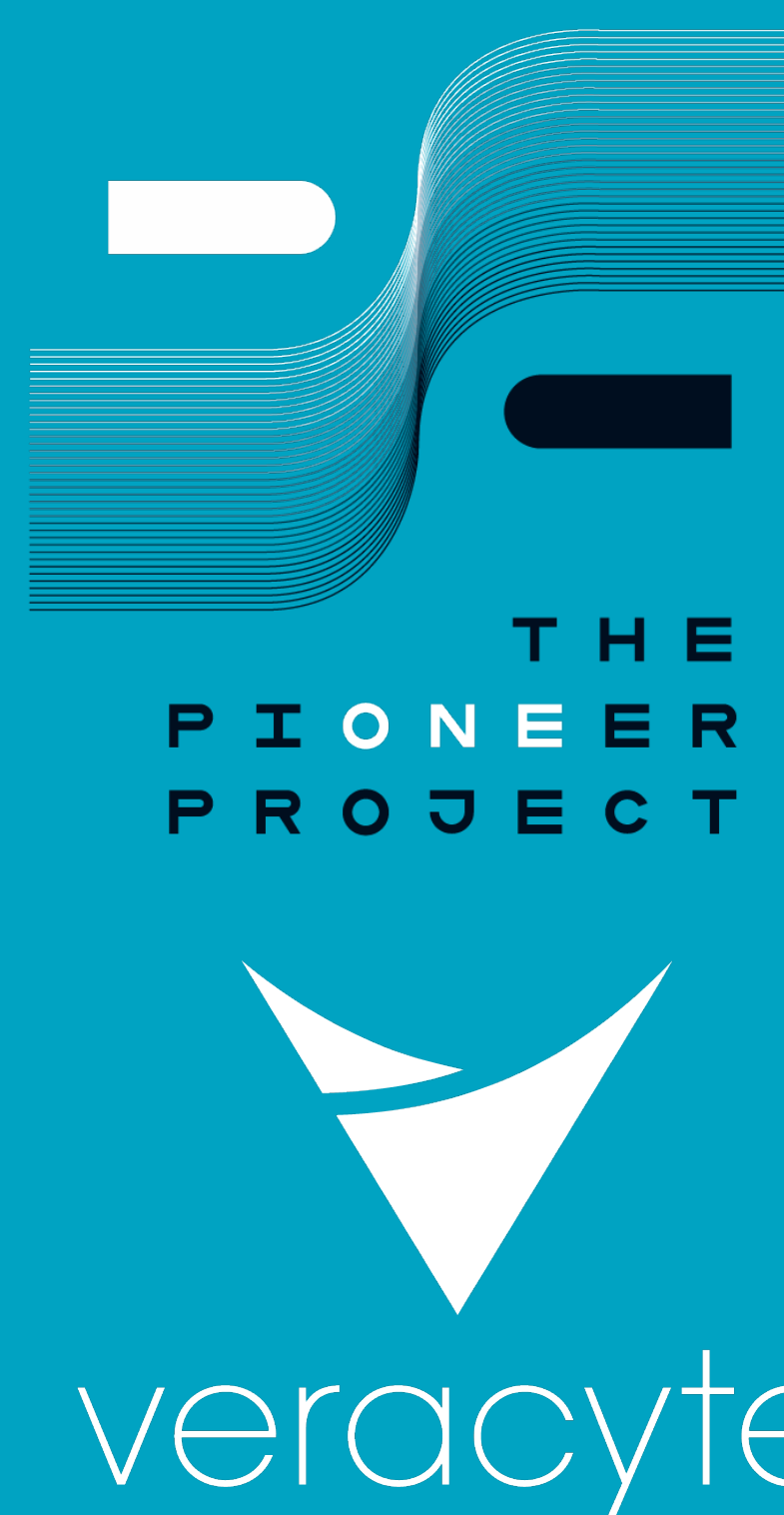


Spatial distribution of infiltrating T lymphocytes with Immunoscore® CR T Cells Exhaustion test helps stratification of NSCLC patients treated with PD1 / PDL1 inhibitors in the PIONeeR project

