Abstract# 8535

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Genomic and immunologic characterization of large-cell neuroendocrine carcinoma of the lung

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Introduction

- Large-cell neuroendocrine carcinoma (LCNEC) is a rare type of lung cancer consisting of 1-3% of lung cancer cases with a poor prognosis.
- Due to its rarity, molecular characterization of LCNEC is not well elucidated.
- 50-60% of patients present with stage IV disease and no large randomized clinical trial data are available to determine the optimal treatment strategy.
- We aim to understand the genomic and immunologic landscape of LCNEC to identify molecular alterations and relevant biological pathways with potential therapeutic value.

Methods

- Comprehensive molecular profiling including whole exome sequencing (WES), targeted next-generation sequencing (NGS), whole transcriptome sequencing (WTS), and immunohistochemistry (IHC) for PD-L1 (22c3 pharmDx) was performed.
- Tumor mutational burden (TMB) was calculated by counting all non-synonymous missense, nonsense, in-frame insertion/deletion and frameshift mutations found per tumor that had not been previously described as germline alterations.
- LCNEC was categorized as small cell lung cancer (SCLC)-like LCNEC (*TP53/RB1* co-mutated) and non-small-cell lung cancer (NSCLC)-like LCNEC (wild type for one or both of *TP53/RB1*).
- Molecular features of LCNEC were compared among the subcategories and with those of SCLC using the Chi-Square test with Benjamini & Hochberg correction.

@chulkimMD

Results

Table 1. Types of tumor samples included in analysis

Tumor type	Number of samples
LCNEC *	467
SCLC-like LCNEC**	112 (24%)
NCSLC-like LCNEC**	335 (73%)
SCLC	442

* LCNEC Cohort excludes cases with indeterminant results

** See reference for LCNEC subtype definitions (Rekhtman et al. CCR 2016)

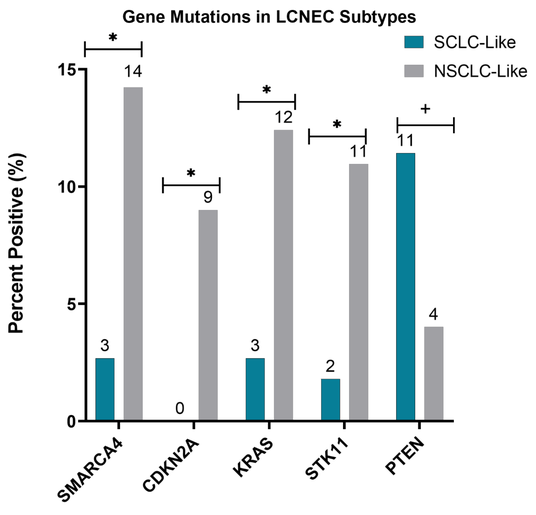
Table 2. Actionable genomic alterations, TMB, and PD-L1 expression in LCNEC

Mutations (types, %)	*EGFR* exon 19 del *	0.48%
	EGFR L858R*	0.48%
	ALK fusion*	1.7%
	KRAS G12C	2.9%
	RET fusion	Not detected
	NTRK fusion	Not detected
	BRAF V600E	Not detected
	MET exon 14 skipping	2.4%
High TMB**	40.6%	
PD-L1 positivity	21.5%	

* Actionable mutations exclusive to NSCLC-like LCNEC

** Defined as ≥ 10 Mut/MB

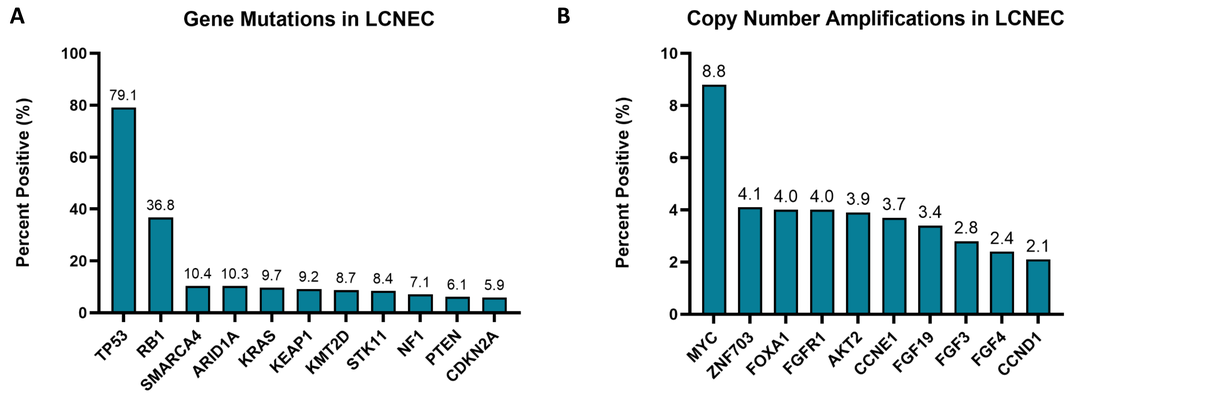
Figure 2. NSCLC-like LCNEC vs. SCLC-like LCNEC



