Comparison of pulmonary versus extra-pulmonary small cell neuroendocrine carcinomas demonstrate distinct genomic alterations

Poster # B16

Mohamed, A[1], Teslow, E[2], Jaeger, E[2], Stoppler, M[2], Asa, SL[1], Tirumani, SH[1], Qiubai, Li[1], Mahipal, A[1], Bajor, D[1], Chakrabarti, S[1], Selfridge, JE[1], Lumish, M[1],Conces, M[1], Hoehn, RS[1], Winter, J[1], Ammori, J[1], Hardacre, J[1], Henke, LE[1], Dowlati, A[1]

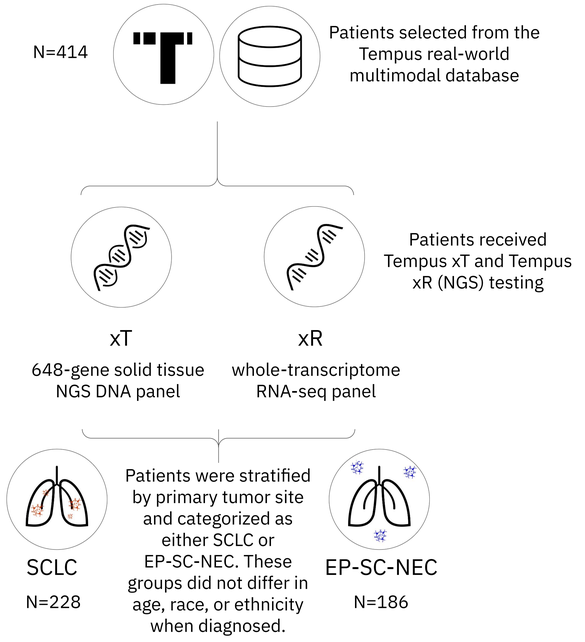
[1] University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH, [2] Tempus AI, Inc., Chicago, IL

INTRODUCTION

Small cell neuroendocrine carcinomas (SC-NECs) are uncommon but aggressive tumors with poor prognosis. Although both small cell lung cancer (SCLC) and extra-pulmonary small cell NEC (EP-SC-NEC) have similar histological and morphological characteristics, whether they are biologically distinct is still unknown. We assessed and compared the genomic profiles of SCLC and EP-SC-NECs to identify distinct mutations that may allow for more personalized therapeutic options.

METHODS

In this retrospective study, patients with a histological diagnosis of SC-NEC were selected from the de-identified Tempus real-world multimodal database and stratified by primary tumor site and categorized as SCLC or EP-SC-NEC. Patients received Tempus xT and xR NGS testing.



Patient demographic/clinical characteristics and genomic data were described as N (%) or median (IQR), min, and max and compared between groups by Chi-squared/Fisher's Exact tests or Wilcoxon rank-sum tests. The prevalence of somatic mutations (SNVs, CNVs, and fusions) was compared similarly, with a false-discovery rate correction for multiple comparisons. Analyses were two-sided, with statistical significance evaluated at the 0.05 alpha level.

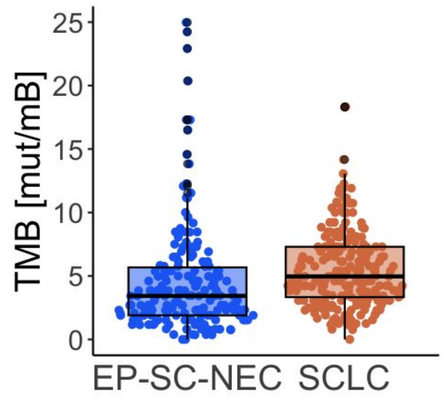
RESULTS

TMB and MSI between pulmonary and EP-SC NEC

SCLC samples had significantly higher median tumor mutational burden (TMB) than EP-SC-NEC samples (5.0 vs 3.4 mut/MB, p<0.001). MSI-H was rare in both groups (SCLC 0.4% vs EP-SC-NEC 2.7%, p=0.10).

Table 1.	Overall, N = 414[1]	EP-SC-NEC, N = 186[1]	SCLC, N = 228[1]	p-value[2]
TMB (mut/Mb)				<0.001
Median (IQR)	4.2 (2.5, 6.9)	3.4 (1.9, 5.8)	5.0 (3.3, 7.3)	
Range	0.0, 103.0	0.0, 103.0	0.0, 73.0	
TMB (mut/Mb)				>0.9
<10	372 (90%)	167 (90%)	205 (90%)	
>=10	42 (10%)	19 (10%)	23 (10%)	
MSI				0.10
Stable	404 (99%)	181 (97%)	223 (100%)	
High	6 (1.5%)	5 (2.7%)	1 (0.4%)	
Unknown	4	0	4	

[1] n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test



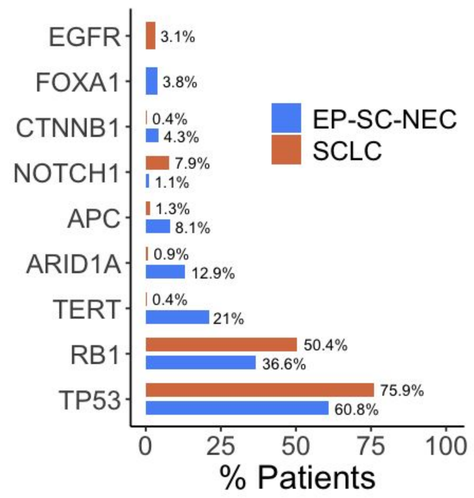
(y-axis truncated at 25 mut/mB)

Somatic short variant alterations between SCLC and EP-SC-NEC

There were significant differences in somatic single nucleotide variants (SNVs) between SCLC and EP-SC-NEC. *TP53*, *RB1*, *EGFR*, and *NOTCH1* mutations were more common and *TERT*, *ARID1A*, *APC*, *FOXA1*, and *CTNNB1* mutations were less common in SCLC (q<0.05). SCLC had significantly fewer *CCNE1* amplifications than EP-SC-NEC. Pathogenic fusions were more frequent in EP-SC-NEC vs SCLC (q<0.001), with 24% of EP-SC-NEC fusions being TMPRSS2-ERG.

Table 2.	EP-SC-NEC, N = 186[1]	SCLC, N = 228[1]	p-value[2]	q-value[3]
TERT	39 (21%)	1 (0.4%)	<0.001	<0.001
ARID1A	24 (13%)	2 (0.9%)	<0.001	<0.001
TP53	113 (61%)	173 (76%)	<0.001	0.006
APC	15 (8.1%)	3 (1.3%)	<0.001	0.006
NOTCH1	2 (1.1%)	18 (7.9%)	0.001	0.006
FOXA1	7 (3.8%)	0 (0%)	0.003	0.014
RB1	68 (37%)	115 (50%)	0.005	0.016
CTNNB1	8 (4.3%)	1 (0.4%)	0.013	0.038
EGFR	0 (0%)	7 (3.1%)	0.018	0.049

[1] n (%)
[2] Pearson's Chi-squared test; Fisher's exact test
[3] False discovery rate correction for multiple testing



SUMMARY

- Despite the histological and morphological overlap between SCLC and EP-SC-NECs, our data revealed heterogeneous molecular characteristics between both groups
- These distinct molecular signatures could impact therapeutic decisions for SC-NEC according to their site of origin

ACKNOWLEDGMENTS

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Correspondence: Amr.Mohamed@uhhospitals.org