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Introduction

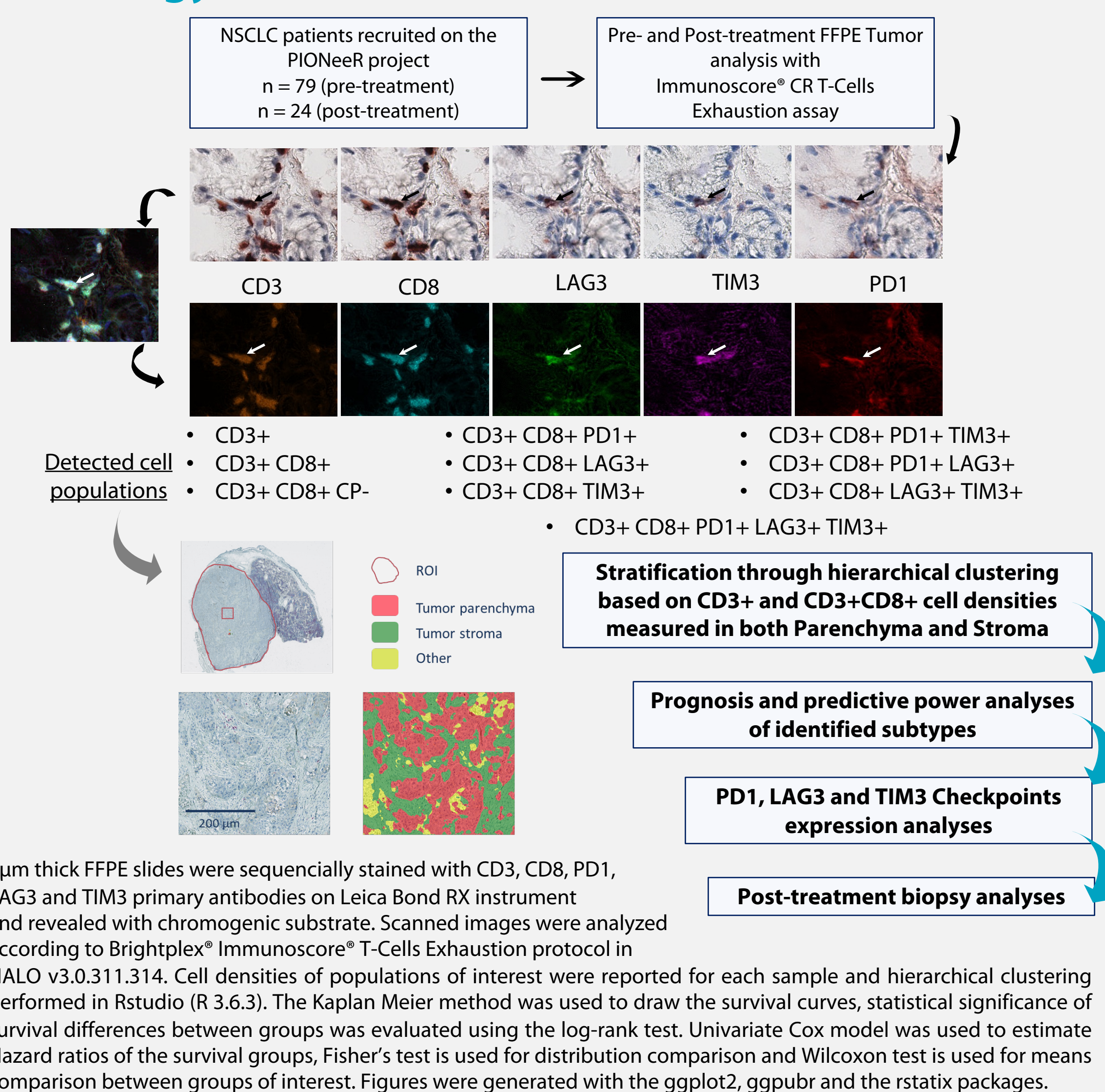
Immune checkpoint inhibitors (ICI), and particularly anti-PD1/L1, improved long-term outcome in ~20% of NSCLC patients, meaning that 80% present primary or secondary resistance and need to be identified at diagnostic to avoid inefficient therapy [1]. To date, neither PD-L1 tumor cell status nor TMB, both approved as companion diagnostics, can efficiently predict resistance.

