

SEZ6 is Expressed Across Major Clinical and Demographic Groups of SCLC Patients: Evidence From a US Clinicogenomic Database

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OBJECTIVE

To characterize seizure-related homolog protein 6 (SEZ6) expression prevalence using real-world data and its association with molecular features in small cell lung cancer (SCLC)

CONCLUSIONS

In this real-world SCLC database, broad prevalence of SEZ6 positivity was observed in the SCLC population, with expression lowest in patients with the inflamed subtype using two molecular clustering algorithms

Increased SEZ6 expression was also associated with increased expression of other SCLC neuroendocrine biomarkers, including ASCL1, SYP, CHGA, and DLL3

There was no obvious relationship between SEZ6 expression and survival, and higher SEZ6 didn't necessarily indicate worse survival

These findings support SEZ6 as a promising and widely expressed therapeutic target in SCLC

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Disclosures

Nadine Jahchan, Gregory S. Calip, Yookyung Christy Choi, Yige Luo, Lujia Wang, Yuna Son, Weilong Zhao, Peter Ansell, and Cristiano Ferlini are AbbVie employees and may own stock. Jenny S. Guadamuz reports personal fees from Facion Health (an independent subsidiary of Roche) and grants from the Robert Wood Johnson Foundation. Nan Sethakorn served on advisory boards for Amgen and Johnson & Johnson; reports research funding from the Lung Cancer Research Foundation, the American Lung Association, and the Respiratory Health Association. Anne C. Chiang serves on the advisory boards or holds a consulting role at AbbVie, Amgen, AZ, BI, Daiichi, Fosun, GNE, Janssen, Merck, Zai Labz, has provided internal education lectures for GNE and Jazz Pharmaceuticals, and is a research PI for AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, GNE, Zai Labz.

Funding

AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data as well as review and approval of the abstract. All authors had access to relevant data and participated in the drafting, review, and approval of this abstract. No honoraria or payments were made for authorship.

Medical writing support was provided by Elise Sweetman, PhD, of Avature Health Ltd., and was funded by AbbVie Inc.

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BACKGROUND

- The transmembrane protein SEZ6 is an emerging and potentially actionable target in SCLC^{1,2}
- SEZ6 is highly expressed in patients with SCLC³; however, little is known regarding the expression profile of SEZ6 across diverse molecular subtypes in SCLC
- SEZ6 may have potential clinical applicability across a wide range of SCLC populations; however, its prognostic utility remains to be fully defined

METHODS

Data Source and Patient Population

- This retrospective, cross-sectional analysis used data drawn from the ConcertAI (Plymouth Meeting, PA) RWD360TM database linked to Caris Life Sciences® (Irving, TX) genomic data (cumulative databases during the second quarter of 2025)
- This analysis included patients in the United States with pathologically confirmed SCLC and available genomic and clinical data
- Electronic health record (EHR) data were obtained at the index SCLC diagnosis and throughout the sampling period

RESULTS

Patient Demographics and Characteristics

- Overall, 421 patients were included in this analysis, of which 38 patients were SEZ6 negative and 383 were SEZ6 positive, equating to an overall SEZ6-positivity prevalence of 91%
- Median age was 61–74 years, and most patients were female (57%) and non-Hispanic White (74%)
- Approximately one quarter of patients had brain (26%) or liver (25%) metastasis
- Median delta-like ligand 3 (DLL3) log₂(TPM+1) values were 4.5 and 2.5 among SEZ6-positive and SEZ6-negative groups, respectively
- Median cluster of differentiation 276 (CD276) log₂(TPM+1) values were 6.1 and 6.4 among SEZ6-positive and SEZ6-negative groups, respectively
- Most patients had the NMF1-SCLC-A/N molecular subtype (33%), followed by NMF3-SCLC-I (25%), NMF4-SCLC-P-like (21%), and NMF2-SCLC-Liver-met (14%)
- The prevalence of patients with in-house A, N, P, I subtype was 48%, 39%, 5% and 8%, respectively

