P2.06.93: Distinct Clinical and Biological Features of Five SCLC Subtypes Identified by Plasma Proteomic Analysis

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IASLC 2025 World Conference on Lung Cancer
SEPTEMBER 6-9, 2025
BARCELONA, SPAIN

INTRODUCTION

Small cell lung cancer (SCLC) is a heterogeneous disease with distinct subtypes defined by molecular profiles and neuroendocrine differentiation. Transcription factor-based classification divides SCLC into four major subtypes - SCLC-A, SCLC-N, SCLC-P, and SCLC-I [1]. Each subtype exhibits unique biological features and therapeutic vulnerabilities, highlighting the potential of SCLC subtyping for guiding personalized treatments. Current SCLC subtyping is based on molecular profiling of tumor biopsies. However, intratumoral heterogeneity, subtype switching and the reliance on invasive sampling pose challenges. Here, we explore the potential of plasma proteomic profiling for SCLC subtyping.

Advantages of plasma proteomics-based subtyping

- Requires a minimally invasive blood draw.
- Not limited by intratumoral heterogeneity.
- Samples can be obtained serially, enabling real-time monitoring and the detection of subtype switching during therapy.
- Potential for identifying novel therapeutic targets.

[1] Gay et al., Cancer Cell 2021;39: 346–360.e7

METHODS

- Pretreatment plasma samples were collected from 79 patients with extensive-stage SCLC treated with immune checkpoint inhibitors and chemotherapy - Table 1.
- Proteomic profiling was performed using an aptamer-based assay that quantifies >7000 proteins per sample.
- Consensus clustering analysis was used to identify different plasma proteomics-based SCLC subtypes.
- Bioinformatic analysis and an age predictor model were used to obtain biological and clinical insights per subtype.

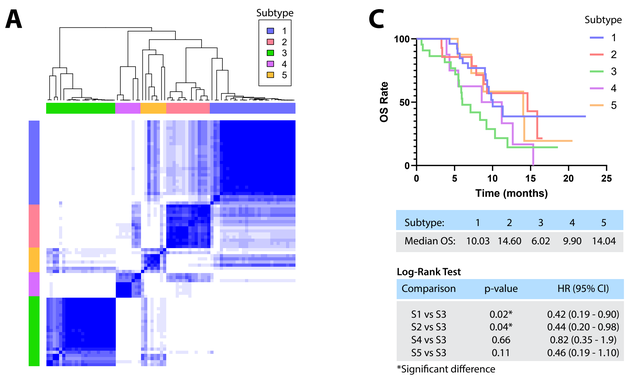
Table 1: Patient Characteristics

Characteristic	Number (%)	CB (%)	NCB (%)
Sex			
• Male	40 (50.6)	18 (22.8)	22 (27.8)
• Female	39 (49.4)	17 (21.5)	22 (27.8)
ECOG			
• 0	24 (30.4)	14 (17.7)	10 (12.7)
• 1	45 (57.0)	17 (21.5)	28 (35.4)
• 2	8 (10.1)	3 (3.8)	5 (6.3)
• Unknown	2 (2.5)	1 (1.3)	1(1.3)
Treatment type			
• Atezolizumab, Carboplatin, Etoposide	63 (79.7)	27 (34.2)	36 (45.6)
• Atezolizumab, Carboplatin, Etoposide, Pegfilgrastim	1 (1.3)	1 (1.3)	0 (0)
• Atezolizumab, Carboplatin, Etoposide, Trilaciclib	7 (8.9)	3 (3.8)	4 (5.0)
• Durvalumab, Carboplatin, Etoposide	6 (7.6)	4 (5.0)	2 (2.5)
• Ipilimumab, Nivolumab	2 (2.5)	0 (0)	2 (2.5)
Treatment line			
• First	74 (93.7)	33 (41.8)	41 (51.9)
• Advanced	4 (5.1)	1 (1.3)	3 (3.8)
• Unknown	1 (1.3)	1 (1.3)	0 (0)
Age, median [Q1, Q3]	65 [58, 70]	64 [57, 69]	65.5 [59, 71]
Total	79 (100)	35 (44.3)	44 (55.7)

CB, clinical benefit (defined as progression-fre survival at 6 months); NCB, no clinical benefit

RESULTS

Plasma proteomics-based SCLC subtypes exhibit distinct clinical characteristics



Subtype:	1	2	3	4	5
Median OS:	10.03	14.60	6.02	9.90	14.04

Log-Rank Test

Comparison	p-value	HR (95% CI)
S1 vs S3	0.02*	0.42 (0.19 - 0.90)
S2 vs S3	0.04*	0.44 (0.20 - 0.98)
S4 vs S3	0.66	0.82 (0.35 - 1.9)
S5 vs S3	0.11	0.46 (0.19 - 1.10)