Tumor-infiltrating lymphocytes (TILs) play a major role in the immune response against malignant cells by infiltrating and interacting with tumor cells to achieve their cytotoxic role.

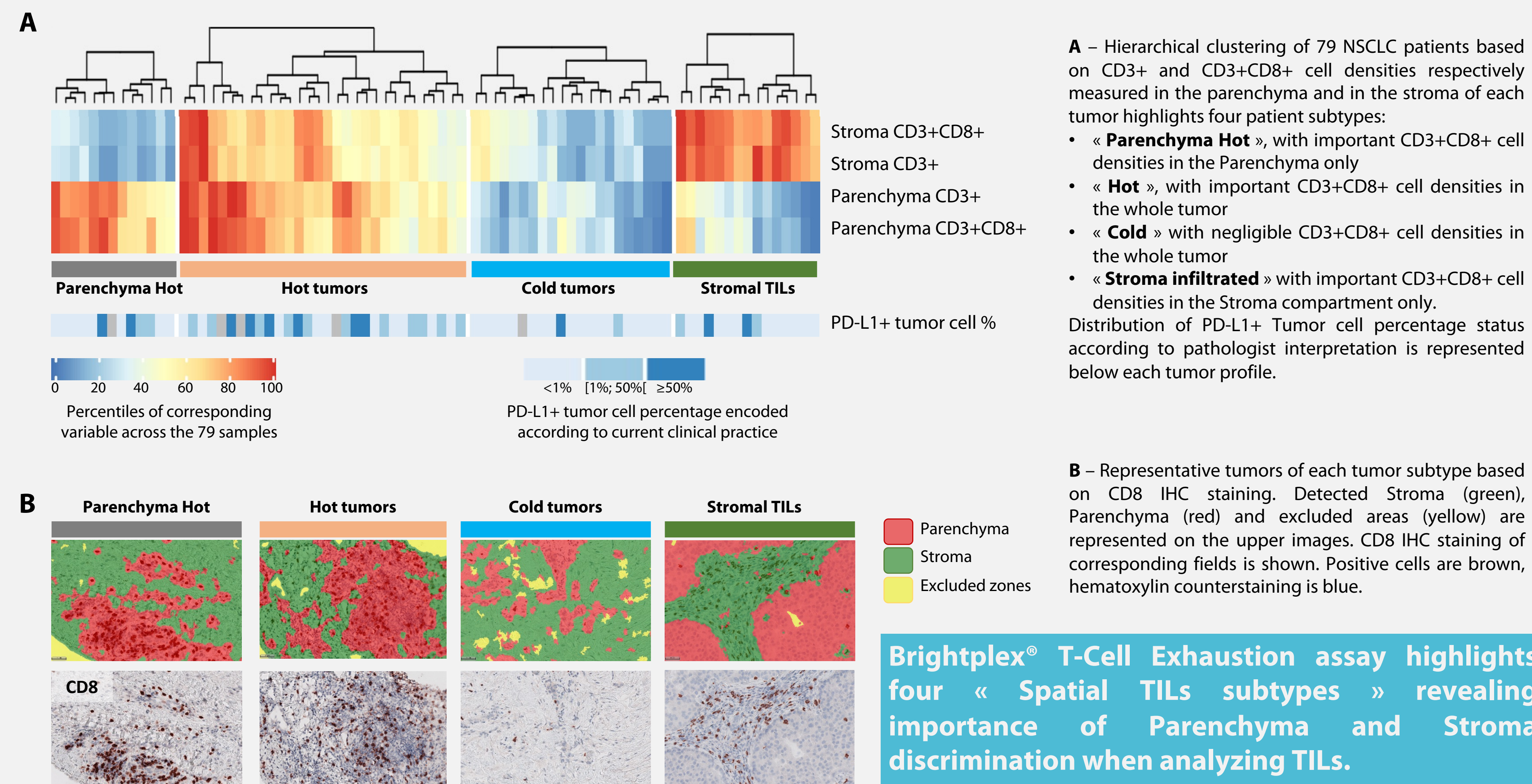
TILs Immune Checkpoints' (CP) expression such as PD1, LAG3 or TIM3 may reflect their anti-tumor activity and be directly involved in response to ICIs through their regulation of T cell activity. Assessing their status within the tumor at diagnostic could help stratifying patients and refine population eligible to ICIs therapy.

