Abstract: 3121

Unmasking High-Grade Neuroendocrine Carcinoma (HGNEC) Biology across tumor types Through Transcriptomic Profiling and validation in lung cancer

Yatian Yang[1], Nishant Gandhi[1], Andrew Elliott[1], Priya Vaidiswaran[2], Sonam Puri[3], Triparna Sen[4], Anish Thomas[5], Stephen V. Liu[6], Balazs Halmos[7], Hossein Borghaei[2], **Parth Desai[2]**

[1] Caris Life Sciences, Phoenix, AZ 85040, USA, [2] **Fox Chase Cancer Center, Philadelphia, PA 19111, USA** , [3] Moffitt Cancer Center, Tampa, FL 33612, USA, [4] The Ohio State University Wexner Medical Center, Columbus, OH 43210, USA, [5] National Cancer Institute, Bethesda, MD 20892, USA, [6] Georgetown University, Washington, DC 20007, USA,[7] Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY 10461, USA

BACKGROUND

- High-grade neuroendocrine carcinomas (HGNECs), including SCLC and LCNEC, are aggressive tumors with high metastatic potential, rapid proliferation, and poor survival outcomes.
- Many HGNECs outside classical SCLC are difficult to identify using routine morphology and neuroendocrine immunohistochemistry alone, leading to potential under-recognition or misclassification.
- Transcriptomic profiling may identify occult HGNEC-like tumors across cancer types and uncover biologically aggressive, therapeutically targetable neuroendocrine programs such as DLL3 and SEZ6.

STUDY OBJECTIVES

- To assess the utility of transcriptome-based approach to identify previously misclassified HGNECs.
- To characterize the clinical behavior of these transcriptomically re-annotated HGNECs compared to other tumors within their respective histology and in overall cohort.
- To evaluate mRNA expression of clinical HGNEC targets

METHODS

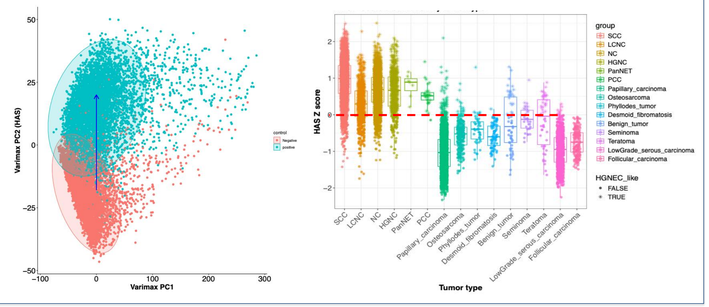
- A total of 49,144 tumors underwent paired DNA and RNA sequencing using the Caris Life Sciences molecular profiling platform. A weighted z-score–based HGNEC activity score (HAS) was developed using 5600 pathologically defined neuroendocrine carcinomas/tumors (pan-cancer dataset).
- Principal component analysis and transcriptomic projection approaches were used to identify SCN/HGNEC-like tumors across NSCLC histologic subtypes **lacking a pathologic (morpho/immunohistochemical) neuroendocrine carcinoma/tumor diagnosis.**
- Clinicopathologic features, overall survival, genomic alterations, proliferation signatures, immune pathways, and expression of neuroendocrine therapeutic targets (DLL3, SEZ6, SSTR2) were compared between HGNEC-like and non-HGNEC-like tumors.

RESULTS

Generation of HGNEC score from CARIS transcriptome (Pan-cancer) cohort

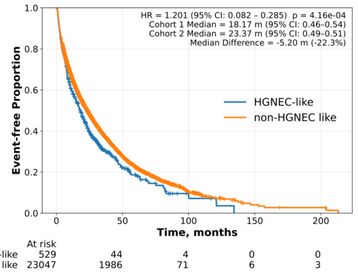
Negative control		
Cancer type	**Histology**	**#**
Bladder Cancer	Papillary Carcinoma	2740
Bone Cancer	Osteosarcoma	271
Breast	Phyllodes Tumor	46
Connective Tissue	Desmoid Fibromatosis	82
Head and Neck	Benign Tumor	59
Testicular Cancer	Seminoma	34
Non Epithelial Ovarian Cancer (non-EOC)	Teratoma	50
Ovarian Surface Epithelial Carcinomas	Low-Grade Serous Carcinoma	1017
Thyroid Carcinoma- Follicular	Follicular Carcinoma	182
	total	4481

Positive control		
Cancer type	**Histology**	**#**
Lung Non-small Cell Lung Cancer (NSCLC)	Small Cell Carcinoma,SCC	2469
Lung Non-small Cell Lung Cancer (NSCLC)	Large Cell Neuroendocrine Carcinoma,LCNC	677
Neuroendocrine Tumors	Neuroendocrine Carcinoma,NC	1929
Neuroendocrine Tumors	High-Grade Neuroendocrine Carcinoma,HGNC	547
Neuroendocrine Tumors	Pheochromocytoma, PCC	27
Neuroendocrine Tumors	Pancreatic Neuroendocrine Tumor, PanNET	7
	total	5656



