

First Name

May-Lucie

Last Name

Meyer

Email

may-lucie.meyer@mssm.edu

Phone

{Empty}

Affiliation - Presenter

Tisch Cancer Institute, Mount Sinai Hospital, New York, NY, USA

Abstract Title

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First Author

First Author First Name

May-Lucie

First Author Last Name

Meyer

Affiliation

Tisch Cancer Institute, Mount Sinai Hospital, New York, NY, USA

Additional Authors

List of Additional Authors

- **First Name:** Hui
Last Name: Yu
Affiliation: Medical Oncology, University of Colorado Anschutz Campus, Aurora, USA
- **First Name:** Zoltan
Last Name: Lohinai

Affiliation: OKTPI-Koranyi National Institute, Budapest, Hungary

- **First Name:** Grace

Last Name: van Hyfte

Affiliation: Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, USA

- **First Name:** Fred

Last Name: Hirsch

Affiliation: Tisch Cancer Institute, Mount Sinai Hospital, New York, NY, USA

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DLL3 Expression in Early-Stage SCLC: Comparative Analysis of IHC and mRNA ISH

May-Lucie Meyer¹, Hui Yu², Christopher Rivard², Zoltan Lohinaj³, Shivaun Lueke Pickard², Grace Van Hyfte⁴, Fred R Hirsch¹
¹Center for Thoracic Oncology, Tisch Cancer Institute at Mount Sinai, New York, NY, USA; ²Division of Medical Oncology, University of Colorado Anschutz Campus, CO, USA; ³National Korányi Institute of Pulmonology, Budapest, Hungary; ⁴Institute for HealthCare Delivery Science, Department of Population Health Science and Policy, ISMMS, New York, NY



PURPOSE

Small cell lung cancer (SCLC) is a highly malignant disease, accounting for 15% of lung cancers and characterized by a poor prognosis.¹ Exploring novel therapeutics based on the expression of biomarkers in SCLC tumors shows promise.

Delta-Like Canonical Notch Ligand 3 (DLL3) is commonly overexpressed in SCLC and is a target for new therapies. DLL3 positivity has been reported in 80% to 93% of SCLC, with most of the studies in advanced SCLC.² Tarlatamab, a bispecific T-cell engager targeting DLL3 and CD3, has recently demonstrated an overall response rate of 40% in pretreated patients.³ Expression pattern of DLL3 and its role as biomarker in early-stage SCLC has not been described in large series, and there is currently no standardized evaluation method.

This study aimed to assess DLL3 expression in early-stage SCLC using immunohistochemistry (IHC) and mRNA in situ hybridization (ISH), correlate these assays and correlate DLL3 expression with outcomes and characteristics.

METHODS

This monocentric retrospective study evaluated 248 resected samples from patients with early-stage SCLC from 1978 to 2013. IHC staining used the Ventana Benchmark XT autostainer and SP347 Antibody Assay. For mRNA ISH, a Leica Bond RX autostainer was used. IHC positivity was defined as an H-score ≥ 1 (0-300), mRNA ISH positivity as a score of ≥ 1 with the ACD approved method (0-3). Linear correlation between IHC and mRNA ISH was calculated. Univariable and multivariable Cox regression were conducted. PASW Statistics 22.0 package and R versions 3.5.2 and 4.3.1 were used.

RESULTS

From 1978 to 2013, 248 patients with histologically confirmed early-stage SCLC were included. 233 were evaluable with IHC and 58% were positive. 235 samples evaluable with mRNA ISH, 87% were positive.

IHC and mRNA ISH were correlated (Spearman's rank, $p < 0.001$, Figure 3). Clinical characteristics and survival data were available only for a subset of patients (N=137), and are presented in Table 1. DLL3 positivity was not correlated with patients' characteristics.

There was a non-significant trend toward better median overall survival (mOS) with IHC score < 1 , with a mOS of 27.1 months (95% CI: 12.5-59.0) vs 21.0 months (95% CI: 18.2-30.4), $p = 0.893$. The same was observed with mRNA ISH score < 1 : mOS of 38.9 months (95% CI: 26.6-NA) vs 18.9 months (95% CI: 14.9-28.8) $p = 0.221$.

Characteristics	N = 137
Age	
<65	110 (81%)
65+	25 (19%)
Unknown	2
Gender	
Male	101 (74%)
Female	36 (26%)
Smoking status	
Non-smoker	2 (1.5%)
Former smoker	8 (5.8%)
Current smoker	70 (51%)
NA	57 (42%)
COPD	
0	76 (55%)
1	44 (32%)
NA	17 (12%)
Hypertension	
0	76 (56%)
1	42 (31%)
NA	17 (13%)
Unknown	2
Diabetes	
0	105 (78%)
1	13 (9.6%)
NA	17 (13%)
Unknown	2
Adjuvant chemotherapy	
No	75 (59%)
Yes	53 (41%)
Unknown	9

Table 1. Baseline characteristic

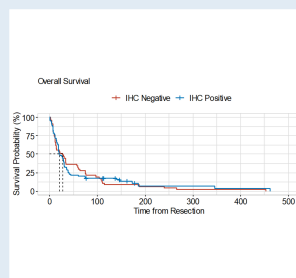


Figure 1. Kaplan-Meier curves for overall survival (months) according to IHC H-score.

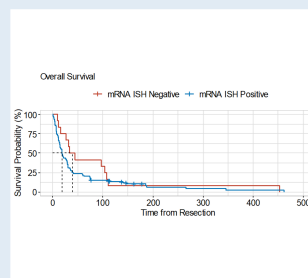


Figure 2. Kaplan-Meier curves for overall survival (months) according to ISH score.

RESULTS

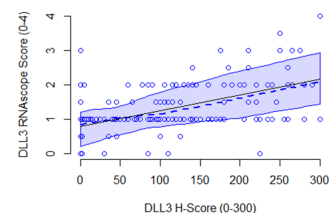


Figure 3. Comparison of DLL3 expression. Linear regression fitted line (black), LOESS smoothing line (dashed blue), 95% confidence bands (solid blue), Spearman's rank correlation $\rho = 0.557$.

CONCLUSION

In 248 early-stage SCLC cases, positivity for DLL3 was 58% with IHC and 87% with mRNA ISH. No significant correlation with clinical characteristics or survival was observed. Future studies on DLL3 might improve the treatment of SCLC.

CONTACT INFORMATION

may-lucie.meyer@mssm.edu
 X/twitter handle: @mayluciemeyer
 ORCID 0000-0003-2091-9578

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