

Background

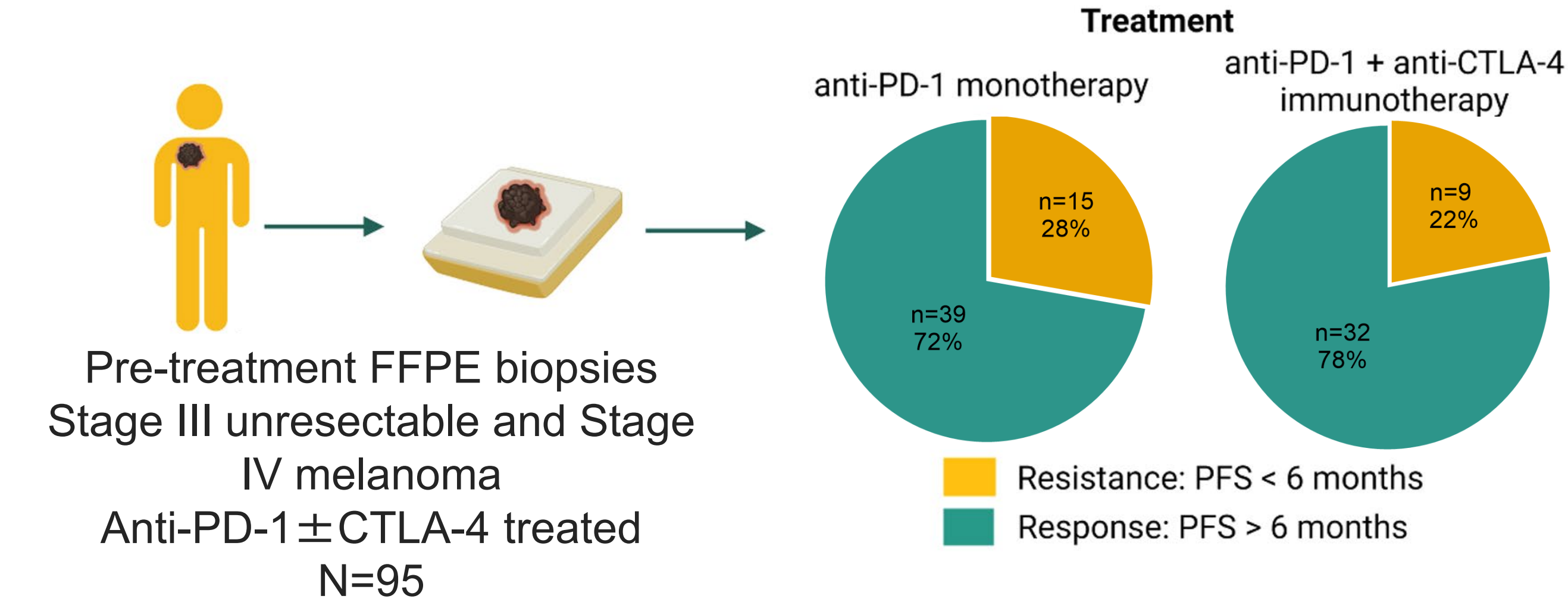
- Immune checkpoint inhibitors targeting the PD-1 and CTLA-4 receptors have greatly enhanced clinical outcomes for patients with metastatic melanoma¹.
- Despite this progress, around 50% of patients do not survive beyond five years².
- Metabolic reprogramming, a key characteristic of cancer, has been linked to reduced T-cell activity and diminished effectiveness of immunotherapies^{3,4}.