The PIONeeR project aims to predict the response/resistance to PD1/L1 ICIs in advanced NSCLC patients through a comprehensive agnostic multiparametric biomarkers assessment. Here, we aim to define clinicopathological implications of activated and exhausted TILs in a cohort of 79 patients through the multiplex immunohistochemistry (IHC) Brightplex® CR T-Cells Exhaustion assay. Among these patients, 24 were re-biopsied 6 weeks after anti-PD1/L1 treatment initiation, allowing comprehensive analysis of treatment action.

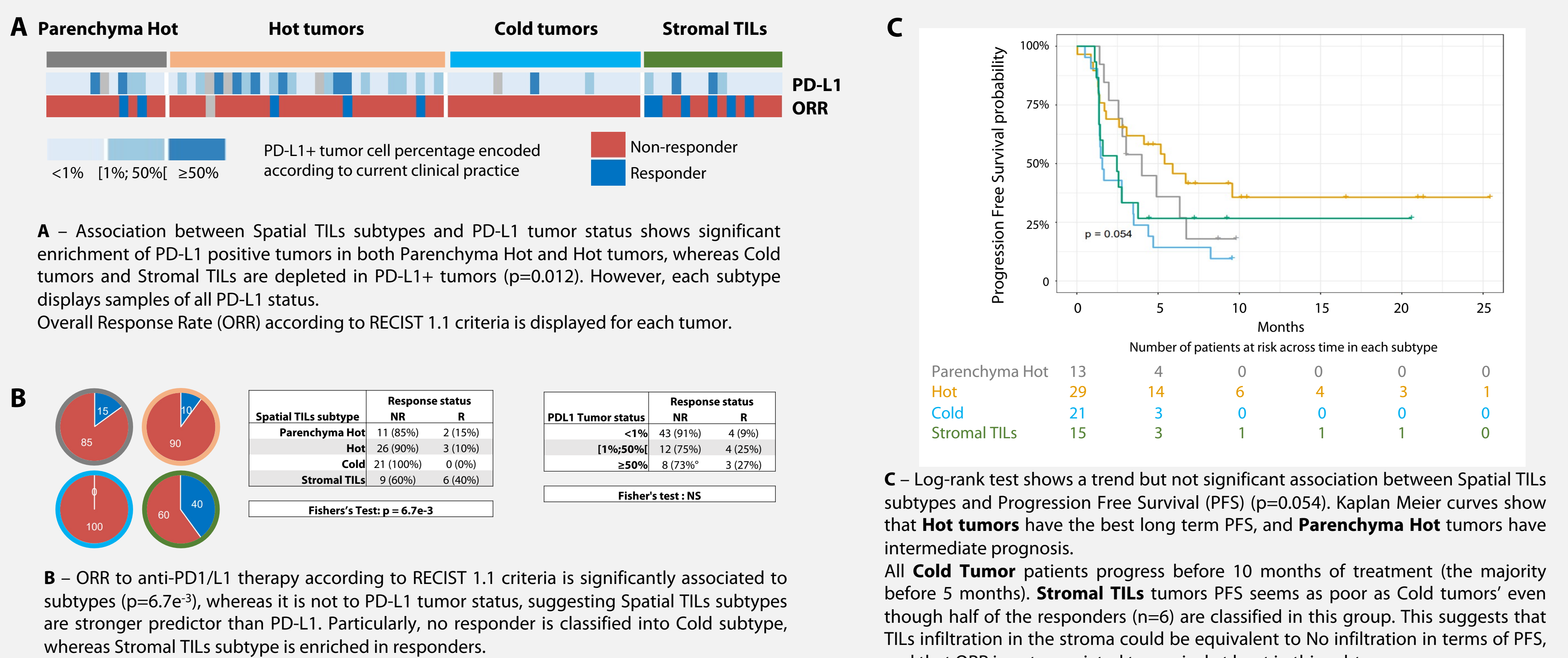
1. Strategy, Materials and Methods



2. Spatial distribution of TILs stratifies NSCLC patients into 4 subtypes

