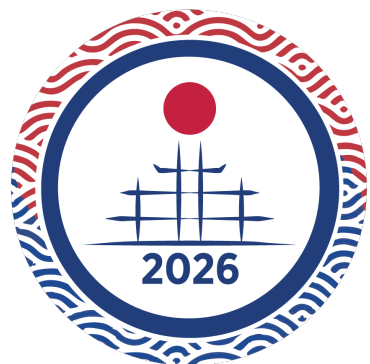


P2.089: Gene Expression-Based Immune Signatures Identify Clinically Relevant Immunophenotypes for Immunotherapy in Non-Small Cell Lung Cancer

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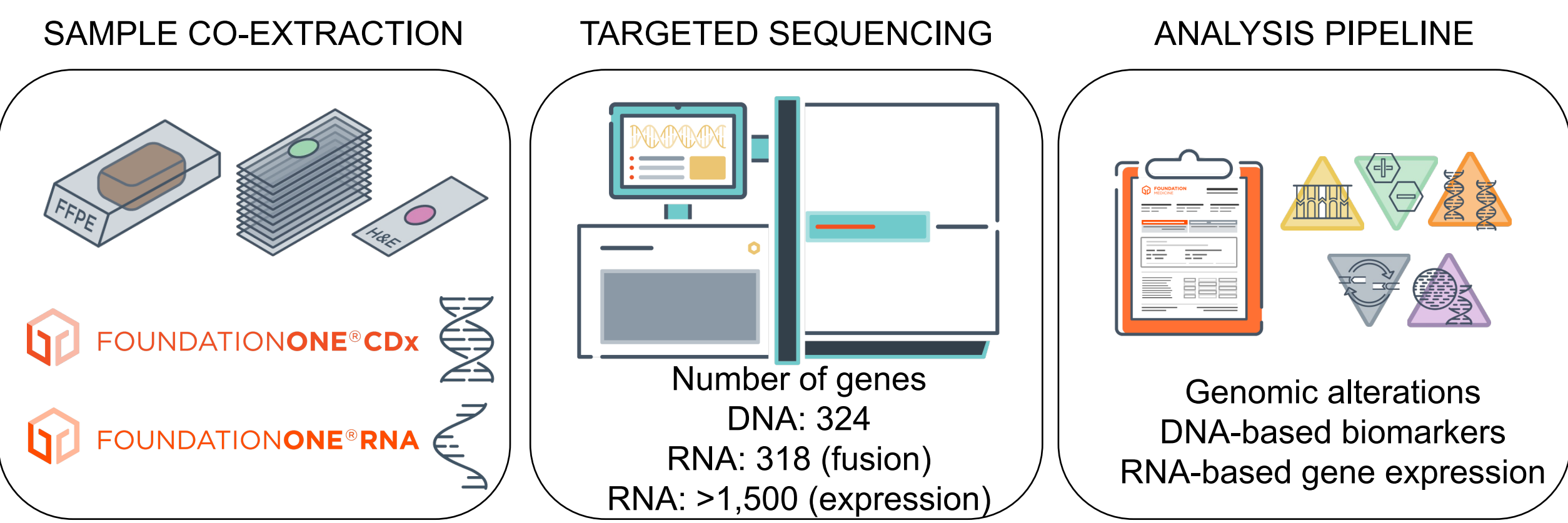
IASLC 2026 World
Conference on Lung Cancer
SEPTEMBER 12 – 15, 2026
SEOUL, REPUBLIC OF KOREA

INTRODUCTION

Immunotherapy, specifically immune checkpoint inhibition (ICI), is the standard of care for patients with metastatic non–small cell lung cancer (NSCLC), particularly for tumors lacking actionable driver alterations, and is increasingly utilized in earlier-stage disease. Approved companion diagnostics for ICI include PD-L1 immunohistochemistry (IHC) and tumor mutational burden (TMB). However, with the increased use of clinical RNA sequencing (RNAseq) in NSCLC, we sought to leverage RNAseq-based gene expression patterns of immune cell populations to derive an ICI biomarker representing tumor microenvironment (TME)-reflective immunophenotypes and evaluated its clinical relevance for ICI treatment strategies in NSCLC.

