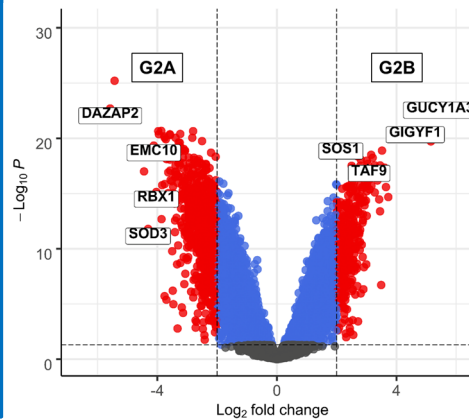


## Background:

In the 2021 World Health Organization (WHO) classification of lung cancers, lung neuroendocrine neoplasms (LNENs) are *classified as low-grade, intermediate-grade and high-grade based on mitotic count but not Ki67 index, as for GEP-NENs*. In order to test a hypothetical Ki67-based classification supported by genomic and transcriptomic data, we performed the molecular characterization of a well-known series of LNENs with a very broad range of Ki67 indices.

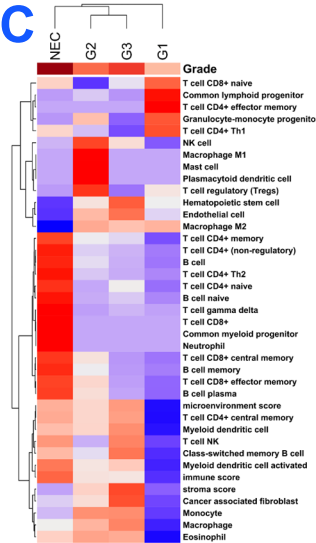
## B



## Methods:

**126 LNENs** were assessed for **transcriptomic and genomic** profiling. Two approaches:  
1) Supervised, grouping samples in 4 categories according their Ki67 index  
2) Unsupervised.

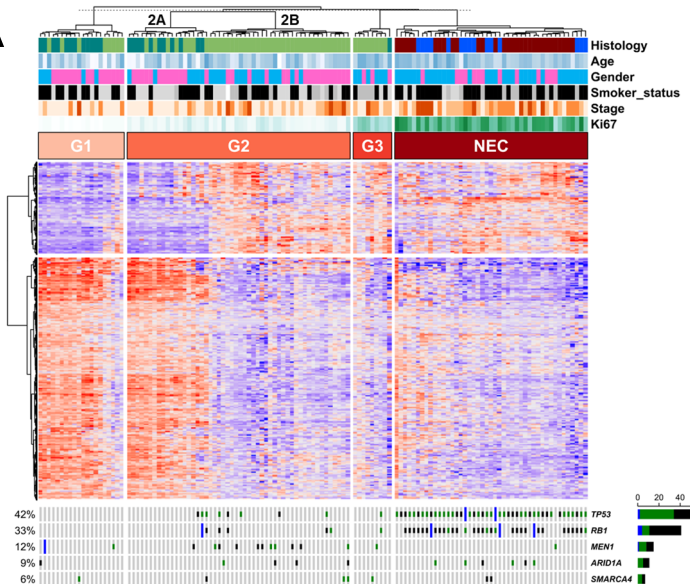
## C



## Conclusions:

- A **transitional molecular entity** ranging from low- to high-grade overcoming Ki67-based classification was observed.
- Molecular features of rare entities such as **LNEN G3** and **supra-carcinoids** were identified.

## A



## Results:

- Increased alteration in **TP53/RB1** genes and **TML** values from G1 to NEC ( $p < 0.001$ ) was observed while alteration in **MEN1** was enriched in the G2 group ( $p = 0.04$ ) (A).
- A **double** transcriptomic profile emerged in the **G2 group**, one related to the G1 and the other to the G3/NEC group (B).
- A secretory environment supported by **CAFs** and inflammatory processes was highlighted in the **G3 group** (C).
- unsupervised approach, identified **3 molecular groups** with a transitional ones characterized by **MEN1** alteration and intermediate survival outcome (D).

## D

