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#P3.03.44: High Frequency of *SMARCA4* Inactivating Mutations in Advanced NSCLC and Their Association with Low PD-L1 Expression

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INTRODUCTION

While immune checkpoint inhibitors (ICI) have significantly improved survival among patients with non-small cell lung cancer (NSCLC), the emergence of resistance mechanisms remains a challenge.

We aim to elucidate the underlying resistance mechanisms by characterizing the genomic and molecular features of tumor immunogenicity in a cohort of NSCLC patients.



METHODS

Patients diagnosed with NSCLC treated with ICI-based strategies at the Catalan Institute of Oncology-ICO Badalona, were prospectively enrolled (ImmunoLung PI-19-275):

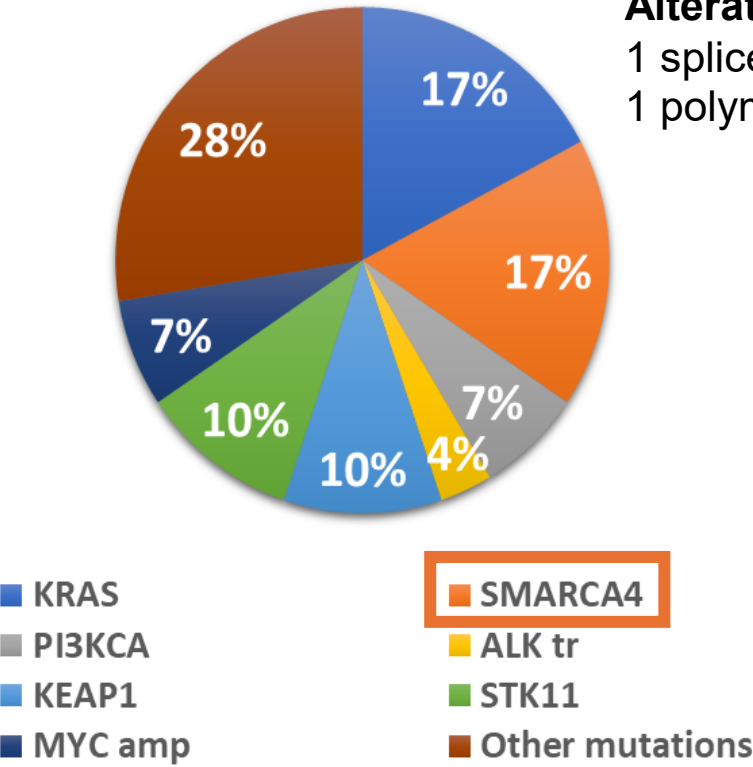
- 48 samples were obtained through flexible bronchoscopy during diagnosis process.
- PD-L1 (SP Ventana 263) immunohistochemistry (IHC) expression was performed in formalin-fixed paraffin-embedded (FFPE) tissues.
- 29 from 48 samples had enough quality material to perform comprehensive tumor genomic profiling: Whole-exome sequencing (WES) and RNA sequencing (RNA-seq) was conducted at the National Center for Genomic Analysis.
- Molecular profiles were associated with clinical outcomes.

RESULTS

1. Patients Characteristics (n=29)

Patients charact.	N=29 (100%)
Age (mean)	66 (43-85) y-old
Gender	
Male	24 (83%)
Female	5 (17%)
Smoking status	
Current/former	27 (93%)
Never	2 (7%)
ECOG PS	
0/1	24 (83%)
2	5 (17%)
Histology	
ADC	16 (55%)
SCC	9 (31%)
NOS	4 (14%)
Stage at diagnosis	
III	12 (40%)
IV	17 (60%)
PDL1 IHC (%)	
Negative/Low (<50%)	21 (75%)
High (≥50%)	7 (25%)
Unknown	1