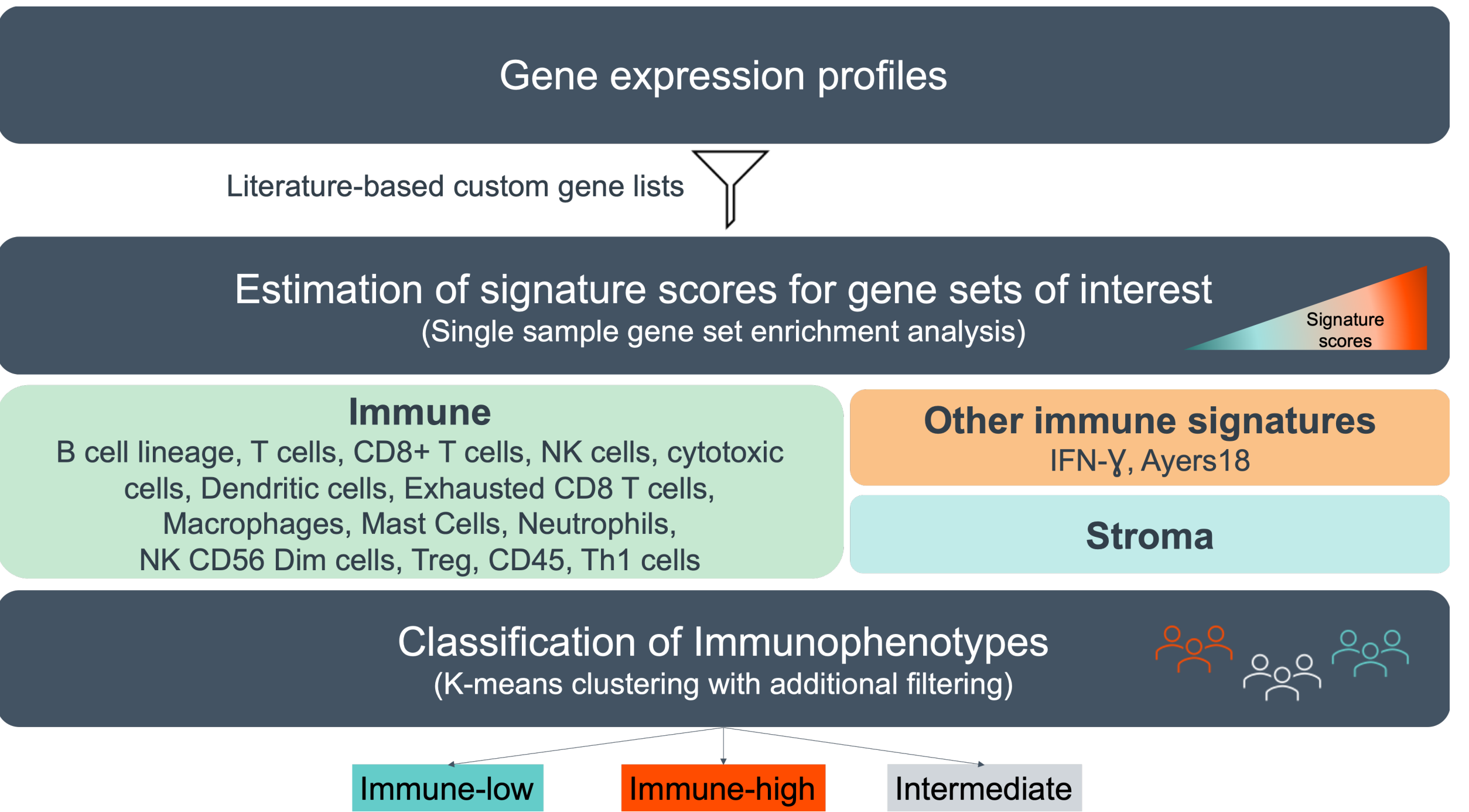
METHODS

TARGETED RNA PROFILING



Tumor tissue from 5,074 patients with NSCLC underwent targeted RNAseq using FoundationOne®RNA, which interrogates expression of >1,500 genes (Research Use Only)¹ and is performed through sample co-extraction with FoundationOne®CDx, without any additional tissue.