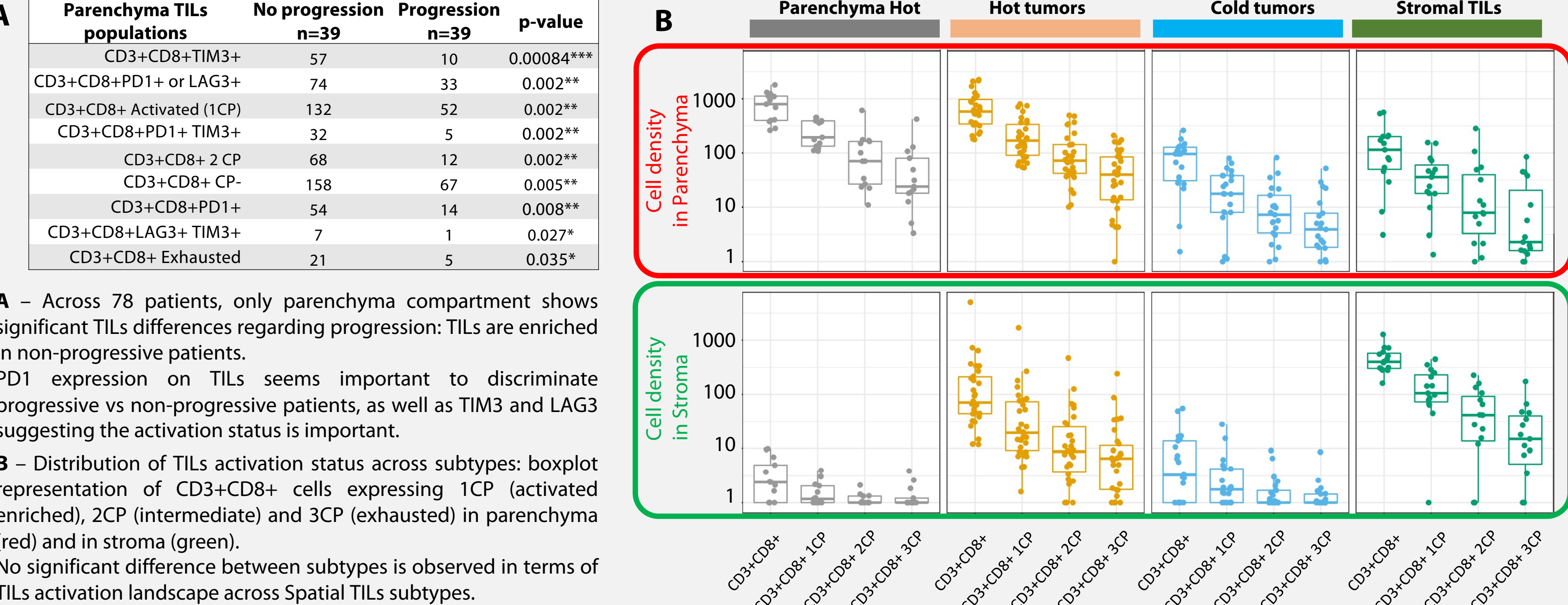


3. Spatial TILs stratification enriches anti-PD1/L1 immunotherapy responders' group

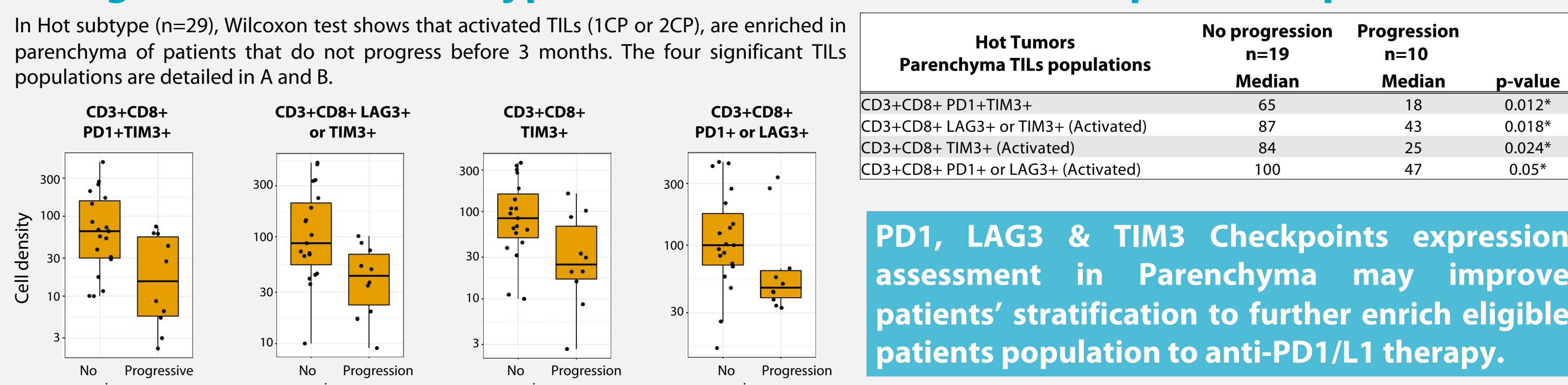


Spatial TILs subtypes may improve NSCLC patients' stratification regarding anti-PD1/L1 therapy response and progression-free survival.

