# Identifying proliferative and immune-modulatory drivers of small cell lung cancer (SCLC)

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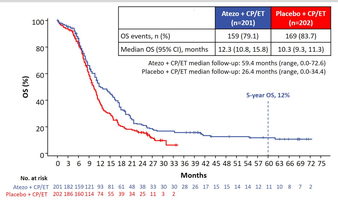
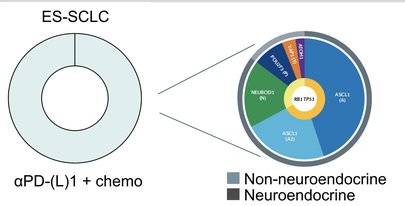
## Small cell lung cancer (SCLC)



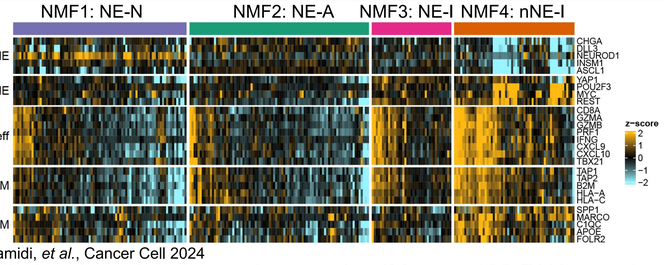

Liu *et al.*, WCLC 2023




Rudin *et al.*, Nature Reviews Disease Primers (2021)

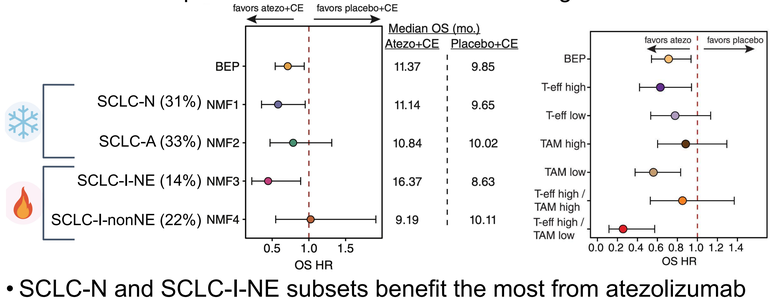
- SCLC is a deadly disease with median OS around 12 months
- SCLC represents ~15% of all lung cancers
- More than 200K patients die from SCLC every year across the globe
- >97% of SCLC patients are former or current smokers
- 70% of patients present as extensive stage (ES) diagnoses (Grade IV)
- ES-SCLC patients receive anti-PD-(L)1 + chemo on all-comer basis
- Atezolizumab is the standard-of-care ICB (66% US market share)
- SCLC subtypes have traditionally been defined using tumor-intrinsic features, such as transcription factor expression
- Key Objectives:
  - Stratify patients by immunotherapy response
  - Reveal the MOA behind immunotherapy response and resistance

## Transcriptional subtyping of SCLC - IMpower133



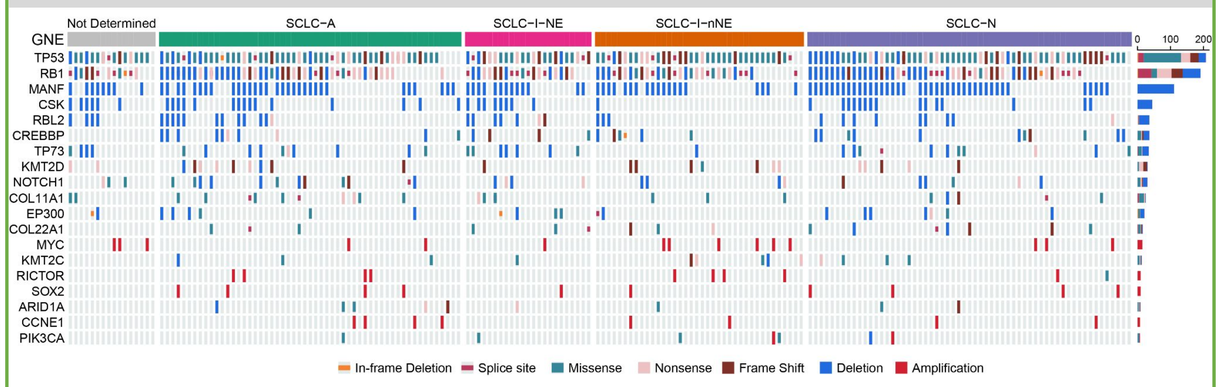

Nabet, Hamidi, *et al.*, Cancer Cell 2024

- Stratified patients into four subsets using IMpower133 RNA-seq data
- SCLC-N and SCLC-A are neuroendocrine (NE) and immune-cold
- Two subsets are immune-inflamed/APM-high and either NE (SCLC-I-NE) or non-neuroendocrine (SCLC-I-nonNE)
- SCLC-I-nonNE patients show enrichment of TAM signature



