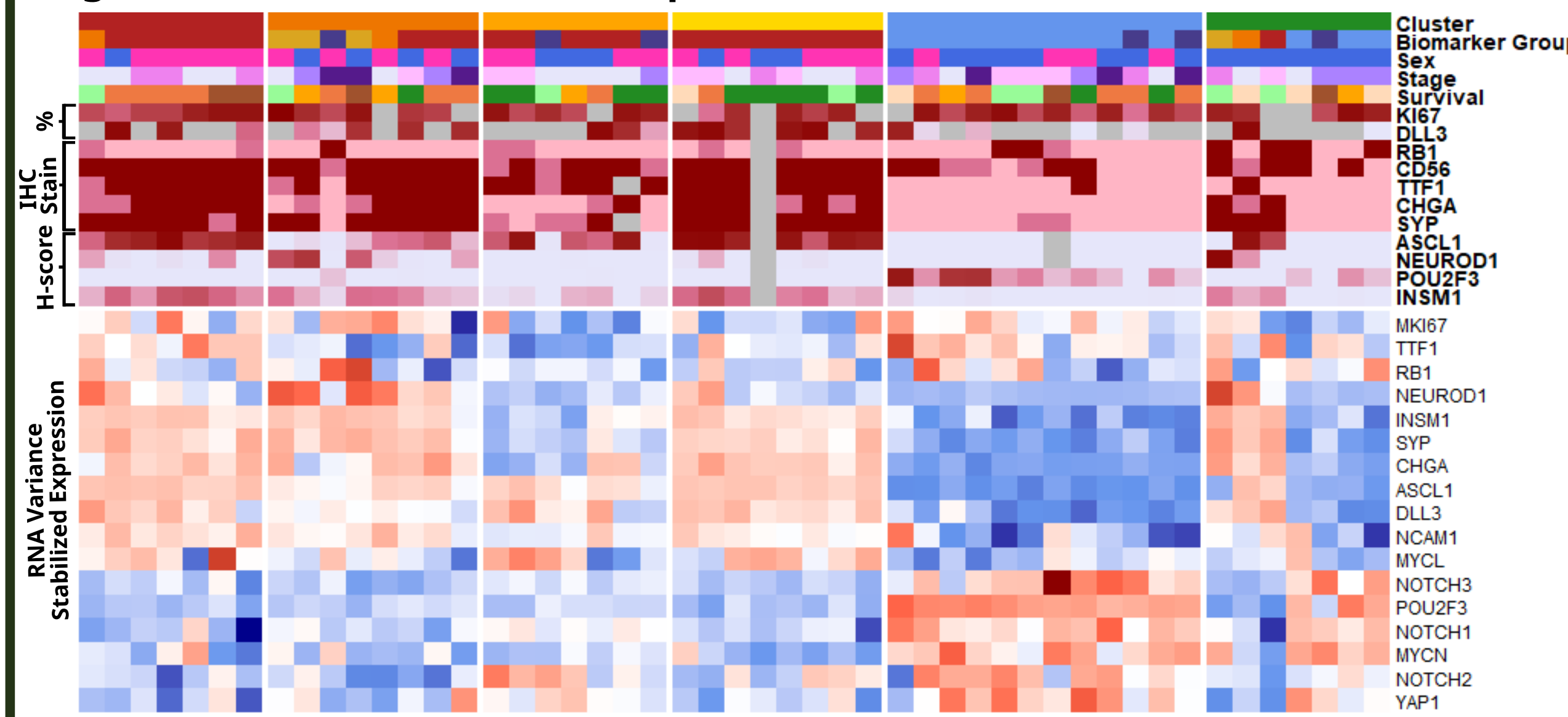
Results

Figure 1. Survival-Informed Transcriptomic Cluster Tracking



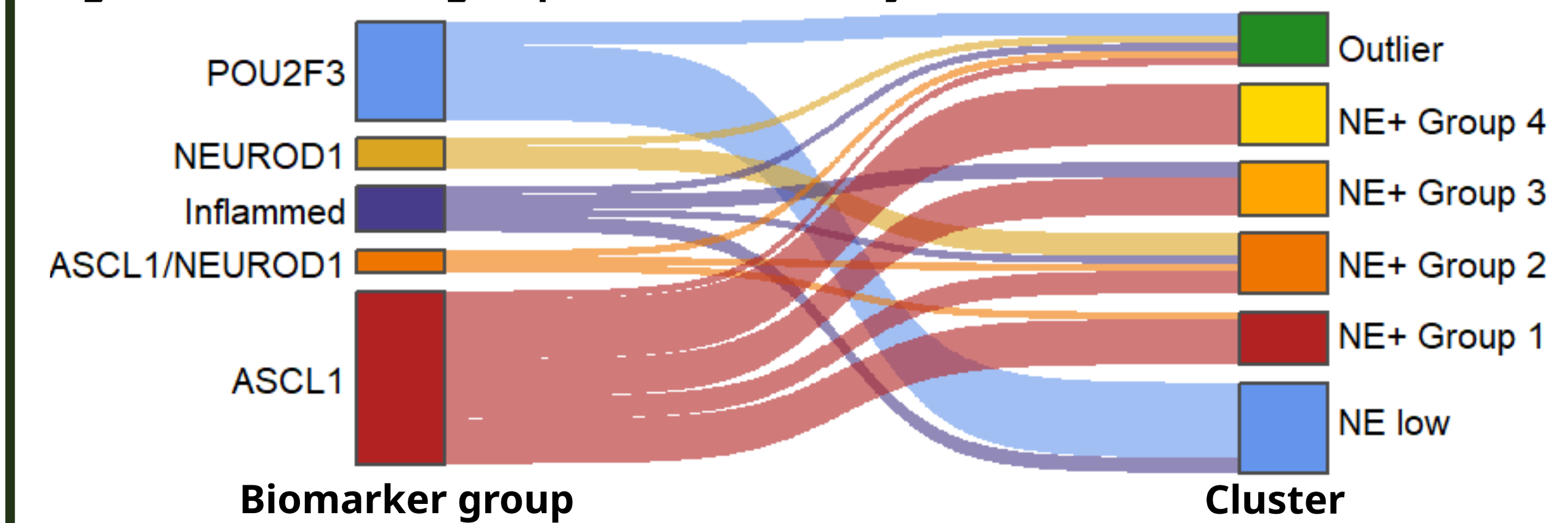
Normalized RNA expression of 389 tumor-enhanced genes selected by an elastic net regression model of overall survival, and scaled by hazard ratios, was PAM-clustered. **Five high-consensus clusters were identified.** The rest (n=7) were considered outliers.

Figure 2. Cohort Profile Heatmap



Two NE+ clusters composed mostly of stage 1 tumors with strong NE expression demonstrate the most extreme differences in overall survival; **NE+ Group 1 has the worst outcome, and NE+ Group 4 has the best outcome, despite similar tumor biomarker expression levels.** NE+ Groups 2 & 3 show intermediate NE biomarker expression. Sex at birth is mostly female in NE+ Group 1, and male in non-NE tumors.

Figure 3. Biomarker group → Cluster Sankey



Comparison of biomarker classification and proposed survival based-classification

Discussion & Future Directions

We demonstrate that a bottom-up approach that clusters integrated SCLC patient outcome and transcriptomic data can determine differentially enriched traits associated with prognosis in early-stage resected tumors.

Our clusters distinguish five groups, each with a unique combination of neuroendocrine and immune activity, supported by RNA and protein expression data (i.e. IHC, CyTOF).

Unlike the previously proposed biomarker groups, we transcriptomically identified multiple inflamed clusters associated with immune infiltration, improved prognosis, and a range of NE gene expression intensity.

In the future, we plan to identify specific biomarkers associated with each group, and validate our findings in an external SCLC cohort.

