Molecular landscape of extra-pulmonary small cell neuroendocrine carcinomas based on site of origin

Poster # B17

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], Conces, M[1], Lumish, M[1], Hoehn, RS[1], Winter, J[1], Ammori, J[1], Hardacre, J[1], Henke, LE[1], Dowlati, A[1]

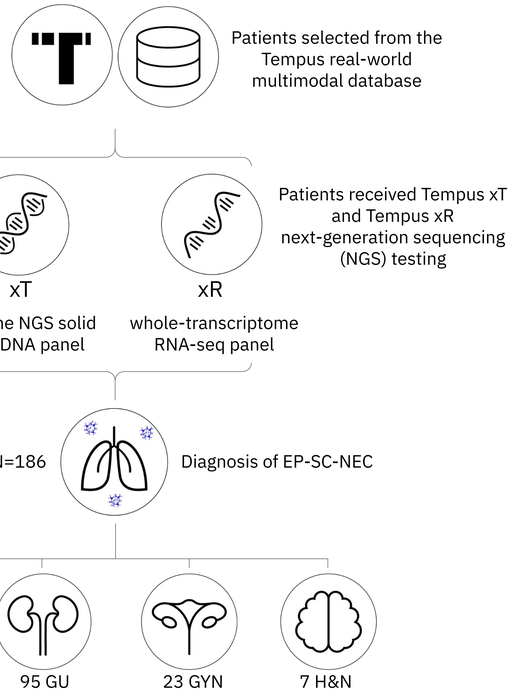
[1] University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH, [2] Tempus AI, Inc., Chicago, IL

INTRODUCTION

Extra-pulmonary small cell neuroendocrine carcinomas (EP-SC-NECs) are uncommon but aggressive malignancies. Although they are treated with similar chemotherapy regimens, their distinct genomic profiles have not been fully explored. We investigated the genomic profile of these tumors to characterize distinct molecular subgroups of EP-SC-NECs and to identify mutations that could enable more personalized therapy.

METHODS

In this retrospective study, patients with a diagnosis of EP-SC-NEC were selected from the de-identified Tempus real-world multimodal database and further stratified by primary tumor site into gastrointestinal (GI), genitourinary (GU), head and neck (H&N), and gynecological origin (GYN). 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 primary tumor site groups by Chi-squared/Fisher's Exact tests or Kruskal-Wallis rank-sum test. The prevalence of somatic mutations, tumor mutational burden high (TMB-H) and MSI high (MSI-H) were 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. TMB and MSI by cancer type in EP-SC-NECs

	Summary					p-values		
	Overall, N = 186[1]	**GI**, N = 61[1]	**GU**, N = 95[1]	**GYN**, N = 23[1]	**H&N**, N = 7[1]	**GI vs. GU**[2]	**GI vs. GYN**	**GI vs. H&N**[3]
TMB (mut/Mb)						0.3	0.026	0.14
Median (IQR)	3.4 (1.9, 5.8)	3.8 (1.9, 5.4)	3.9 (2.3, 6.7)	2.1 (1.0, 3.9)	1.9 (1.2, 3.3)			
Range	0.0, 103.0	0.8, 39.2	0.0, 38.8	0.0, 103.0	0.8, 7.3			
TMB (mut/Mb)						0.4	>0.9	>0.9
<10	167 (90%)	56 (92%)	83 (87%)	21 (91%)	7 (100%)			
>=10	19 (10%)	5 (8.2%)	12 (13%)	2 (8.7%)	0 (0%)			
MSI						0.3	>0.9	>0.9
Stable	181 (97%)	58 (95%)	94 (99%)	22 (96%)	7 (100%)			
High	5 (2.7%)	3 (4.9%)	1 (1.1%)	1 (4.3%)	0 (0%)			