*Significant difference

D

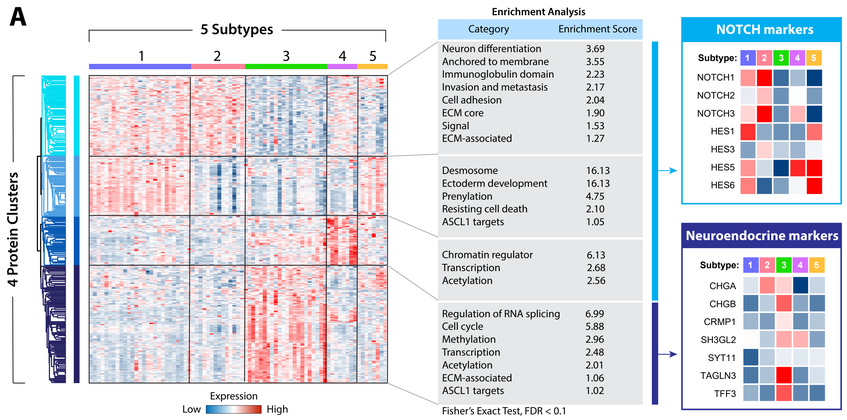
Enrichment Analysis of Clinical Parameters

Subtype	Category	Category value	Enrichment factor	Benj. Hoch. FDR
1	ECOG	0	1.46	0.158
1	OS event	0	1.37	0.169
3	ECOG	2	2.24	0.158
3	CB	NCB	1.31	0.172
3	ECOG	1	1.28	0.166
3	OS event	1	1.17	0.169
4	OS event	1	1.41	0.169

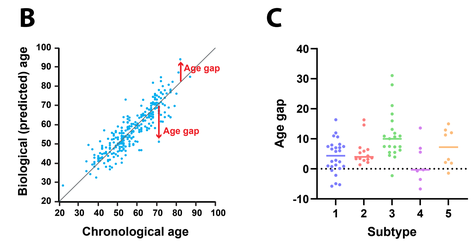
Fisher's Exact Test, FDR < 0.2
CB, clinical benefit; NCB, no clinical benefit

A. Consensus clustering identified five SCLC subtypes based on pretreatment plasma proteomic patterns.
B. Principal component analysis (PCA), where each dot represents a patient, shows that subtype-3 is highly distinct from the other subtypes.
C. Patients classified by subtype displayed differential overall survival (OS). The subtype-3 population displayed the poorest OS, significantly shorter than subtype-1 and subtype-2 populations.
D. Poor prognostic factors, such as high ECOG performance status and OS events, were significantly enriched among patients classified as subtype-3.

Biological insights from differentially expressed proteins



A. There are 469 differentially expressed proteins between the five subtypes, clustered into four main expression groups (ANOVA test, FDR<0.01). Differential protein expression patterns suggest unique biological characteristics per subtype. Subtype-3 exhibited high expression of multiple neuroendocrine biomarkers and proteins associated with neuroendocrine-high subtypes such as SCLC-A. In contrast, subtypes 1, 2 and 5 displayed the highest expression of NOTCH pathway proteins associated with non-neuroendocrine subtypes.



B. Plasma proteomics has been used to quantify the gap between an individual's chronological and biological (predicted) age. A higher biological age relative to chronological age may suggest impaired health or poor clinical prognosis.
C. Samples were analyzed using a published age prediction model [2]. Subtype-3 displayed the highest median age gap, aligning with the poorer survival outcomes observed in this population.

[2] Lehallier et al., Nature Medicine 2019; 25(12): 1843-1850

ACKNOWLEDGMENTS

The Ohio State University · Jefferson · Thoraxklinik Universitätsklinikum Heidelberg · NHS · Roswell Park Comprehensive Cancer Center · West Cancer Center & Research Institute · Mayo Clinic · Rabin Medical Center Beilinson • Hasharon · Sheba Tel HaShomer City of Health · Emek Medical Center · Meir Medical Center

CONCLUSIONS

- The current study reveals novel SCLC subtyping based on pretreatment plasma proteomic patterns.
- One subtype displayed more neuroendocrine-related characteristics and poor prognostic outcomes, while three others displayed non-neuroendocrine features.
- Ongoing research is focused on identifying therapeutic vulnerabilities per subtype and identifying new potential targets for intervention based on soluble markers.

Abstract number: 3247
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