Select patient demographics and clinical characteristics

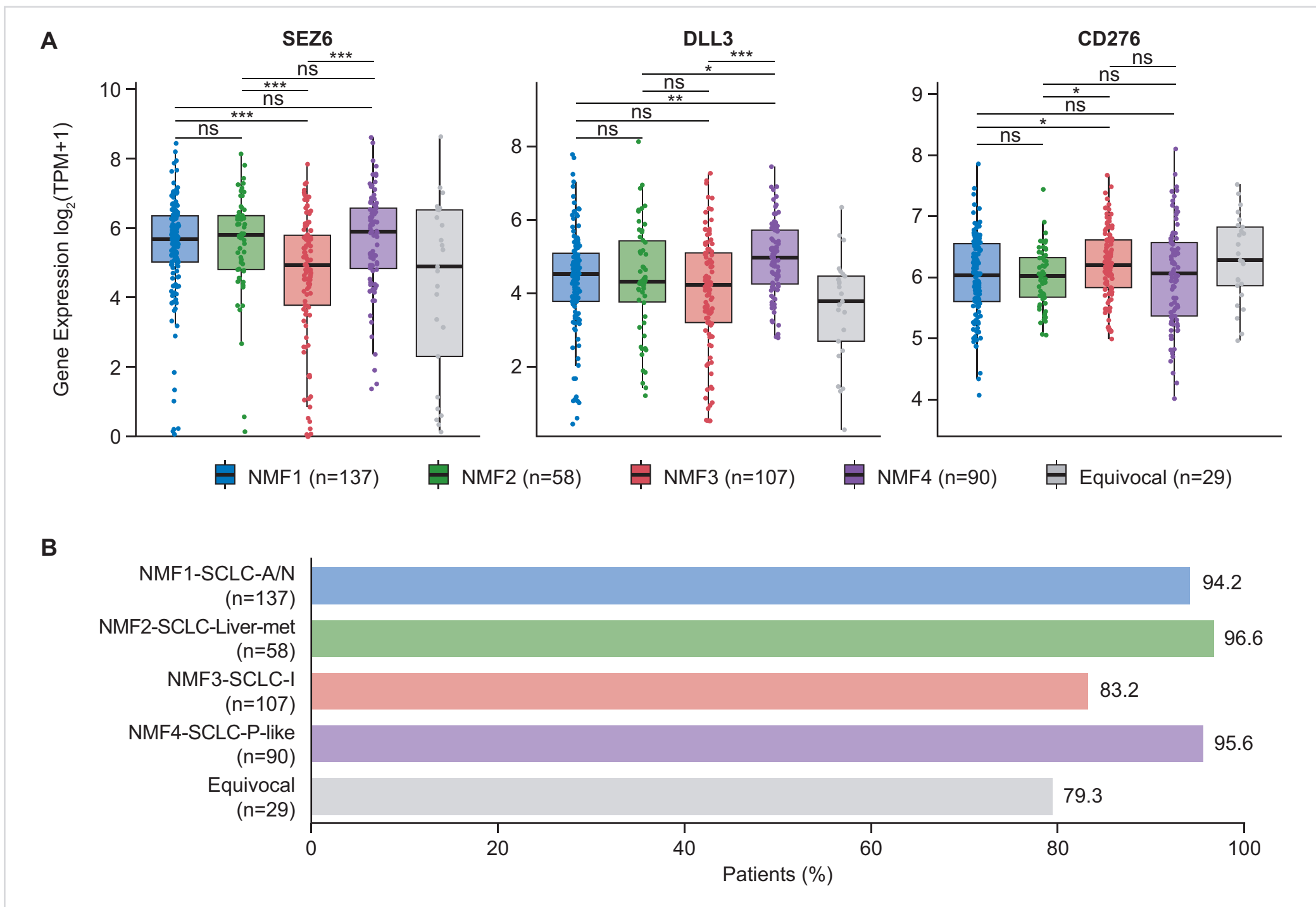
		All patients N=421	SEZ6 negative n=38	SEZ6 positive n=383
Age	Years, median*	61–74	63–78	61–74
Sex	Female	57%	45%	58%
Race and ethnicity	Non-Hispanic White	74%	74%	74%
Specimen site	Lung	39%	45%	38%
	Lymph node	26%	16%	27%
	Liver	20%	13%	21%
	Brain	3%	3%	3%
	Other	12%	24%	11%
Metastases	Brain*	26%	5%	28%
	Liver*	25%	11%	26%
Gene expression*	DLL3 expression	4.5	2.5	4.5
	CD276 expression	6.1	6.4	6.1
NMF subtype*	NMF1-SCLC-A/N	33%	21%	34%
	NMF2-SCLC-Liver-met	14%	5%	15%
	NMF3-SCLC-I	25%	47%	23%
	NMF4-SCLC-P-like	21%	11%	23%
ANPI subtype*	A (ASCL1)	48%	29%	50%
	N (NEUROD1)	39%	16%	41%
	P (POU2F3)	5%	3%	6%
	I (Inflamed)	8%	53%	3%

*Age uniformly derived from time of patients' index sampling in the clinicogenomic database. *Presence of brain and liver metastases refers to patient-level prevalent metastatic sites at time of tissue sampling. *Median log₂(TPM+1). *NMF molecular subtypes were derived using NMF clustering of bulk RNA-seq gene expression data from SCLC tumors in the ConcertAI-Caris RWD360TM database. *ANPI subtypes defined by DIVES AbbVie.¹ ASCL1, achaete-scute homolog 1; CD276, cluster of differentiation 276; DLL3, delta-like ligand 3; NEUROD1, neurogenic differentiation 1; NMF, non-negative matrix factorization; POU2F3, POU class 2 homeobox 3; RNA, ribonucleic acid; SCLC, small cell lung cancer; SEZ6, seizure-related homolog protein 6; TPM, transcripts per million.