Real world survival outcomes of transcriptome defined HGNEC-like tumors across NSCLC histological subtypes

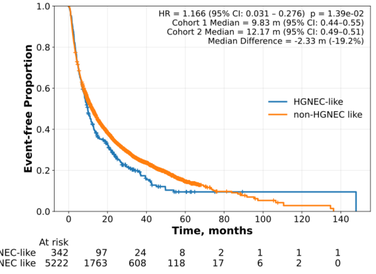
Non-squamous NSCLC (HAS cut-off Z=3)
HGNEC-like (3%) mOS – 18.17m
Non-HGNEC-like mOS- 23.37m



At risk

HGNEC-like	529	44	4	0	0	
non-HGNEC like	23047	1986	71	6	3	

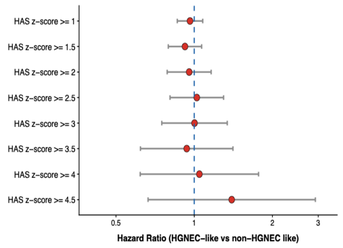
NSCLC-NOS-Mixed HAS cut-off Z=1
HGNEC-like (6%) mOS – 9.83m
Non-HGNEC-like mOS- 12.17m



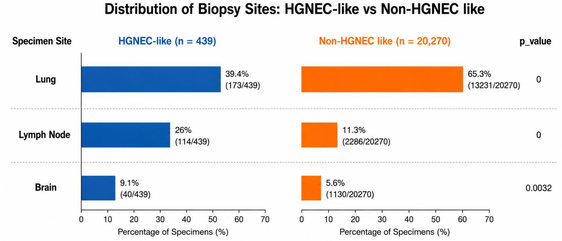
At risk

HGNEC-like	342	97	24	8	2	1	1	1
non-HGNEC like	5222	1763	608	118	17	6	2	0

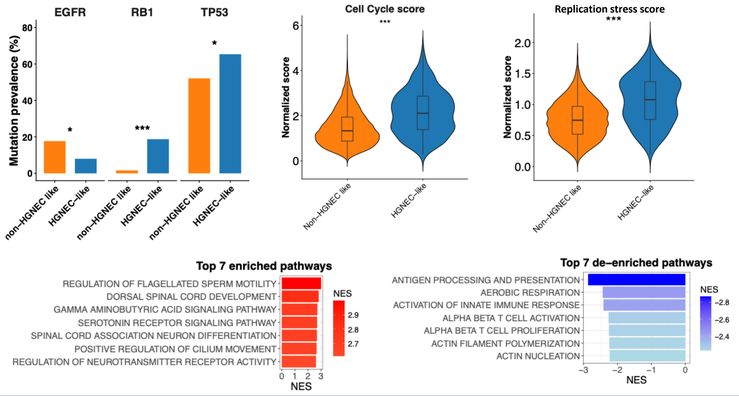
NSCLC- Squamous/Basaloid
No HAS cut-off with survival differences



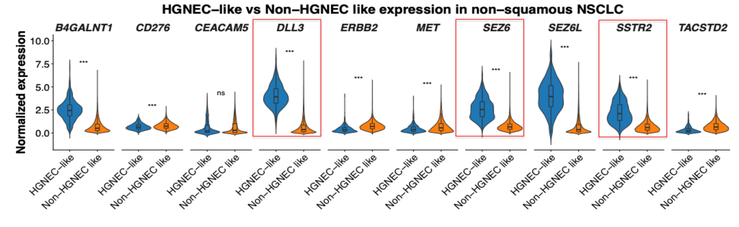
Clinical Features	Non-HGNEC-like	HGNEC like
Age	69 years	68 years
Male: Female	50.3 : 49.7	46.7: 53.3
Smoking Status		
Current/Prior	99%	99%
Lifelong Never smoker	0.8%	0.6%
Race		
Caucasian	76%	77%
African American	8%	9%
Hispanic	9%	8%



Mutational and biological profile of HGNEC-like Non-squamous NSCLC



Gene expression (transcriptomic) of clinically actionable targets



CONCLUSIONS

- **Transcriptomics identifies a hidden HGNEC-like subset within non-squamous and mixed/NOS NSCLC (not defined as NEC by usual morphology/immunohistochemistry pathway).**
- **HGNEC-like NSCLC has worse clinical outcomes (Non-squamous, mixed).**
- **Biology resembles SCLC (higher incidence of *TP53*, *RB1* LOF mutations, high replication stress and cell cycling rate).**
- **Higher *DLL3*, *SEZ6*, and *SSTR2* expression support transcriptomic stratification for NEC/SCLC-directed clinical trials in future.**