Molecular subtypes and their correlation with clinical oucomes in a real-world study of patients with extensive stage small cell lung cancer (ES-SCLC) undergoing combined chemo-immunotherapy

Núria M. Zellweger[1*], Sabine Schmid[2,3*], Martin Früh[3,4], Martina Bertschinger[5], Christine Waibel[6], Tereza Losmanová[7], Ferdinando W. Cerciello[2], Patrizia R. Frösch[8], Michael T. Mark[9,10], Adrienne Bettini[11], Pirmin Häuptle[12], Veronika Blum[13], Stefanie Hayoz[14], Katrin Gobat[14], Laetitia A. Mauti[5], Ilaria Alborelli[15], Spasenija Savic Prince[35], Sacha I. Rothschild[1,6]

[1]University Hospital Basel, Department of Medical Oncology, Basel, [2]University Hospital Bern, Inselspital, Department of Oncology, Bern, [3]University of Bern, Medical Faculty, [4]Cantonal Hospital St. Gallen, Department of Oncology and Hematology, St. Gallen, [5]Cantonal Hospital Winterthur, Department of Oncology, Winterthur, [6]Cantonal Hospital Baden, Department of Oncology and Hematology, Baden, [7]Univesity of Bern, Institute of Tissue Medicine and Pathology, Bern, [8]Oncology Institute of Southern Switzerland, Locarno, [9]Cantonal Hospital Graubünden, Division of Oncology/Hematology, Chur, [10]Università della Svizzera Italiana, Faculty of Biomedical Sciences, Lugano, [11]HFR Fribourg – Hôpital fribourgeois, Department of Oncology, Fribourg, [12]Cantonal Hospital Baselland, Division of Oncology/Hematology, Liestal, [13]Cantonal Hospital Lucerne, Department of Oncology, Luzern, [14]Swiss Cancer institute, Competence Center, Bern, [15]University Hospital Basel, Institute of Medical Genetics and Pathology, Basel

*these authors contributed equally for first authorship / #these authors contributed equally for last authorship

Background

For patients with extensive disease small cell lung cancer (ED-SCLC), combined chemo-immunotherapy is the standard first-line therapy. Currently, the most widely accepted subtype of SCLC is based on the expression levels of mammalian achaete-scute homolog-1 (MASH1), neurogenic differentiation factor 1 (NEUROD1), and POU class 2 homeobox 3 (POU2F3). Additionally, lower expression of Schlafen 11 (SLFN11) has been reported to correlate with worse prognosis and emerged as a predictive marker to several drugs, but its predictive role to chemo-immunotherapy stills needs to be elucidated. In this study we investigate the outcome after chemo-immunotherapy based on immunohistochemical SCLC subgroups, SLFN11 expression and RNA-based T cell receptor (TCR) analyses.

Methods

Patients with ED-SCLC who received first-line ICI in combination with platinum-based chemotherapy at **10 cancer centers in Switzerland** were included in this retrospective analysis. Initial tumor biopsies were centrally collected. Immunohistochemical analysis for **MASH1**, **NEUROD1**, **PO2F3** and **SLFN11** was performed using standard protocols. Total RNA was extracted and used for **TCR sequencing** with the Oncomine TCR SR Assays. Molecular subtypes, **TCR evenness**, **Shannon diversity**, and **number of clones** were analyzed and the association between the mentioned variables and progression-free survival (PFS), overall survival (OS) and overall response rate (ORR) was investigated using Cox regression models and Kruskal-Wallis tests.