SEZ6 Expression Across SCLC Molecular Subtypes (NMF and ANPI Subtype Algorithms)

- SEZ6 positivity was high and broadly prevalent across all SCLC molecular subtypes and SEZ6 expression did not differentiate subtypes; similar findings were observed for the other known SCLC targets DLL3 and CD276
- Although SEZ6 prevalence was lower among patients with NMF3-SCLC-I (83%) subtype, it was still abundantly expressed

SEZ6 gene expression (A) and prevalence (B) by SCLC NMF molecular subtypes



*p<0.05, ***p<0.001, ****p<0.0001 as determined by Wilcoxon rank sum tests. CD276, cluster of differentiation 276; DLL3, delta-like ligand 3; NMF, non-negative matrix factorization; ns, not significant; SCLC, small cell lung cancer; SEZ6, seizure-related homolog protein 6; TPM, transcripts per million.

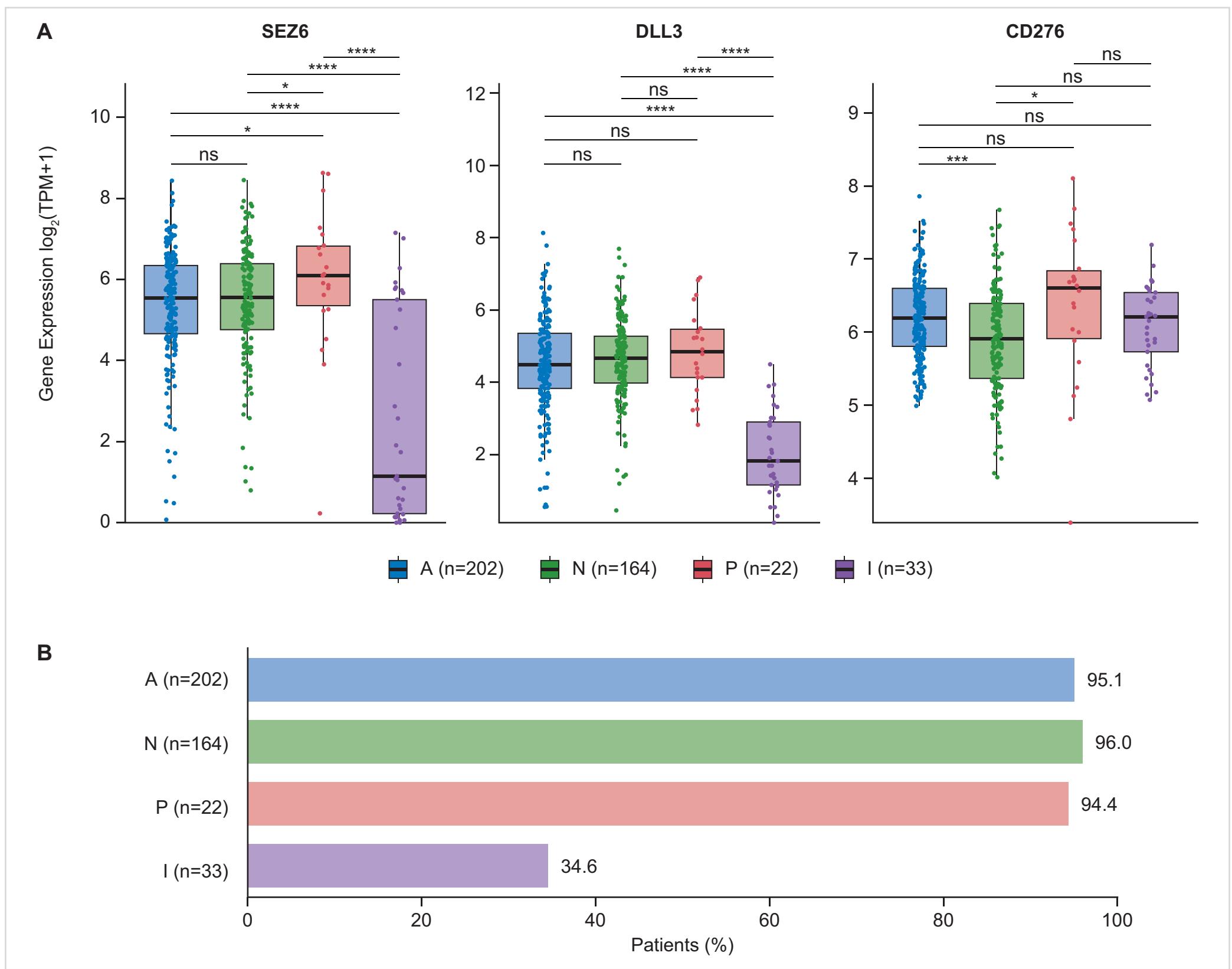
- Similarly, when patients were stratified by traditional SCLC A/N/P/I molecular subtypes, SEZ6 positivity was high and broadly prevalent across the A, N, and P subtypes but lower among patients with the inflamed I subtype; a similar pattern was observed for DLL3
- Previously published data suggested SEZ6 expression was significantly lower in the P-like subtype⁷; however, we did not find any significant difference in this study