Figure 4A. Biomarker Overall Survival (5-year)

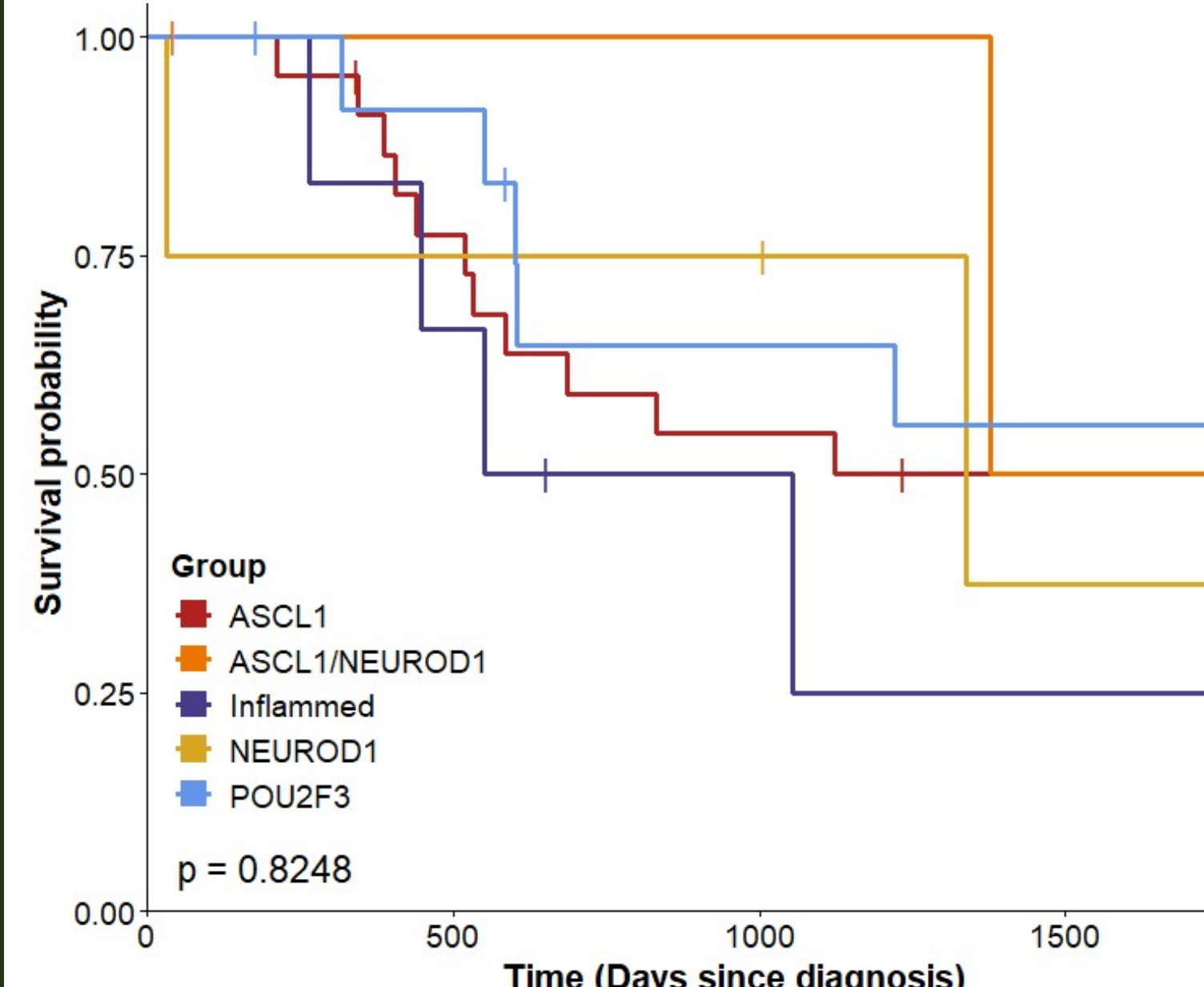
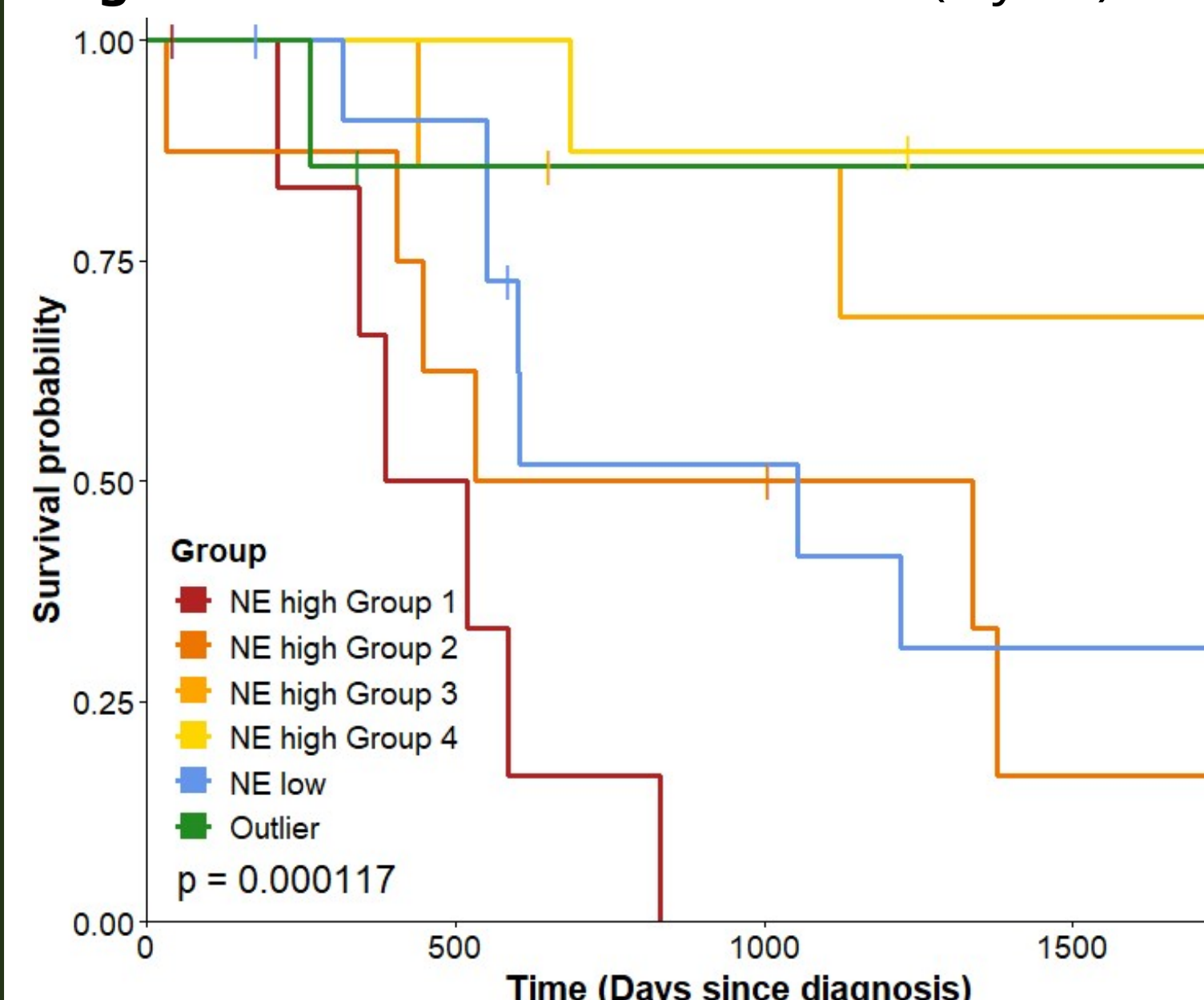