* Denotes q value < 0.05; + Denotes a trend

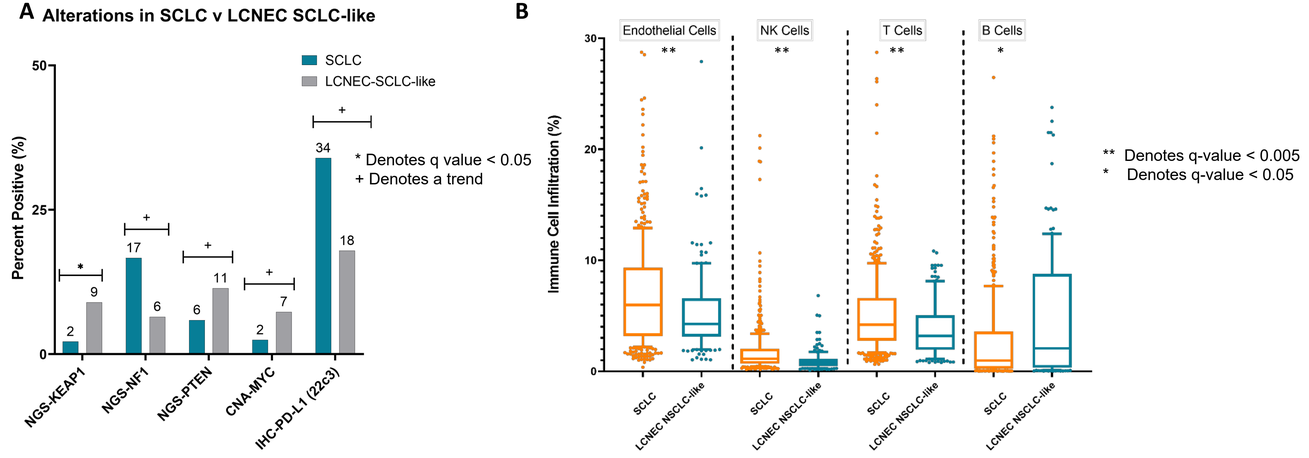
- Compared with SCLC-like LCNEC, mutations in *KRAS*, *STK11*, *SMARCA4*, and *CDKN2A* were more common in NSCLC-like LCNEC (**Figure 2**).

Figure 1. Gene mutations (A) and copy number aberrations (B) in LCNEC



- Alterations described in SCLC and NSCLC were observed in LCNEC with the most common alterations being *TP53/RB1* mutations (**Figure 1A**).
- CNA analysis notable for amplifications of cell-cycle genes, and genes in the AKT/mTOR pathway and the FGF signaling pathway (**Figure 1B**).

Figure 3. Comparison of SCLC vs. SCLC-like LCNEC (A) and evaluation of transcriptome-based immunologic profiles of SCLC vs. NSCLC-like LCNEC



- Molecular analysis showed *KEAP1* mutations enriched in SCLC-like LCNEC compared to SCLC (**Figure 3A**) and distinctive immune gene signatures in LCNEC compared with SCLC (**Figure 3B**).
- Upon re-examination of the data, *SFLN11*:*SFLN12* fusion events in SCLC we reported in the abstract were likely due to an analytical error.

Conclusions

- LCNEC and SCLC share molecular features, but distinct patterns of genomic alterations and transcriptomic profiles were demonstrated.
- These findings present opportunities for therapeutic targeting and inform a future framework for development of therapeutics for LCNEC.

Future Directions

- Comparison of transcriptomic features between LCNEC and SCLC (SCLC-A, N, Y, P).
- Understand treatment outcomes of LCNEC and predictors of response to various treatments including immunotherapy.