2. Oncogenic driver mutations and IFNγ related mutations detected in primary lung tumors:

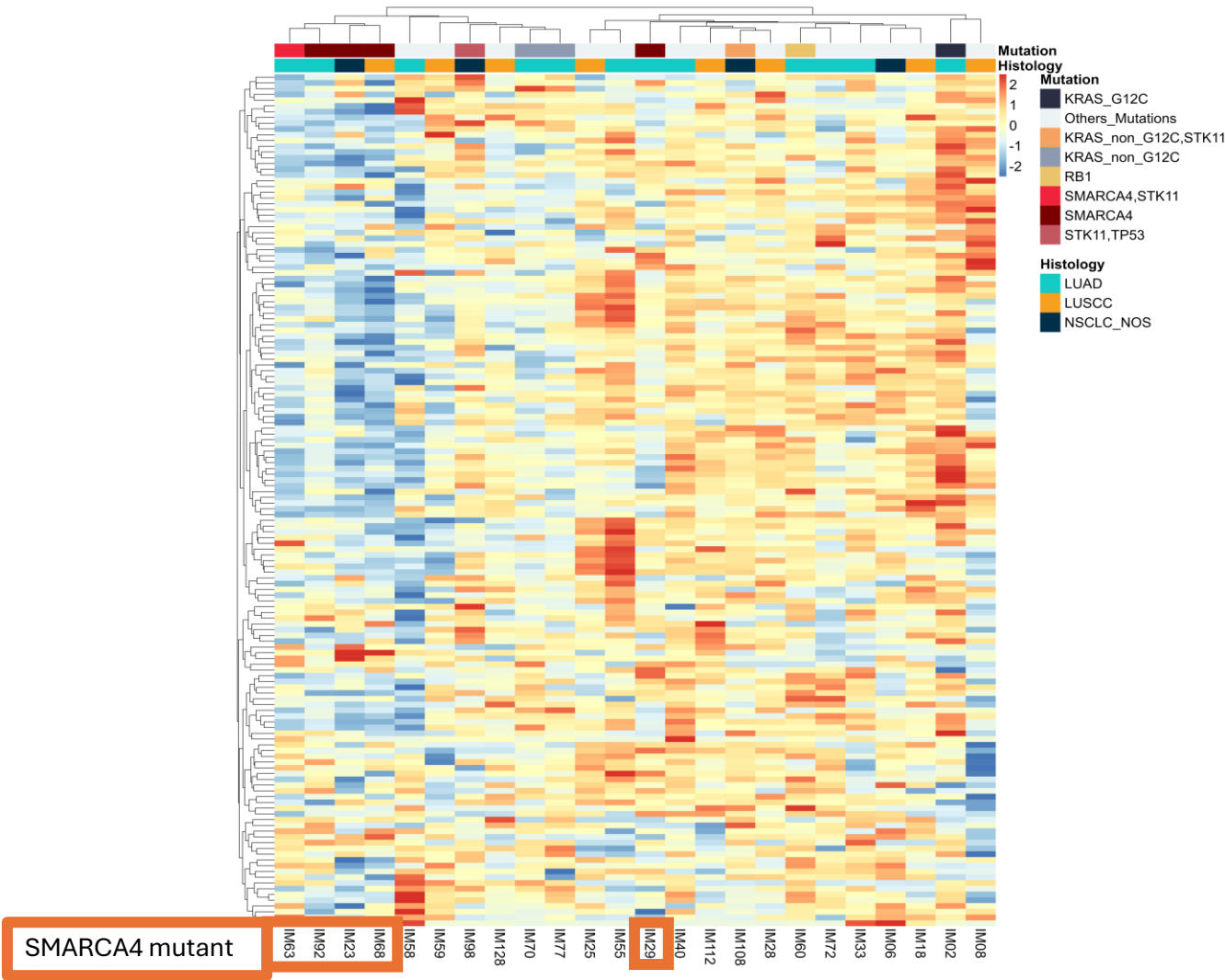


Alterations in the IFNγ signaling pathway:
1 splice site mutation in **JAK2** (c.2131A>G, p.Ile711Val)
1 polymorphism in **TAP2** (c2059T>C, p.Ter687Gln)

We detected **high prevalence (n=5, 17%) of truncating SMARCA4 mut**, a key regulator of chromatin remodeling complex associated with poor cancer prognosis

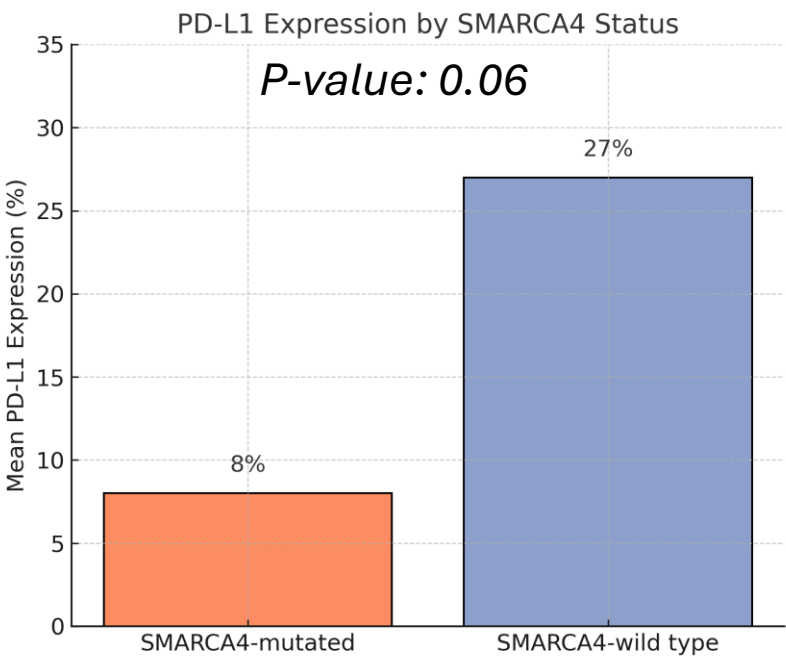
*ADC: Adenocarcinoma, SCC: Squamous cell carcinoma, NOS: Not otherwise specified