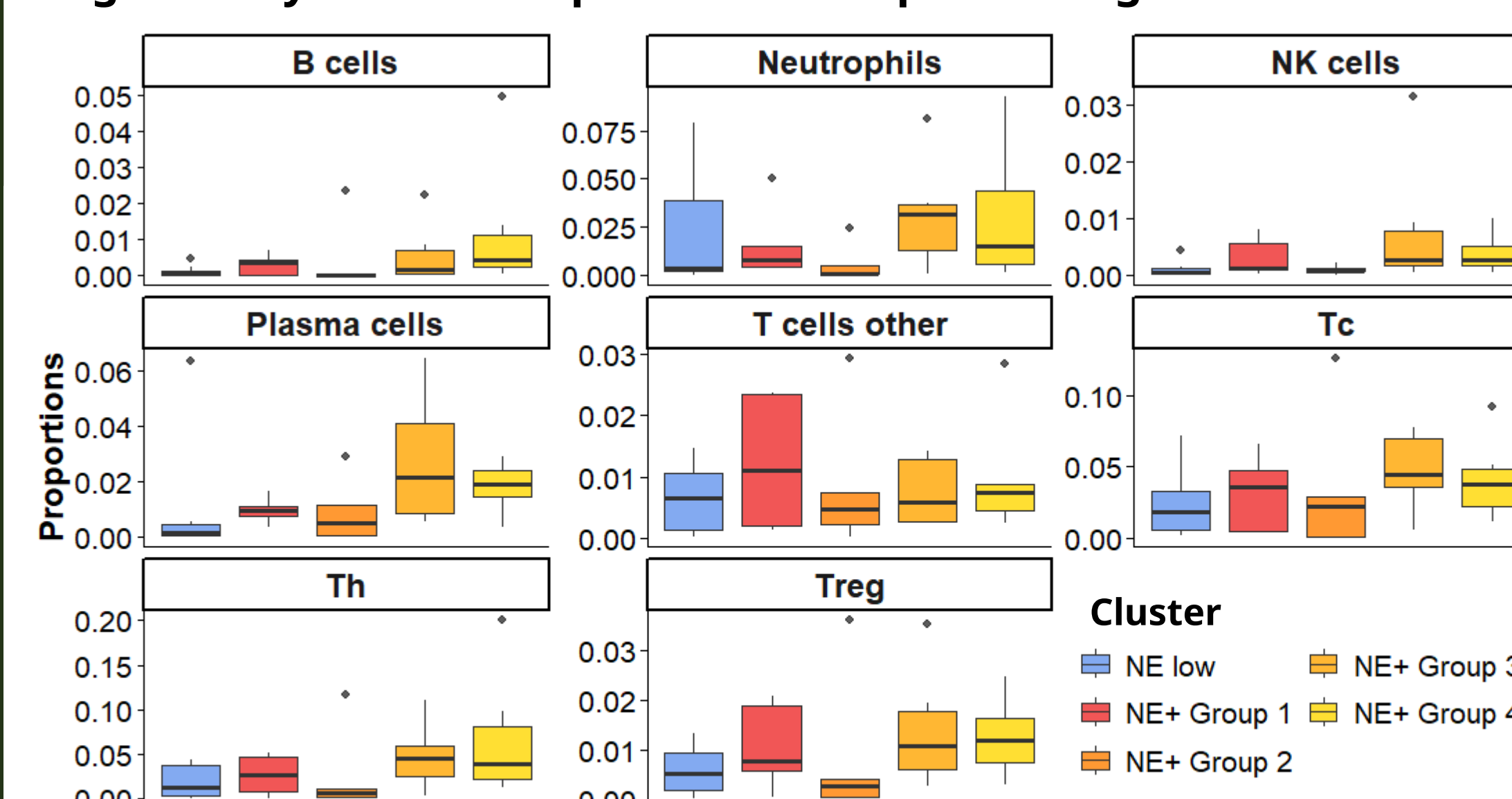


