Uncovering genomic differences between small and large cell extra-pulmonary neuroendocrine carcinomas

Poster # B18

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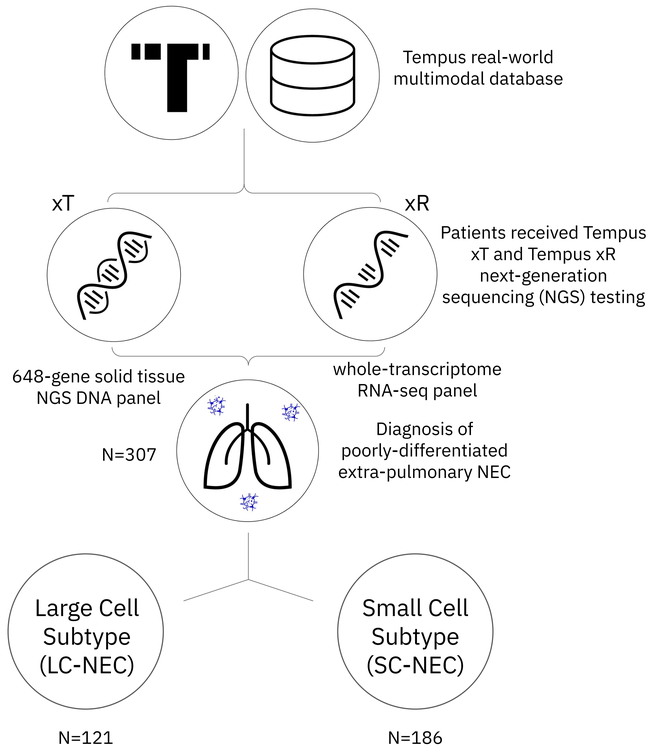
INTRODUCTION

Extra-pulmonary neuroendocrine carcinomas (EP-NECs) are rare and aggressive cancers that include two morphological subtypes: large cell NEC (LC-NEC) and small cell NEC (SC-NEC). Although they are treated with similar chemotherapy regimens, they are distinct diseases, and their genomic profiles have not been compared. We investigated the genomic profile of the extra-pulmonary LC-NEC and SC-NEC to identify mutations that could enable more personalized therapy.

METHODS

In this retrospective study, Patients diagnosed with poorly differentiated extra-pulmonary NECs (LC-NEC and SC-NEC subtypes) were selected from the de-identified Tempus real-world multimodal database. Patients received Tempus xT and xR NGS testing.



Demographic/clinical characteristics and genomic data were described as N (%) or median (IQR), min, and max and compared between subgroups by Chi-squared/Fisher's Exact tests or Wilcoxon rank-sum tests. The prevalence of somatic mutations (SNVs, CNVs, and fusions) was described and 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

Table 1.

Characteristic	LC-NEC, N = 121[1]	SC-NEC, N = 186[1]	p-value[2]	q-value[3]
APC	39 (32%)	15 (8.1%)	<0.001	<0.001
RB1	23 (19%)	68 (37%)	<0.001	0.005
KRAS	26 (21%)	15 (8.1%)	<0.001	0.005
TERT	8 (6.6%)	39 (21%)	<0.001	0.005
BRAF	12 (9.9%)	3 (1.6%)	<0.001	0.005
DAXX	4 (3.3%)	0 (0%)	0.023	0.094
NOTCH1	7 (5.8%)	2 (1.1%)	0.032	0.11
SMARCA4	5 (4.1%)	1 (0.5%)	0.037	0.11
FOXA1	0 (0%)	7 (3.8%)	0.045	0.12
KMT2D	5 (4.1%)	19 (10%)	0.052	0.13
PTEN	5 (4.1%)	17 (9.1%)	0.1	0.2
FBXW7	2 (1.7%)	9 (4.8%)	0.2	0.4
CDKN1A	1 (0.8%)	6 (3.2%)	0.3	0.4
ZFHX3	1 (0.8%)	6 (3.2%)	0.3	0.4
ARID1A	19 (16%)	24 (13%)	0.5	0.7
ARID1B	2 (1.7%)	7 (3.8%)	0.5	0.7
CTNNB1	3 (2.5%)	8 (4.3%)	0.5	0.8
TP53	70 (58%)	113 (61%)	0.6	0.8
PIK3CA	6 (5.0%)	12 (6.5%)	0.6	0.8
CREBBP	8 (6.6%)	10 (5.4%)	0.7	0.8
BRCA2	4 (3.3%)	4 (2.2%)	0.7	0.8
KDM6A	4 (3.3%)	6 (3.2%)	>0.9	>0.9
KMT2C	4 (3.3%)	6 (3.2%)	>0.9	>0.9
PIK3R1	3 (2.5%)	6 (3.2%)	>0.9	>0.9