Objectives

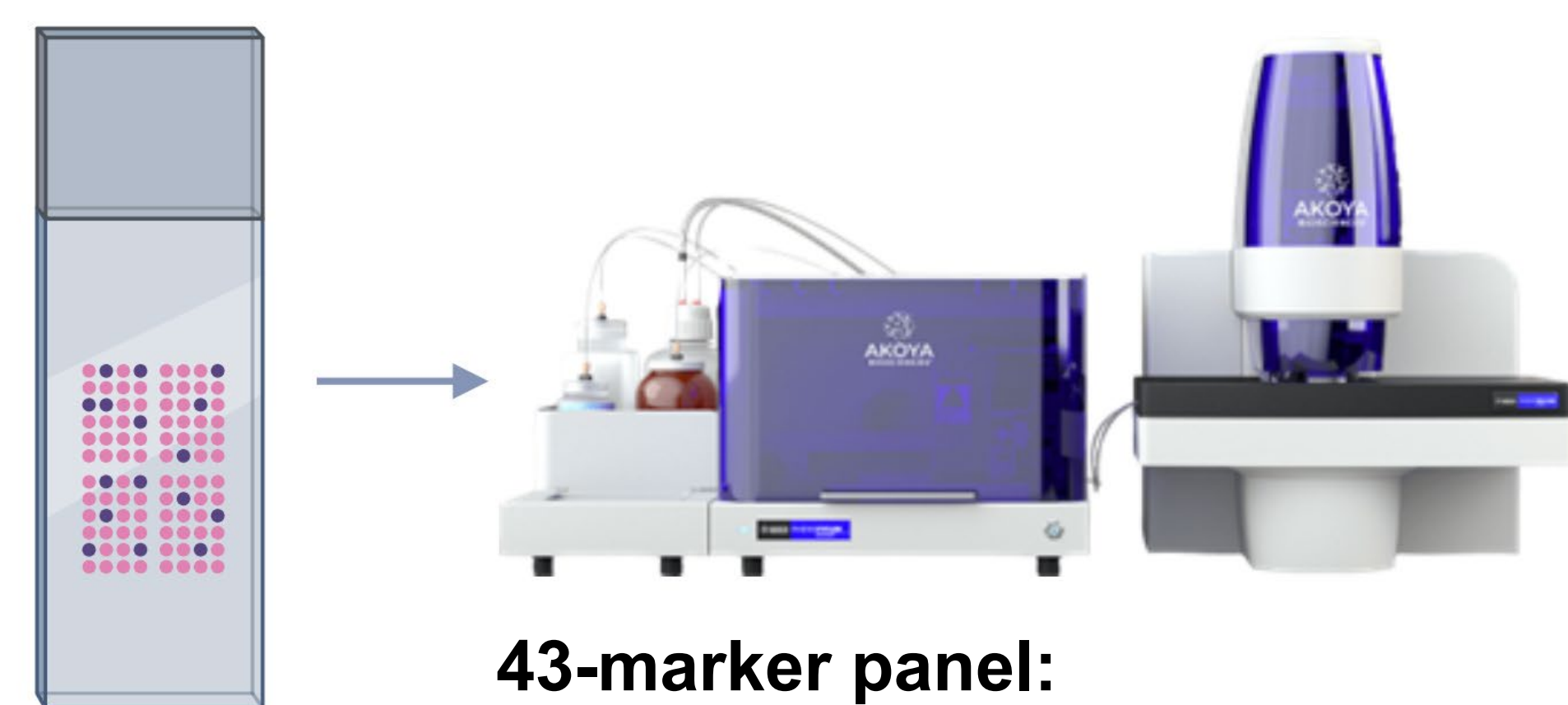
To investigate the baseline metabolic profiles and spatial organisation of tumour associated vasculature for associations with response or resistance to anti-PD-1 +/- anti-CTLA-4 immunotherapy.

Methods

Patient cohort



Multiplex staining on PhenoCycler-Fusion

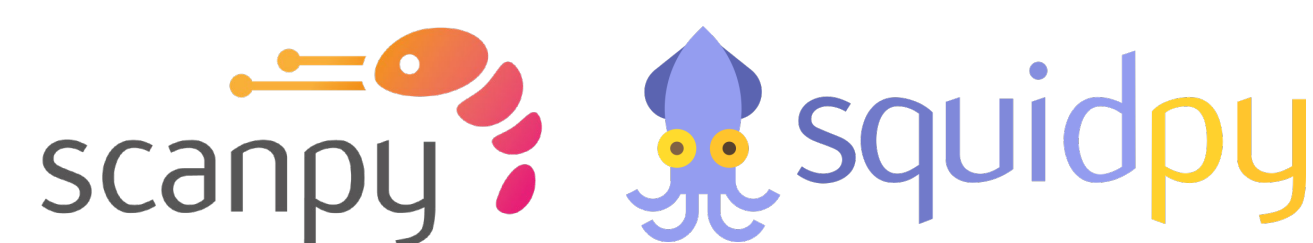


43-marker panel:
29 cell lineage and immune markers
14 metabolism-related proteins: Fatty acid metabolism, Amino acid metabolism, Hypoxia, Glycolysis