METHODS (CONT.)

Outcomes

- SEZ6 positivity was defined as tissue mRNA levels corresponding to an immunohistochemistry staining intensity of 1+ in ≥1% of cells¹
- Non-negative Matrix Factorization (NMF) molecular subtypes were derived using NMF clustering of bulk-RNA-sequencing gene expression data from SCLC tumors in the ConcertAI-Caris RWD360TM database following previously published methodologies^{3,4}
- Four NMF clusters were defined corresponding to known SCLC transcriptional programs and immune features^{4,5}:
 - NMF1-SCLC-A/N - classic neuroendocrine (NE) subtype with high proliferation signatures, immune cold
 - NMF2-SCLC-Liver-met - metabolic subtype associated with liver metastasis
 - NMF3-SCLC-I - *YAP1/REST*-high, immune-enriched subtype with concurrent stromal signals (*TGF-β*/fibrosis signatures)
 - NMF4-SCLC-P-like - admixed subtype with high *POU2F3* and *NEUROD1*, mucin secretion and neuronal features
- ANPI subtypes were defined using K-means clustering on the expression profiles of the 13-gene signature (ASCL1, NEUROD1, POU2F3, CD274, APOE, FCER1G, HLA-E, CD74, HLA-DRA, IFITM1, HLA-DQA1, C1QA, and C1QC)³
- The clusters were annotated according to their dominant marker expression as Subtype A (ASCL1-high), Subtype N (NEUROD1-high), Subtype P (POU2F3-high), and Subtype I (Inflamed; enriched for the remaining immune/inflammatory genes)⁵

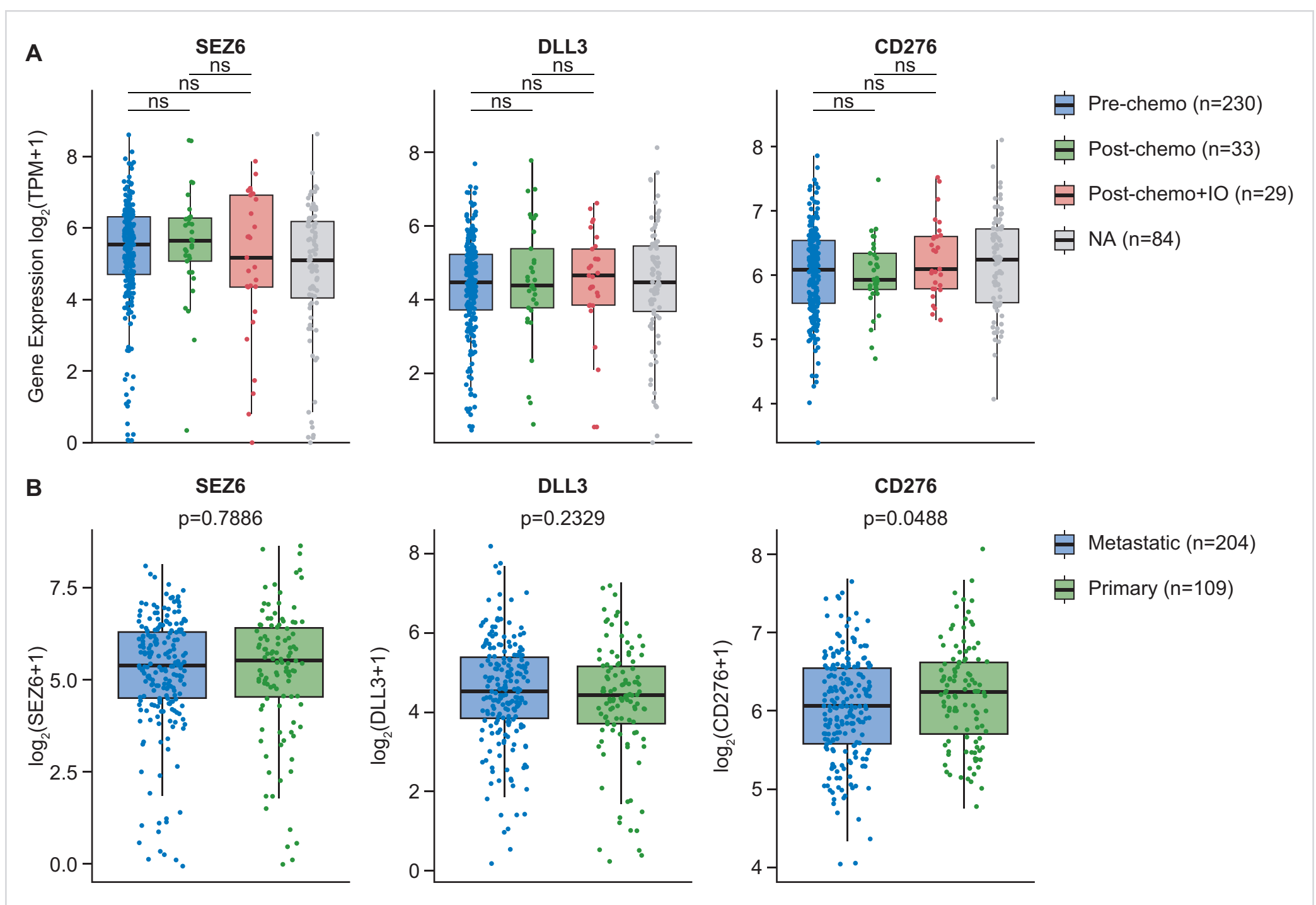
SEZ6 gene expression (A) and prevalence (B) by SCLC A/N/P/I molecular subtypes



