Preexisting tumor host immunity delineates clinical outcomes in resectable NSCLC

Pedro Rocha[1,2], Maite Rodrigo[3], Laura Moliner[1], Alejandro Ríos[1], Laura Masfarré[1], Nil Navarro[1], Silvia Menendez[2], Álvaro Taus[1], Alberto Rodríguez[4], Rafael Aguiló[4], Josep Belda[4], Raúl Del Rey-Vergara[2], Miguel Galindo[2], L. Comerma[3], E. Arriola[1,3]

[1]Medical Oncology, [3]Pathology, [4]Thoracic and Cardiovascular Surgery, University Hospital del Mar, Barcelona, Spain, [2]Cancer Research Program, IMIM, Barcelona, Spain.

Background

- Neoadjuvant and adjuvant immune checkpoints blockade (ICB) have recently shown promising results in resectable NSCLC[1,2]. Yet, biomarkers that inform patient benefit with this approach remain largely unknown[3]. Here, we interrogated the tumor immune microenvironment (TIME) in early-stage NSCLC patients that underwent up-front surgery

Methods

- A total of 185 treatment-naïve early-stage NSCLC patients, that underwent curative surgical treatment between 2006 and 2018 at Hospital del Mar were included. None of the patients received adjuvant immunotherapy **Table1.**
- Core biopsies from the surgical specimens were included in a tissue microarray. Immunohistochemistry of PD-L1, CD3, CD4, CD8, CD68, CD103 and FOXP3 were evaluated by digital image analysis (QuPath software) **Figure 1.**
- TIME was categorized into four groups using PD-L1 expression in tumor cells (<1% or ≥1%) and tumor infiltrating lymphocytes (TILs) based on intratumoral CD3 percentage (cut-off calculated using Youden's index – 26.32%): 1) PD-L1-/TILs -, 2) PD-L1-/TILs+, 3) PD-L1+/TILs-, 4) PD-L1+/TILs+. TIME patterns and immune markers were statistically compared based on clinicopathological and molecular features and survival outcomes.

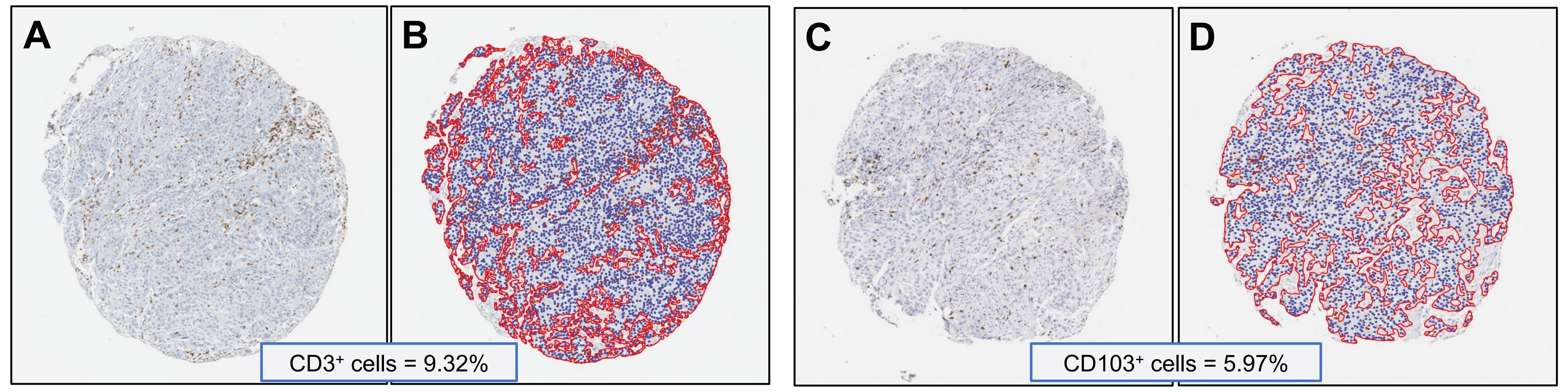

Figure 1. Immunohistochemistry evaluation of CD3 (**A**) and CD103 (**B**). Digital image analysis using QuPath software, showing the correct detection of CD3+ cells (**B**) and CD103+ (**D**). Red line represents the tissue delimitation. Red dots = positive cells, Blue dots = negative cells.