Analysis

Image analysis using QuPath

Single cell spatial analysis using Scanpy and Squidpy



Tumour and TIL regions included in TMA

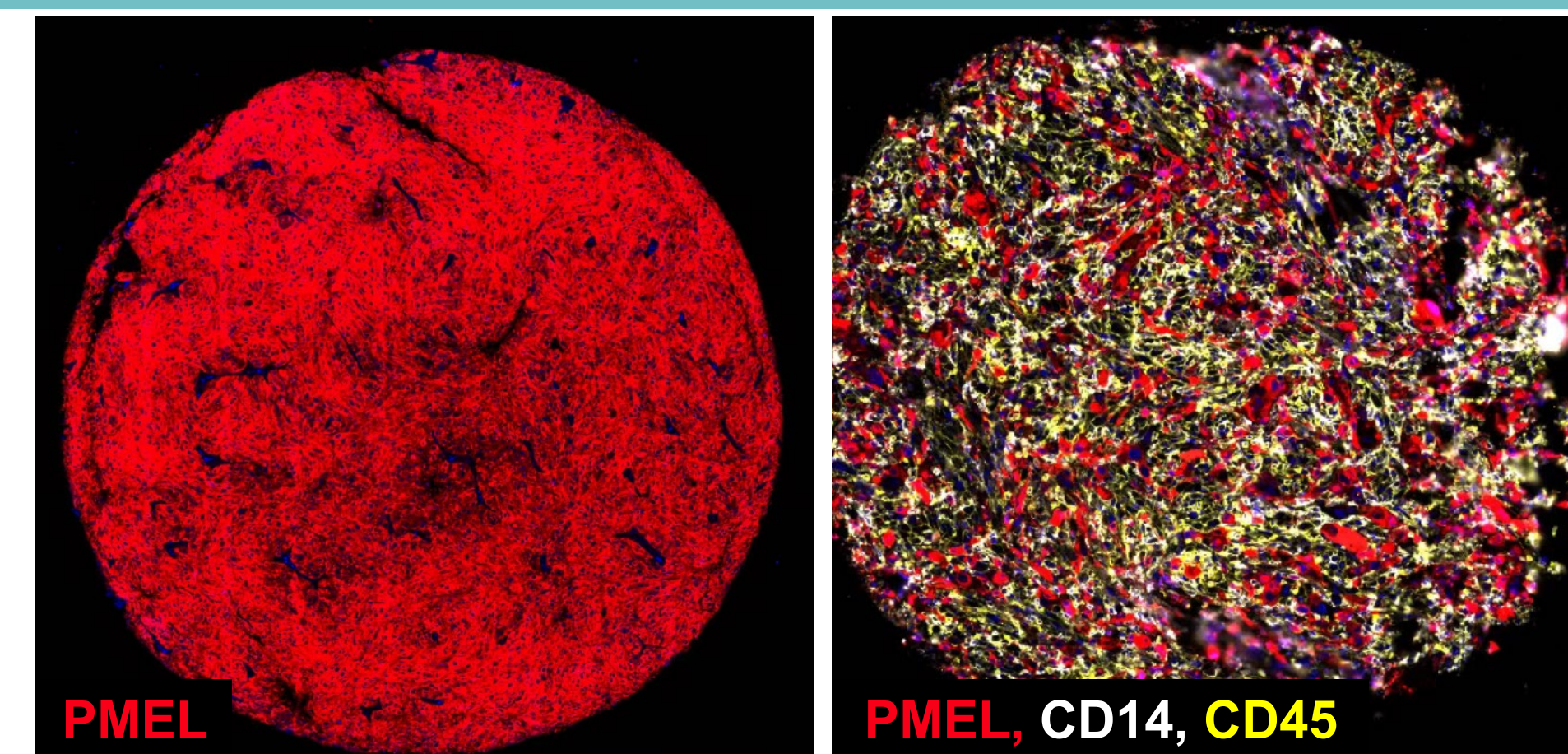


Figure 1: Representative images of high-plex staining in a high tumour and high TIL (tumour-infiltrating lymphocyte) tissue core