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

Table 2. Somatic short variants and copy number alterations

	GI, N = 61[1]	**GU**, N = 95[1]	**GYN**, N = 23[1]	**H&N**, N = 7[1]	**p-value**[2]	**q-value**[3]
TERT	2 (3.3%)	38 (40%)	0 (0%)	0 (0%)	<0.001	<0.001
TP53	41 (67%)	70 (74%)	3 (13%)	3 (43%)	<0.001	<0.001
KRAS	14 (23%)	1 (1.1%)	1 (4.3%)	0 (0%)	<0.001	0.003
RB1	30 (49%)	60 (63%)	4 (17%)	1 (14%)	<0.001	0.006
SLC35F5	1 (1.6%)	0 (0%)	0 (0%)	2 (29%)	0.002	0.083
RET	4 (6.6%)	1 (1.1%)	3 (13%)	2 (29%)	0.003	0.12
PTEN	2 (3.3%)	21 (22%)	4 (17%)	0 (0%)	0.004	0.12
APC	13 (21%)	4 (4.2%)	1 (4.3%)	0 (0%)	0.005	0.12
ABI1	0 (0%)	0 (0%)	2 (8.7%)	1 (14%)	0.005	0.12
GATA3	0 (0%)	0 (0%)	2 (8.7%)	1 (14%)	0.005	0.12
IL2RA	0 (0%)	0 (0%)	2 (8.7%)	1 (14%)	0.005	0.12
PIK3R1	6 (9.8%)	0 (0%)	2 (8.7%)	0 (0%)	0.007	0.14
CUX1	0 (0%)	0 (0%)	1 (4.3%)	1 (14%)	0.011	0.2
ERCC6	0 (0%)	0 (0%)	1 (4.3%)	1 (14%)	0.011	0.2
PALB2	0 (0%)	0 (0%)	1 (4.3%)	1 (14%)	0.011	0.2
PAX8	2 (3.3%)	1 (1.1%)	0 (0%)	2 (29%)	0.014	0.2

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

Figure 1. Genes with q-value ≤ 0.05

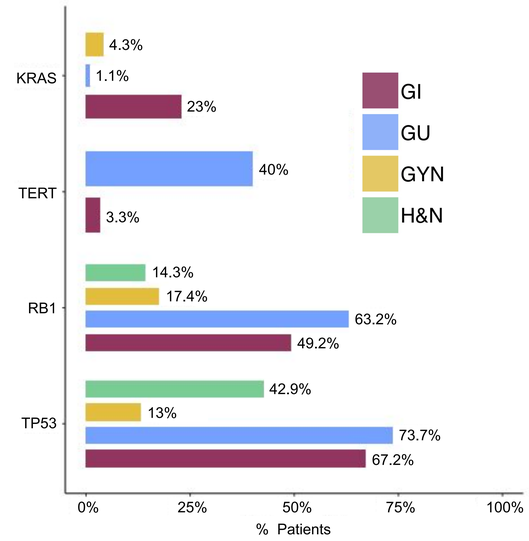


Table 1. GI and GU SC-NECs have higher median TMB, and results were significant when comparing GI to GYN SC-NECs (3.8 vs 2.1 mut/MB, p=0.026). MSI-H was rare in all groups, with no significant differences (p>0.9).

Table 2. There were differences in copy number alterations among the four groups, with H&N having the highest frequency of *PAX8*, *RET*, and *SLC3F5* deletions, while GYN and H&N SC-NECs had higher rates of *CDKN1B* amplification. However, these were not significant after correction for multiple testing.

TP53 and *RB1* mutations differed between cancer types and were more frequent in GI and GU compared to GYN and H&N SC-NECs (q<0.001 and 0.006, respectively).

KRAS and *APC* mutations differed between cancer types and were more frequent in GI (q=0.003 and 0.12, respectively), while GU SC-NECs had more *TERT* mutations compared to other groups (q<0.001). Also shown in **Figure 1.**

SUMMARY

- Our results demonstrated that EP-SC-NEC possess distinct heterogeneous genomic profiles associated with different primary origins despite their histological and morphological similarities.
- These distinct molecular signatures could impact precision therapeutic decisions for EP-SC-NEC according to their primary site of origin.

ACKNOWLEDGMENTS
We thank Dana DeSantis from the Tempus Science Communications team for poster development.

Correspondence:
Amr.Mohamed@uhhospitals.org