*p<0.05, ****p<0.0001 as determined by Wilcoxon rank sum tests. CD, cluster of differentiation; DLL3, delta-like ligand 3; ns, not significant; SCLC, small cell lung cancer; SEZ6, seizure-related homolog protein 6; TPM, transcripts per million.

- SEZ6 prevalence in any SCLC molecular subtype was still higher than SEZ6 prevalence in non-small cell lung cancer (7%), suggesting SEZ6 may be a specific marker for SCLC and in all the molecular subtypes (data in QR code supplement)
- SEZ6 prevalence across all molecular subtypes (lowest observed in the I subtype using ANPI subtyping, 35%) far exceeded that in NSCLC (7%)

SEZ6 gene expression by SCLC treatment (A) and tumor site (B)



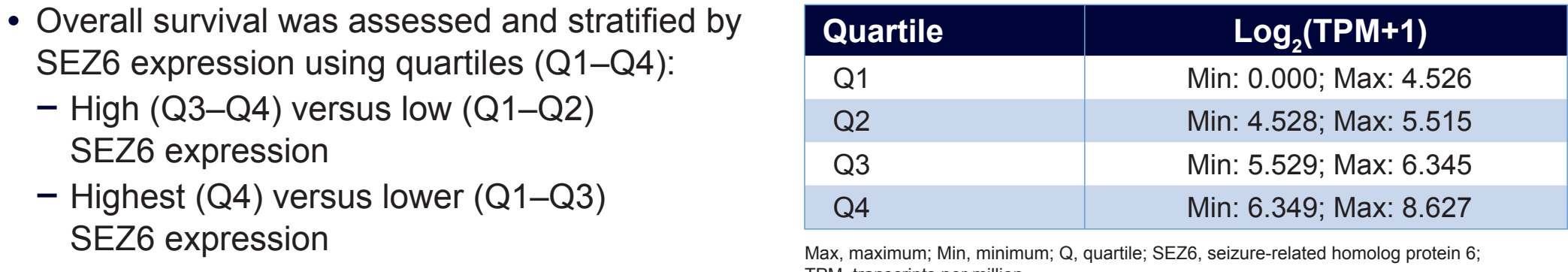
CD276, cluster of differentiation 276; DLL3, delta-like ligand 3; IO, interventional oncology; NA, not applicable; ns, not significant; SCLC, small cell lung cancer; SEZ6, seizure-related homolog protein 6; TPM, transcripts per million.