Characteristics	LUADs %(n=124)	LUSCs %(n=61)
Sex		
Male	71% (88)	87% (53)
Female	29% (36)	13% (8)
Age mean (SD)	65 years (9.5)	67 years (8.2)
Smoking status		
Current	43% (53)	54% (33)
Former	40% (49)	44% (27)
Never	17% (21)	1.6% (1)
NA	0.81% (1)	0% (0)
TNM stage		
1	50% (62)	41% (25)
2	19% (24)	39% (24)
3	31% (38)	20% (12)
PD-L1 IHC (SP263)		
<1%	72% (89)	56% (34)
1-49%	8.1% (10)	11% (7)
≥50%	20% (25)	31% (19)
NA	0% (0)	1.6% (1)
Recurrence		
Relapse	31% (38)	31% (19)
Non-recurrence	69% (86)	69% (42)
Exitus		
Dead	32% (40)	56% (34)
Alive	68% (84)	44% (27)

Table 1. Clinicopathological characteristics from the patients included by histology (LUADs, lung adenocarcinoma; LUSCs, lung squamous carcinoma; NA, not available; PD-L1, programmed death-ligand 1)

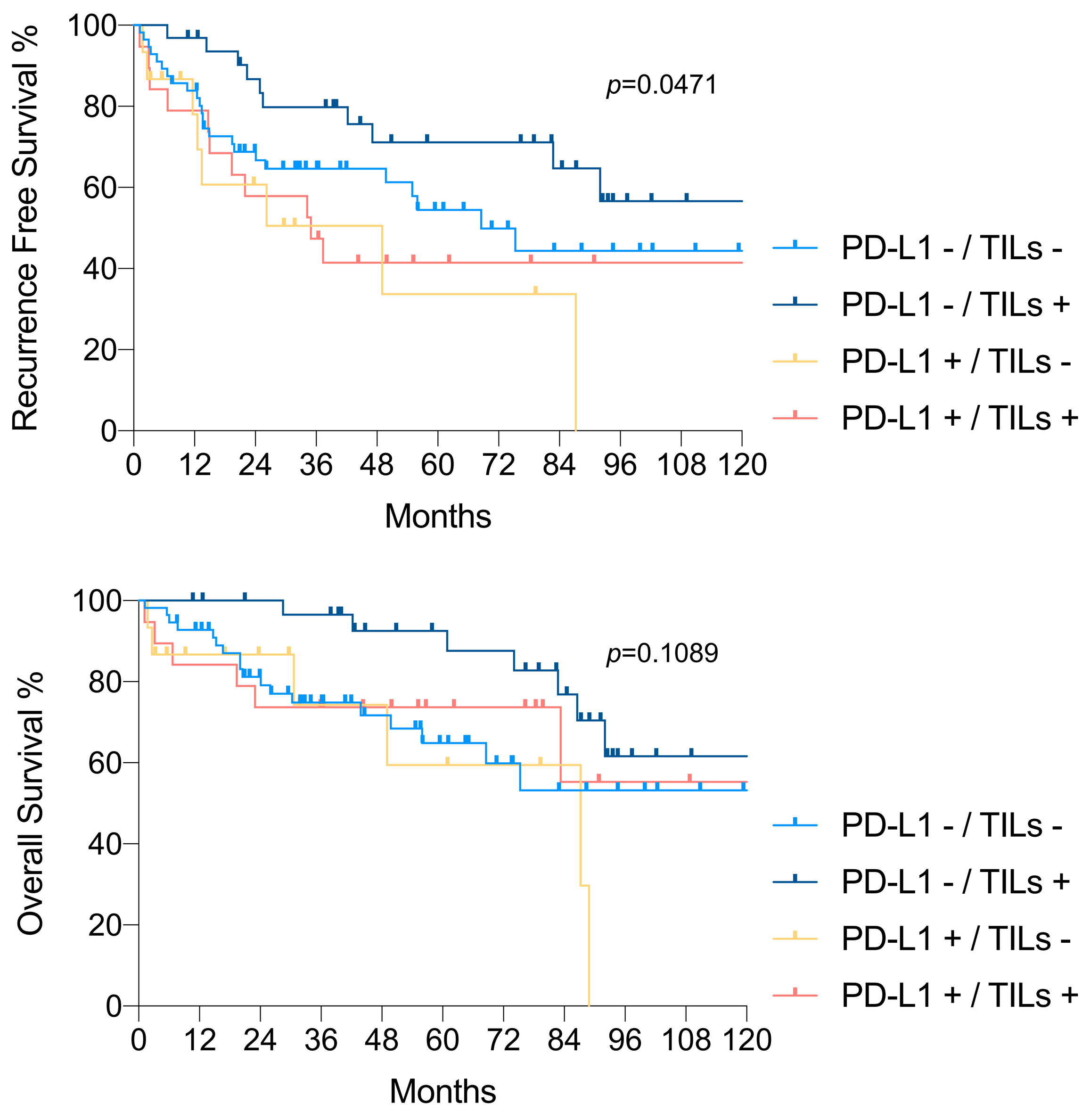

Figure 2. Recurrence free survival and Overall survival Kaplan-meier curves across the four TIME patterns based of PD-L1 tumor expression and intratumor CD3 percentage. PD-L1- and PD-L1+ refers to tumors with <1% and ≥1% of PD-L1 expression. TILs- (<26.32% of intratumor CD3) and TILs+ (≥ 26.32% of intratumor CD3).