IMMUNE SIGNATURES AND IMMUNOPHENOTYPE PREDICTION



Single-sample gene set enrichment analysis (ssGSEA)-based scores were calculated for 17 gene sets^{2,3,4} representing immune and stromal signatures. K-means clustering of Z-score normalized ssGSEA scores was performed to identify two immunophenotypes: immune-high and immune-low. Cases that had a silhouette width <0.25 were annotated as Intermediate.

ASSESSMENT OF CLINICAL ASSOCIATION OF RNA-BASED IMMUNOPHENOTYPES

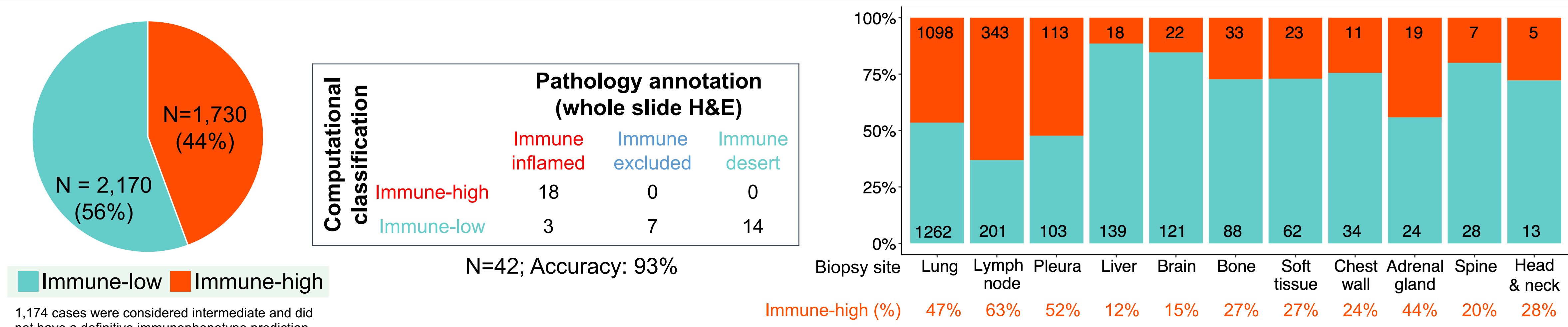
This analysis used the US-based deidentified Flatiron Health-Foundation Medicine NSCLC clinico-genomic database (FH-FMI CGDB)⁵, comprising 102 patients who received first-line ICI monotherapy or ICI in combination with chemotherapy. Clinical data from the Flatiron Health Research Database⁵ are linked to genomic data, derived from FMI’s CGP tests FoundationOne®CDx/FoundationOne®RNA, by deterministic matching, providing a deidentified dataset^{1,6}. Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals for the association between immunophenotypes and real-world overall survival (rwOS). Risk set adjustment was applied to account for left truncation.