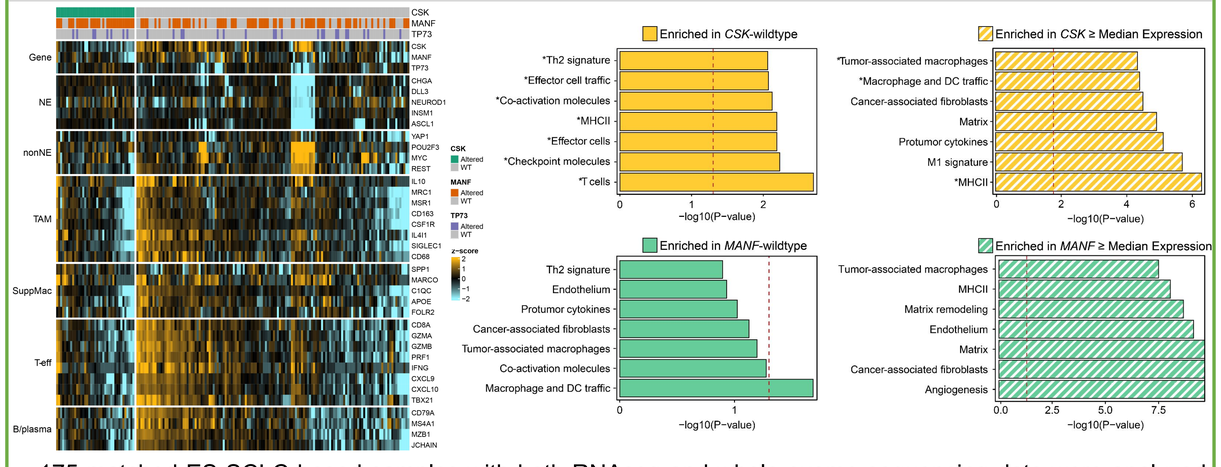

- SCLC-N and SCLC-I-NE subsets benefit the most from atezolizumab
- Tumor-associated macrophage (TAM) signature is associated with limited atezo benefit, even for T-effector signature (T-eff)-high patients

## Whole-exome sequencing analysis of SCLC from IMpower133 (n = 191)




- 191 ES-SCLC baseline samples were profiled for whole-exome sequencing (175 with matched bulk RNAseq)
- Gene alteration frequencies in the IMpower133 ES-SCLC cohort appears similar to previous findings
- Several hits from previously published candidate driver genes, such as *MANF*, *CSK*, and *TP73* from Augert et al. 2020 Cancer Cell study, show high prevalence of copy number loss
- SCLC-I-nonNE exhibit lower frequencies of *CSK* and *TP73* deletion events compared to the other subsets

## SCLC tumors with *MANF* or *CSK* inactivation show depletion of immune signatures




- 175 matched ES-SCLC based samples with both RNAseq and whole-exome sequencing data were analyzed for interactions between immune infiltration, gene expression, and gene alteration status
- Tumors with *CSK* deletion also show lower expression of *CSK* as expected, as well as showing lower expression of non-neuroendocrine genes and immune marker genes
- *MANF*- or *CSK*-competent SCLC tumors, defined as wildtype for genomic alteration or having higher-than-median expression, showed increased enrichment of immune-related signatures
- While *MANF* or *CSK* loss-of-function or lower-than-median expression associated with depletion of immune-related gene signature expression, it did not associate significantly with tumor proliferation signatures

*indicates significant enrichment by both genomic and transcriptomic comparisons

**bars extending beyond graph edge indicates P-value of 0

NE: Neuroendocrine, TAM: Tumor-associated macrophages, SuppMac: Immunosuppressive macrophages, T-eff: T-effector, B/plasma: B/plasma cell signature

## Conclusion

- Genomic landscape of IMpower133 ES-SCLC cohort appears similar as previously published data
- Previously published driver gene candidates such as *MANF*, *CSK*, and *TP73* show high frequency of copy number loss
- SCLC with *MANF* or *CSK* inactivation show decreased expression of immune-related signature genes
- *CSK* and *TP73* inactivation events occur less frequently in non-neuroendocrine SCLC
- Both transcriptomic regulation and somatic alteration of several genes (such as MANF and CSK) may influence the tumor-immune interaction

## Next Steps

- Screen for other candidate driver genes with high alteration frequencies
- Stratify patients by immune infiltration signatures and compare genes that are significantly altered in immune-hot v. -low
- Generation of *MANF*, *CSK*, and *TP73* knockout and overexpression lines in human and mouse SCLC cell lines
- Profile *MANF*, *CSK*, and *TP73*-modulated SCLC lines for changed expression of APM-related genes, MHC I on the cell surface, and cytokine production
- Compare immune infiltration in *MANF*, *CSK*, and *TP73*-modulated mouse SCLC allografts

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