1 n (%)

2 Pearson's Chi-squared test; Fisher's exact test

3 False discovery rate correction for multiple testing

Figure 1.

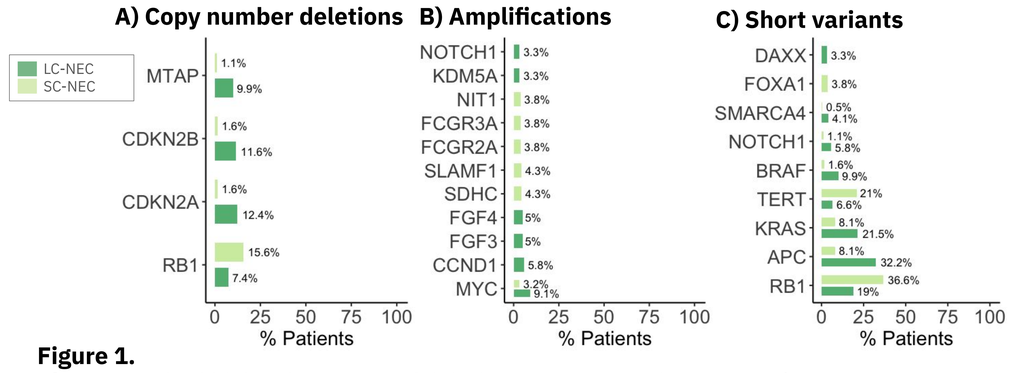


Figure 1.
A) LC-NECs had higher frequency of deletions vs SC-NECs in *CDKN2A* (12% vs 1.6%, q=0.002), *CDKN2B* (12% vs 1.6%, q=0.002), and *MTAP* (9.9% vs 1.1%, q=0.002). SC-NECs had more frequent *RB1* loss compared to LC-NECs, although not significant after correction for multiple testing (16% vs 7.4%, q=0.2).
B) LC-NECs have more common *CCND1*, *FGF3*, *FGF4*, *KDM5A*, *NOTCH1*, and *MYC* amplifications, but less common *SDHC*, *SLAMF1*, *FCGR2A*, *FCGR3A*, and *NIT1* amplifications compared to SC-NECs.
C) Somatic single nucleotide variants (SNVs) in *APC*, *KRAS*, *BRAF*, *DAXX*, *NOTCH1*, and *SMARCA4* mutations were more common in LC-NECs, while *RB1*, *TERT*, and *FOXA1* mutations were more common in SC-NECs.

Figure 2. TMB between LC-NECs and SC-NECs

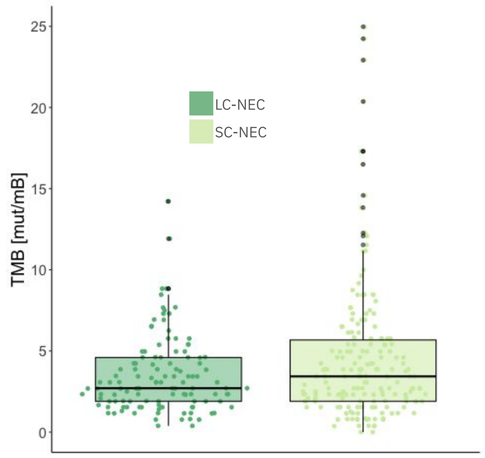


Figure 2.
There were no significant differences in median tumor mutational burden (TMB) between LC and SC-NECs (3.1 vs 3.4 mut/Mb, p=0.2); the majority (92%) had low TMB (<10 mut/Mb).

SUMMARY

- Our results demonstrated that EP-NECs display a broad pattern of genomic alterations according to their histological subtypes.
- These distinct molecular signatures could impact the development of future precision therapeutics for SC-NECs and LC-NECs.

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