Figure 4B. Cluster Overall Survival (5-year)



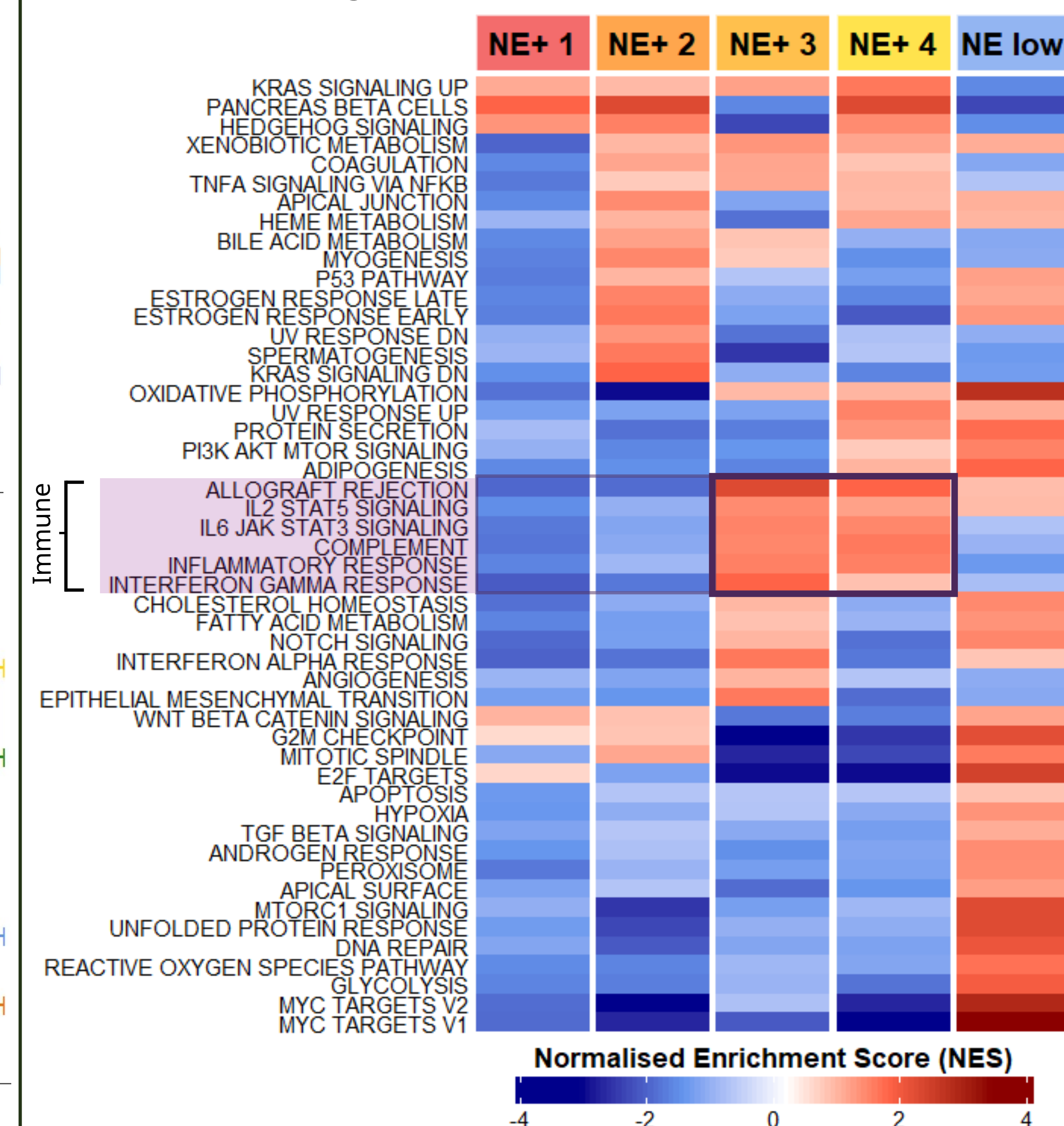
Kaplan-Meier analyses of overall survival demonstrate negligible prognostic value of biomarkers and **strong prognostic value of clusters (Fig4B; p=0.000117).**