ACKNOWLEDGEMENTS AND REFERENCES

This work is supported by Foundation Medicine Inc., Boston, MA, USA. We thank the patients who received comprehensive genomic profiling at Foundation Medicine and consented for research.
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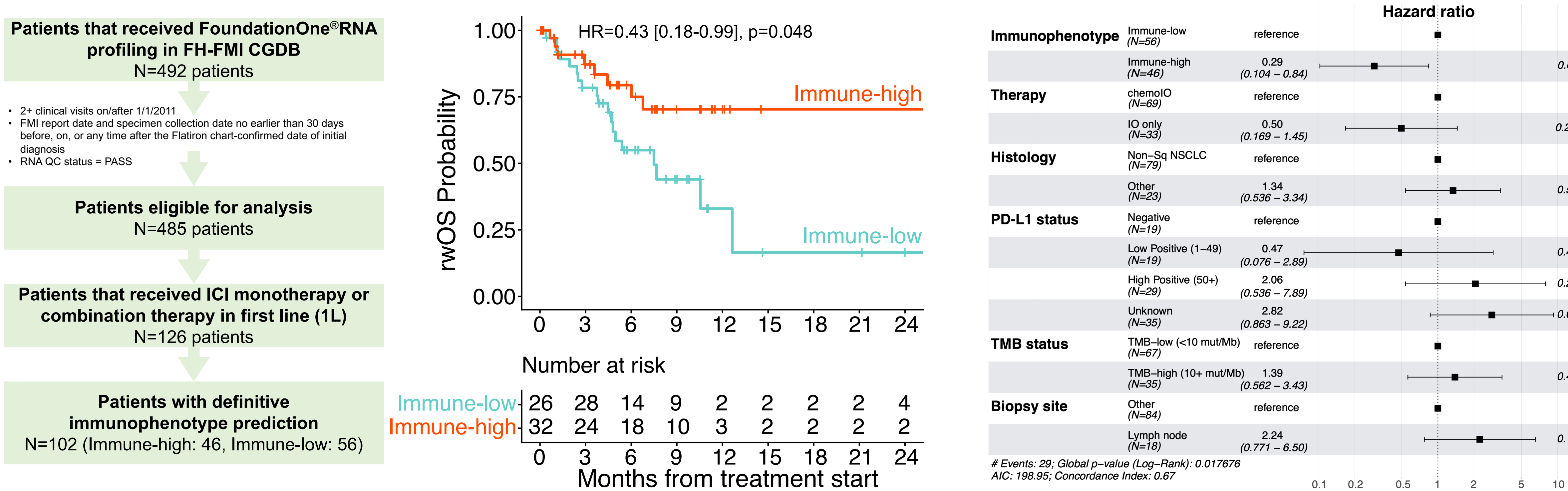
RESULTS

RNA-based immunophenotype prediction identifies 44% of NSCLC as immune-high, exhibits high concordance with pathology-derived morphological annotations and shows biopsy site-specific patterns



The computational approach identified 44% of NSCLC as immune-high and 56% as immune-low. It achieved 93% accuracy with pathologist-derived morphological annotations^{7,8}. Immune activity varied significantly by biopsy site. Brain (n=22/143, 15%) and liver metastases (n=18/157, 12%) were more immunosuppressive and showed lower rates of immune-high tumors compared to local liver biopsies (n=1,098/2,360, 47%) (p<0.0001 each). Consistent with this, distinct immune cell populations and gene signatures (see Methods) also showed site-specific patterns. Notably, IFN-γ⁴ ssGSEA scores were above median in 55% of lung biopsies compared with 25% of brain and 40% of liver metastasis.

RNA-based immunophenotypes are predictive of immune checkpoint inhibitor (ICI) response in NSCLC



In the FH-FMI CGDB cohort, patients with immune-high tumors exhibited prolonged rwOS (median rwOS [mOS] not reached, 2 year rwOS = 70%) compared to those with immune-low tumors, (mOS=7.49 months, 2 year rwOS = 16%) (HR=0.43 [0.18-0.99], p=0.048) after starting an ICI regimen. This association remained significant in a multivariable model adjusted for covariates (e.g., therapy type, histology, biopsy site) and other ICI-associated biomarkers (e.g., PD-L1 IHC status and TMB) (HR=0.29 [0.10-0.84], p=0.022).

DISCUSSION AND CONCLUSION

- Immune signatures derived from targeted RNAseq-based gene expression reveal distinct, site-specific TME profiles in NSCLC.
- These clinically relevant immunophenotypes have the potential to improve patient stratification and provide predictive value beyond current ICI biomarkers.
- Prospective studies are warranted to further explore the additional utility of expression-based immunophenotypes to approved diagnostics for ICI treatment decisions.