SEZ6 Expression by SCLC Treatment and Tumor Site

- SCLC treatment did not affect SEZ6 expression; SEZ6 positivity was high and broadly prevalent pre-chemotherapy and post-chemotherapy with or without interventional oncology
- SEZ6 expression was high and maintained across tissues from both primary and metastatic SCLC
- No meaningful differences were observed for DLL3 and CD276 expression across SCLC treatment or primary versus metastatic tumor tissues
- Similar findings were published previously in SCLC^{6,8}

SEZ6 Gene Expression Correlation Analysis

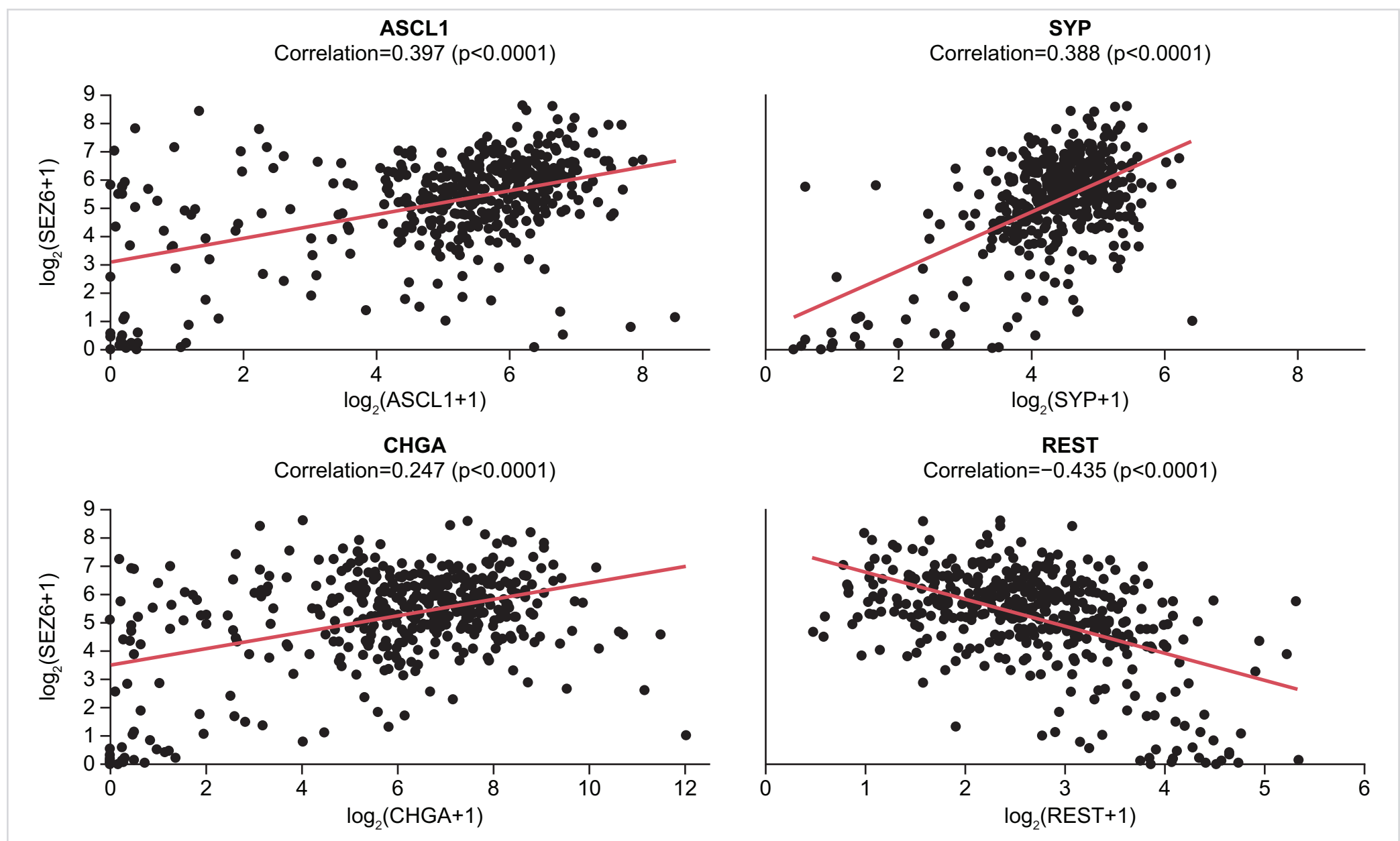
- SEZ6 mRNA expression positively correlated with the NE lineage markers (ASCL1, CHGA, and SYP), and inversely correlated with the NE master transcriptional repressor (REST), supporting SEZ6 as a robust NE lineage marker
- SEZ6 expression was weakly positively correlated with DLL3 expression but no correlation was observed with CD276 expression
- Similar findings were published previously in SCLC^{6,8}
- No correlation was observed with NEUROD1 or POU2F3 expression