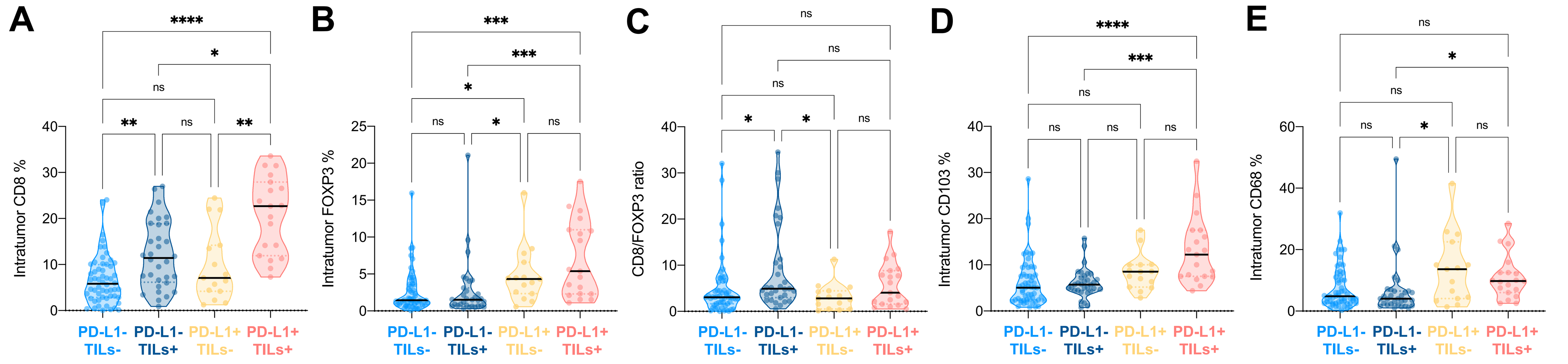

Figure 3. Tumor immune microenvironment (TIME) patterns are characterized by an increase of various immune cells. Violin plots depicting percentage of positive cells for each IHC marker across the four TIME phenotypes. PD-L1- and PD-L1+ refers to tumors with <1% and ≥1% of PD-L1 expression. TILs- (<26.32% of intratumor CD3) and TILs+ (≥ 26.32% of intratumor CD3). P-values were calculated based on the Kruskal-Wallis test, black lines represent median levels, and gray lines correspond to 95% confidence intervals (CIs).*p<0.05; **p<0.001; ***p<0.0001; ns, non-significant.

Results

- PD-L1-/TILs+ tumors showed a reduced risk of relapse compared to PD-L1+/TILs+ (p=0.0471) **Figure 2.**
- PD-L1 +/TILs+ exhibit higher percentage of intratumor $CD8^+$ (cytotoxic T) positive cells compared with the other TIME groups (p<0.05) **Figure 3A**.
- Intratumor FOXP3 $^+$ (regulatory T) positive cells were higher in PD-L1+/TILs+ (p<0.0001) **Figure 3B**.
- Analysis of CD8/FOXP3 ratio showed an increase ratio in PD-L1-/TILs+ tumors (p=0.0109) **Figure 3C**.
- PD-L1 +/TILs+ tumors displayed a higher percentage of intratumor $CD103^+$ (tissue resident memory) positive cells (p<0.0001) **Figure 3D**.
- Intratumor $CD68^+$ (macrophages) positive cells were higher PD-L1+/TILs- tumors (p=0.0055) compared with the other TIME groups **Figure 3E**.

Conclusions

- T cell subpopulations ($CD103^+$, CD8/FOXP3 ratio) exhibited by PD-L1+/TILs+ tumors suggest the potential role of ICB to revert the TIME towards a favorable immune context and thus, improve survival outcomes.
- Tumor immune microenvironment patterns based on tumor PD-L1 expression and the percentage of intratumor $CD3^+$ cells can be used as a tool for tailoring adjuvant strategies.

References

1. E.Felip et al., Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncology. 2021.
2. J. Spicer et al., Surgical outcomes from the phase 3 CheckMate 816 trial: Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer (NSCLC). J. Clin. Oncol. 2021.
3. J. Chaft et al., Evolution of systemic therapy for stages I–III non-metastatic non-small-cell lung cancer. Nature Reviews. 2021.

Poster number:
91P

This work was supported by Instituto de Salud Carlos III (PI19/00003, CIBERONC CB16/12/00241)/FEDER, Generalitat de Catalunya (2017 SGR 507) and unrestricted research funding by Roche. Pedro Rocha is supported by SEOM (Sociedad Española de Oncología Médica) and ESMO (European Society of Medical Oncology).