3. Heatmap: unsupervised hierarchical clustering of the IFN γ genes in tumor samples

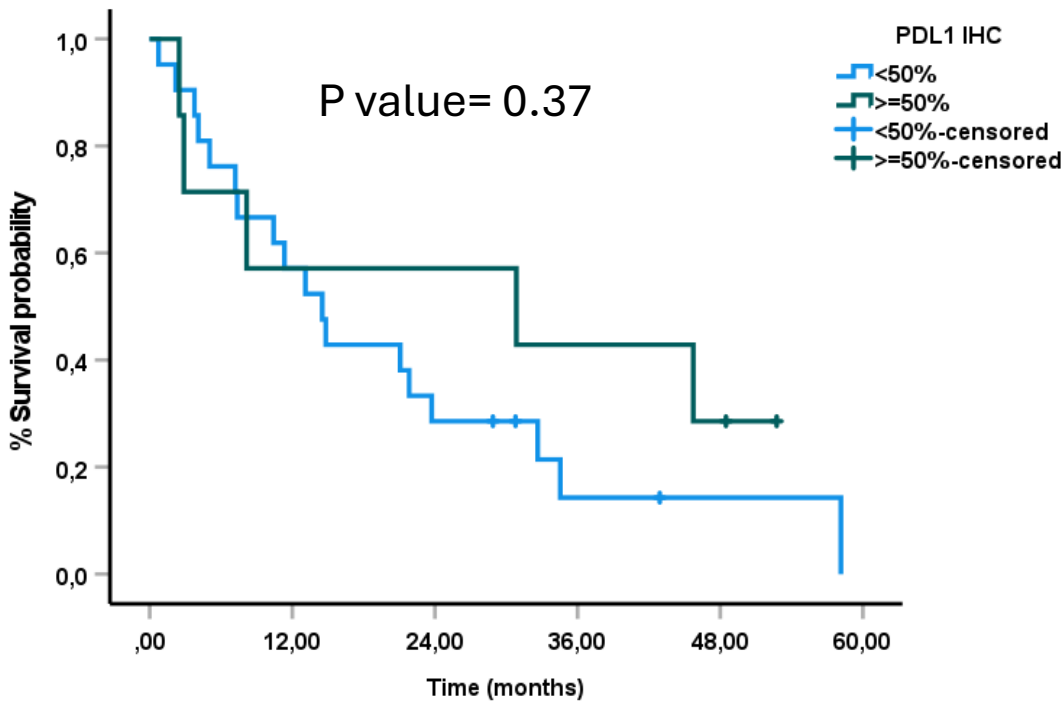


4. PD-L1 expression according to *SMARCA4* mutation

5. Survival curves according to PD-L1 expression



None of the SMARCA4-mutated tumors exhibited high PD-L1 expression, with a mean PD-L1 expression of 8%, compared to 27% in non-SMARCA4-mutated tumors (*p*=0.06)



High PD-L1 expression (≥50%) had a tendency of improved median overall survival (OS) with 30.9 months (95% CI 0-89), compared to 14.5 months (95% CI 9.3-19.7) in tumors with low PD-L1 <50% (*p*=0.37).

CONCLUSIONS

- NSCLC shows significant genomic heterogeneity in tumor immunogenicity.
- Mutations in *SMARCA4*, a key factor of a chromatin remodeling complex, are frequent in advanced NSCLC. These mutations are associated with lower PD-L1 expression, and down-regulation of IFN γ related genes, potentially affecting immune responses to ICI therapy.
- Chromatin remodeling gene alterations, such as *SMARCA4* may serve as predictive biomarkers for ICI response and require further characterization.



REFERENCES

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Thank You



CONQUERING LUNG AND OTHER THORACIC CANCERS WORLDWIDE IN THE 21ST CENTURY