Data Analysis

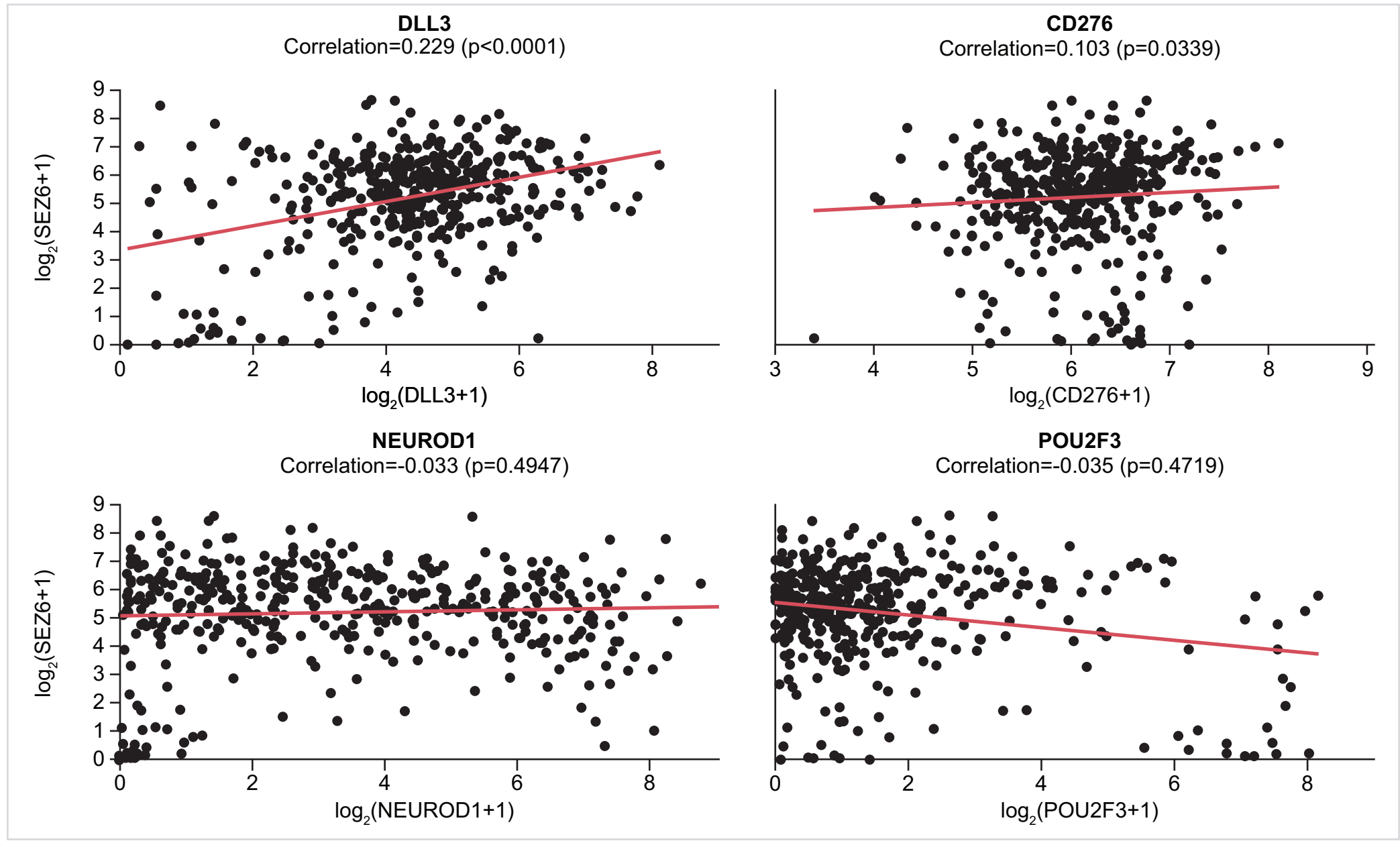
- Spearman's rank correlation tests were performed to assess the correlation between log₂-transformed SEZ6 expression (transcripts per million [TPM]) and each gene of interest
- To test for gene expression differences between subtypes (NMF and ANPI), Wilcoxon rank sum tests were performed between each pair of subtype labels. A false discovery rate correction was performed for each gene of interest
- Survival time was measured from initial lung cancer diagnosis to death or censoring (last EHR activity or October 31, 2024, whichever was earlier), restricted to patients with sample collection and next-generation sequencing (NGS) order dates overlapping within one month of EHR records
- Median overall survival was estimated using a Cox proportional hazards model with left truncation at NGS order date to address immortal time bias, and lag time to account for differential outcome capture

Correlation of SEZ6 gene expression with ASCL1, SYP, CHGA and REST



ASCL1, achaete-scute homolog 1; CHGA, Chromogranin-A; REST, RE1-silencing transcription factor; SEZ6, seizure-related homolog protein 6; SYP, Synaptophysin.