Figure 6. CyTOF Cell Proportions in Proposed Prognostic Clusters



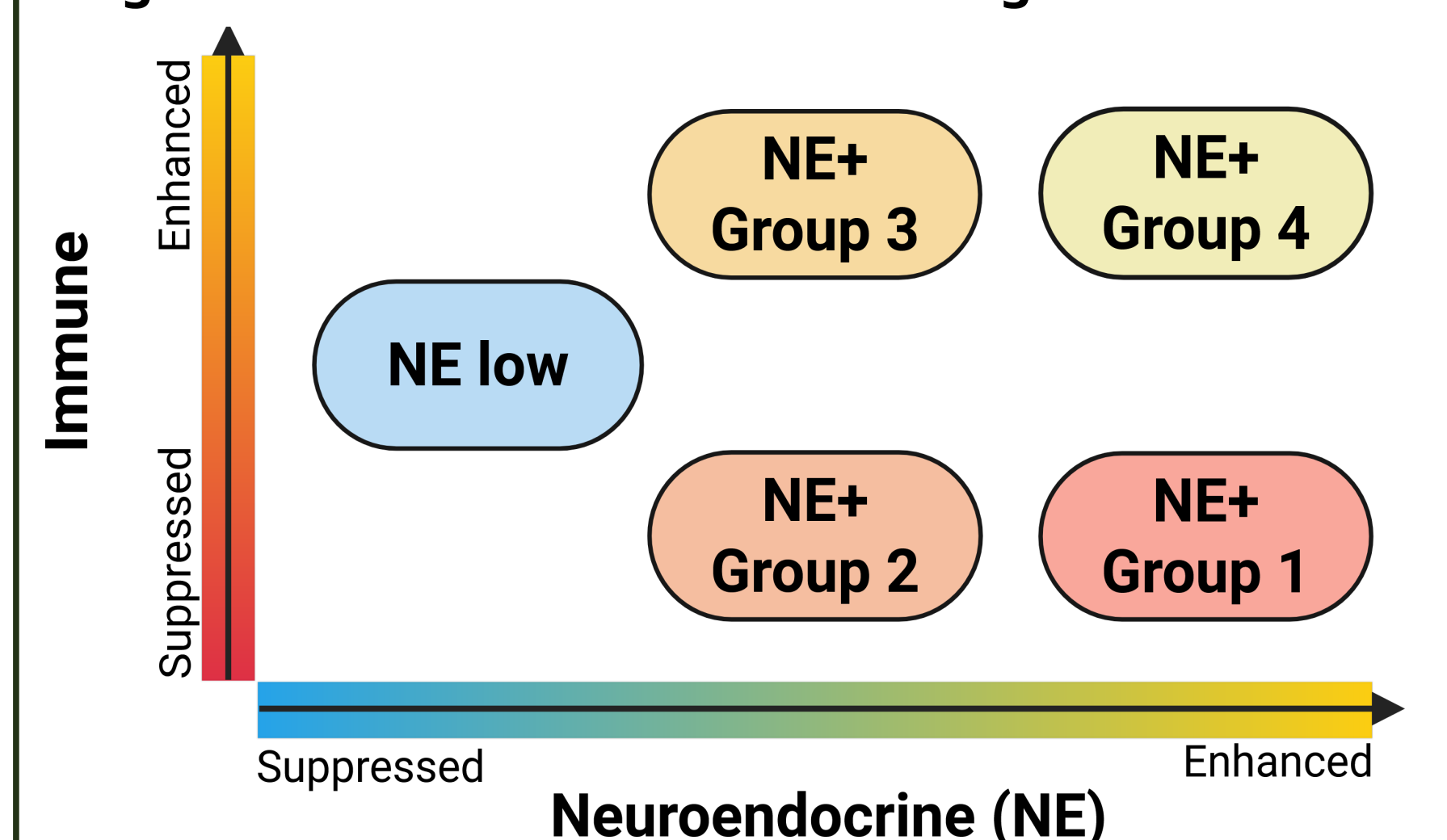
NE+ Groups 3 & 4 are B cell, Neutrophil, NK, Plasma, Tc and Th enriched.

Figure 5. Cluster Hallmark Mean Gene Set Enrichment



NE+ Groups 3 & 4, which have the best outcome, have enriched immune gene set expression. **NE+ Group 4 is distinguished from NE+ Group 1 by immune enrichment.** NE+ Group 3 has enriched EMT and IFN α gene expression.

Figure 7. Schematic Overview of Prognostic Clusters



NE+ Group 1 and 4 both have enriched NE expression, but differ in their immune enrichment. NE+ Groups 2 & 3 are NE intermediate; NE+ Group 3 is also immune-enriched.

References

1. Moore, S. M. et al. The Canadian Small Cell Lung Cancer Database (CASCADe): Results from a Multi-Institutional Real-World Evidence Collaboration. *Journal of Thoracic Oncology* 17, S244 (2022).
2. Rudin, C. M. et al. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. *Nat Rev Cancer* 19, 289–297 (2019).
3. Nabot, B. Y. et al. Immune heterogeneity in small-cell lung cancer and vulnerability to immune checkpoint blockade. *Cancer Cell* 42, 429–443.e4 (2024).

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