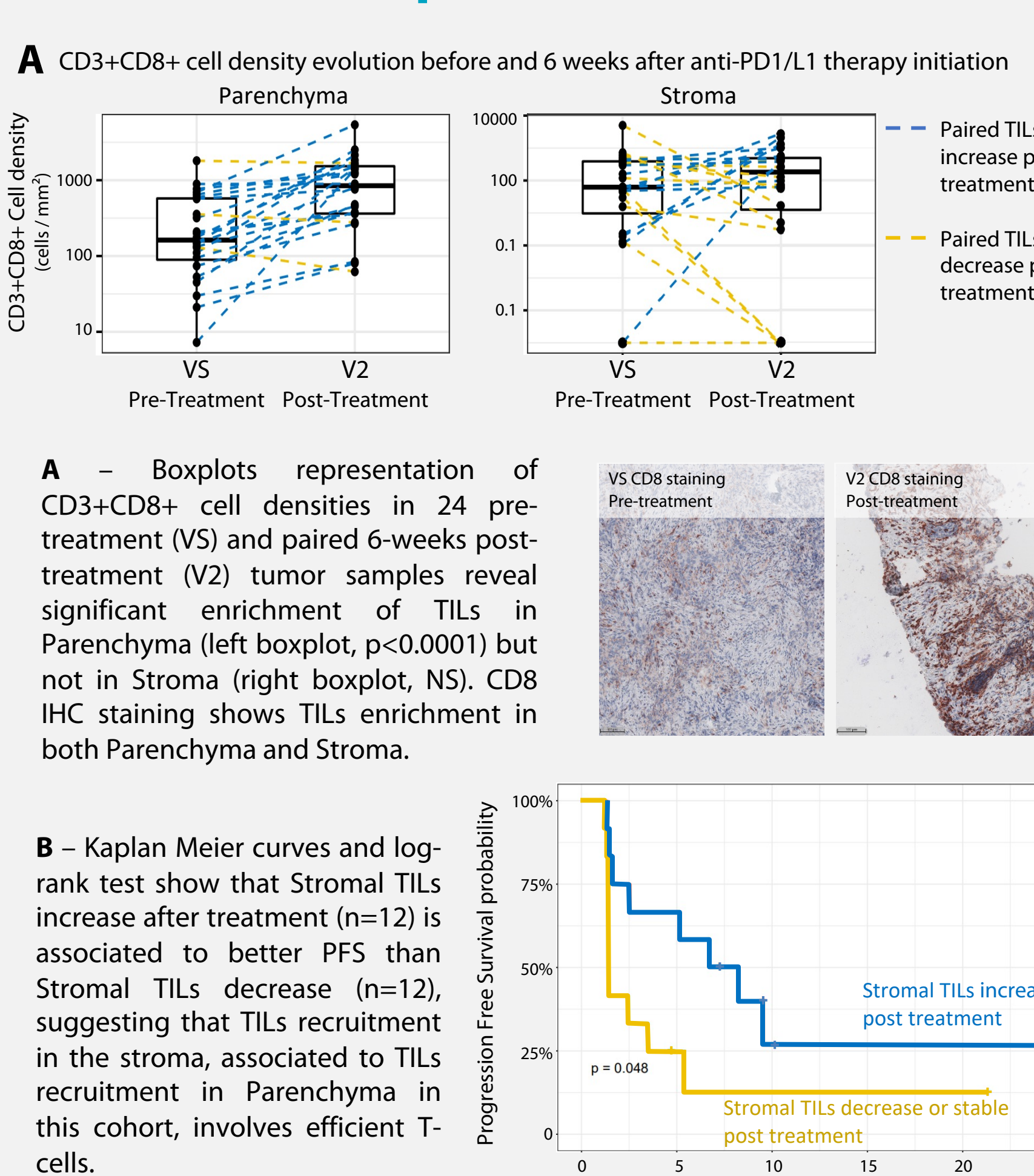
4. Checkpoints expression across progression status and Spatial TILs Subtypes



5. Progression in Hot subtype is associated to lower checkpoints' expression



6. Post-treatment induction of stromal infiltration can predict PFS



Anti-PD1/L1 therapy induces TILs recruitment in the parenchyma. Post-treatment recruitment in Stroma is associated to longer PFS.

Conclusion

Brightplex® T-Cells Exhaustion assay could enrich NSCLC patients' population eligible to anti-PD1/L1 therapy through the stratification into four Spatial TILs subtypes:

- Cold, 100% of patients progress within 10 months despite anti-PD1/L1 treatment
- Stroma-infiltrated, enriched in ORR but with short time to progression
- Parenchyma Hot subtype, with intermediate time to progression
- Hot subtype, enriched in ORR, with long time to progression for more than 40% of patients (>10 months), whatever the PDL1 status

In the Hot subtype, activated T-cell densities are higher in tumors of patients with longer time to progression, suggesting stratification could be even more accurate integrating checkpoints expression such as PD1, LAG3 and TIM3.

Finally, whatever the subtype, anti-PD1/L1 therapy seems to recruit T-cells in the parenchyma, but not as systematically in the Stroma. Tumors with such a Stromal T-cell recruitment present longer time to progression.

These preliminary results based on a first set of patients are under validation on the next 100 patients.

Reference

1 - Nabet et al., 2020, Cell 183, 363–37