Correlation of SEZ6 gene expression with CD276, DLL3, NEUROD1 and POU2F3

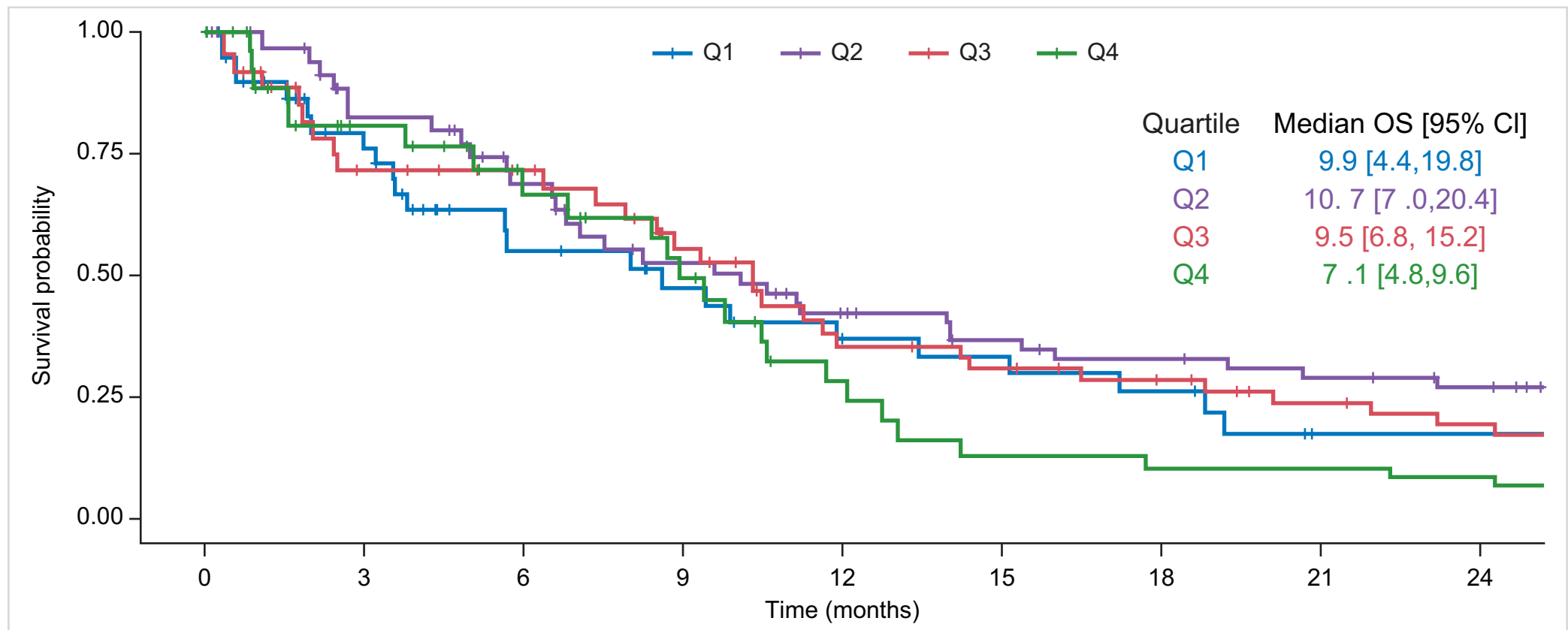


CD276, cluster of differentiation 276; DLL3, delta-like ligand 3; NEUROD1, neurogenic differentiation 1; POU2F3, POU class 2 homeobox 3; SEZ6, seizure-related homolog protein 6.

Overall Survival

- Marginal survival curves exhibited substantial overlap across all SEZ6 expression quartiles, and the overall quartile comparison did not reach statistical significance by log-rank test
- Although the point estimate for median overall survival (derived under left truncation) was numerically shortest in Q4, the pattern across quartiles was non-monotonic and 95% confidence intervals for quartile-specific estimates broadly overlapped
- Similar findings with a smaller real-world dataset were previously reported on SEZ6 expression lacking statistical significance as a prognostic biomarker for overall survival⁶

Overall survival by SEZ6 expression quartiles



CI, confidence interval; OS, overall survival; Q, quartile; SEZ6, seizure-related homolog protein 6.

Limitations and Future Directions

- The survival analysis is exploratory; given substantial overlap of marginal survival curves across quartiles, confirmed violations of the proportional hazards assumption, and the inherent limitations of retrospective clinicogenomic data, these findings should be interpreted as hypothesis-generating rather than as a definitive prognostic determination
- Confirmation of these findings in larger, prospectively ascertained real-world SCLC cohorts is warranted