Results

Variabel	n=20, n (%)
POU2F3	
Negative	17 (85.0)
Positive	0 (0.0)
Missing	3 (15.0)
MASH1	
Negative	4 (20.0)
Positive	15 (75.0)
Missing	1 (5.0)
NEUROD1	
Negative	16 (80.0)
Positive	3 (15.0)
Missing	1 (5.0)
SLFN11	
Negative	7 (35.0)
Positive	11 (55.0)
Missing	2 (10.0)

Variable	n=14 median (min, max)
Clones	648.5 (82.0, 6460.0)
Shannon diversity	8.4 (5.9, 11.1)
Evenness	0.9 (0.8, 1.0)

Variable	n=18 median (min, max)
SLFN11 IHC: % stained nuclei	27.5 (0.0, 90.0)

Table 1: Summary of immunohistochemistry variables

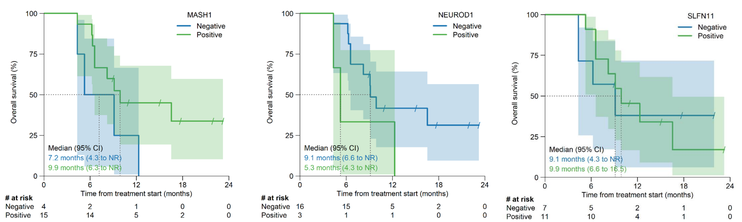

Figure 1: Kaplan-Meier plots for OS by MASH1, NEUROD1 and SLFN11

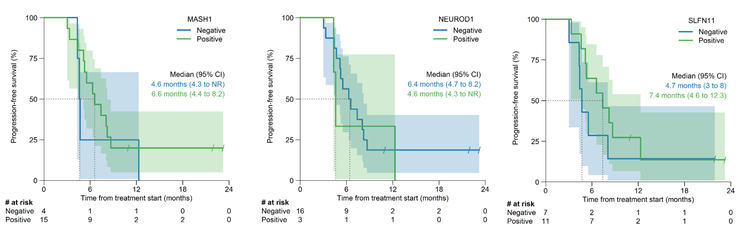

Figure 2: Kaplan-Meier plots for PFS by MASH1, NEUROD1 and SLFN11

Variable	Non responder median (min, max)	Responder median (min, max)	p-value (Kruskal-Wallis Test)
N° of clones	1587.0 (543.0, 2953.0)	571.0 (82.0, 6460.0)	0.31
Shannon diversity	9.6 (8.3, 11.1)	8.2 (5.9, 10.6)	0.14
Eveness	0.9 (0.9, 1.0)	0.9 (0.8, 1.0)	0.59
SLFN11 IHC % stained nuclei	10 (0.0, 70.0)	30 (0.0, 90.0)	0.43

Table 2: Summary of TCR and immunohistochemistry variables by ORR, continuous

Variable	HR (95% CI)	p-value
MASH1	0.37 (0.11 - 1.25)	0.110
NEUROD1	2.85 (0.76 - 10.69)	0.121
TCR Evenness	778310.35 (0.0014 - 4.262252E+14)	0.186

Table 3: Univariable cox regression models for OS by TCR and immunohistochemistry variables

201 patients were included between October 2018 and October 2021. Tumor tissue is available for 60 patients. So far, we have analyzed the tumor tissue of 20 patients. **Patient characteristics of the patients included in this analysis do not differ from the overall population.** Expression of MASH1 (p=0.110), lack of expression of NEUROD1 (p=0.121) and TCR eveness (p=0.186) show a trend towards longer overall survival with chemo-immunotherapy. A lower number of TCR clones (p=0.31) and Shannon diversity (p=0.14) show a trend to a higher overall response rate. SLF11 is expressed in 55% of samples and the subgroup of patients with SLFN11 expressed shows higher overall response rate (40% vs. 69%, p=0.33).

Conclusions

Immunohistochemical subgroups and T cell repertoire diversity are possible factors influencing outcome under chemo-immunotherapy.
Analyses of further tissue samples of the cohort is ongoing and results will be published at a later timepoint.

SOHC SWISS ONCOLOGY & HEMATOLOGY CONGRESS

Poster #8257: Presented at SOHC 2025

Contact: nuria.zellweger@usb.ch, sacha.rothschild@ksb.ch