HLA loss in resistant tumours

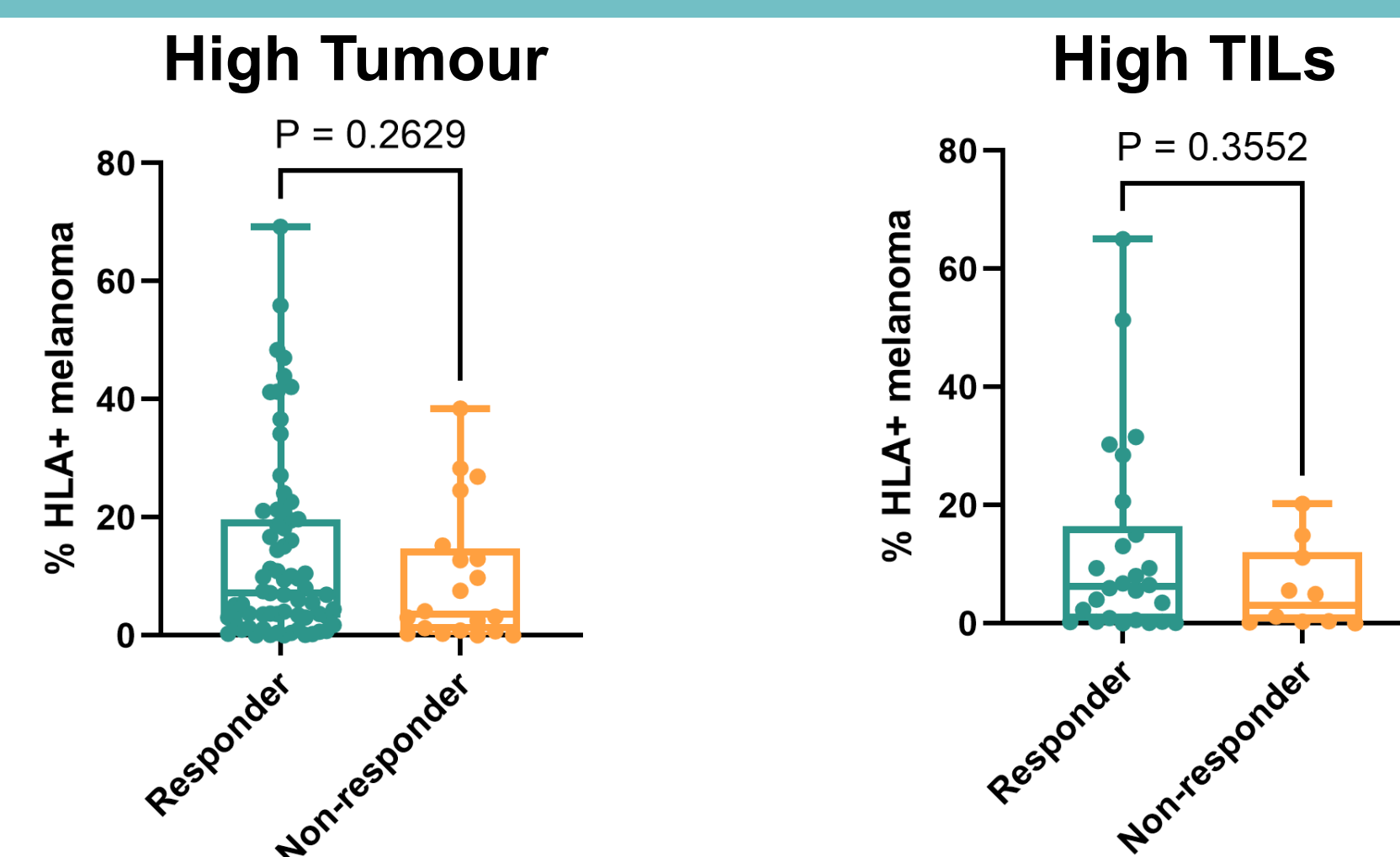


Figure 2: Comparison of % HLA+ melanoma in responders vs non-responders for high tumour and high TIL regions

HLA+ melanoma cells in closer proximity to CD34+ vessels in Responders

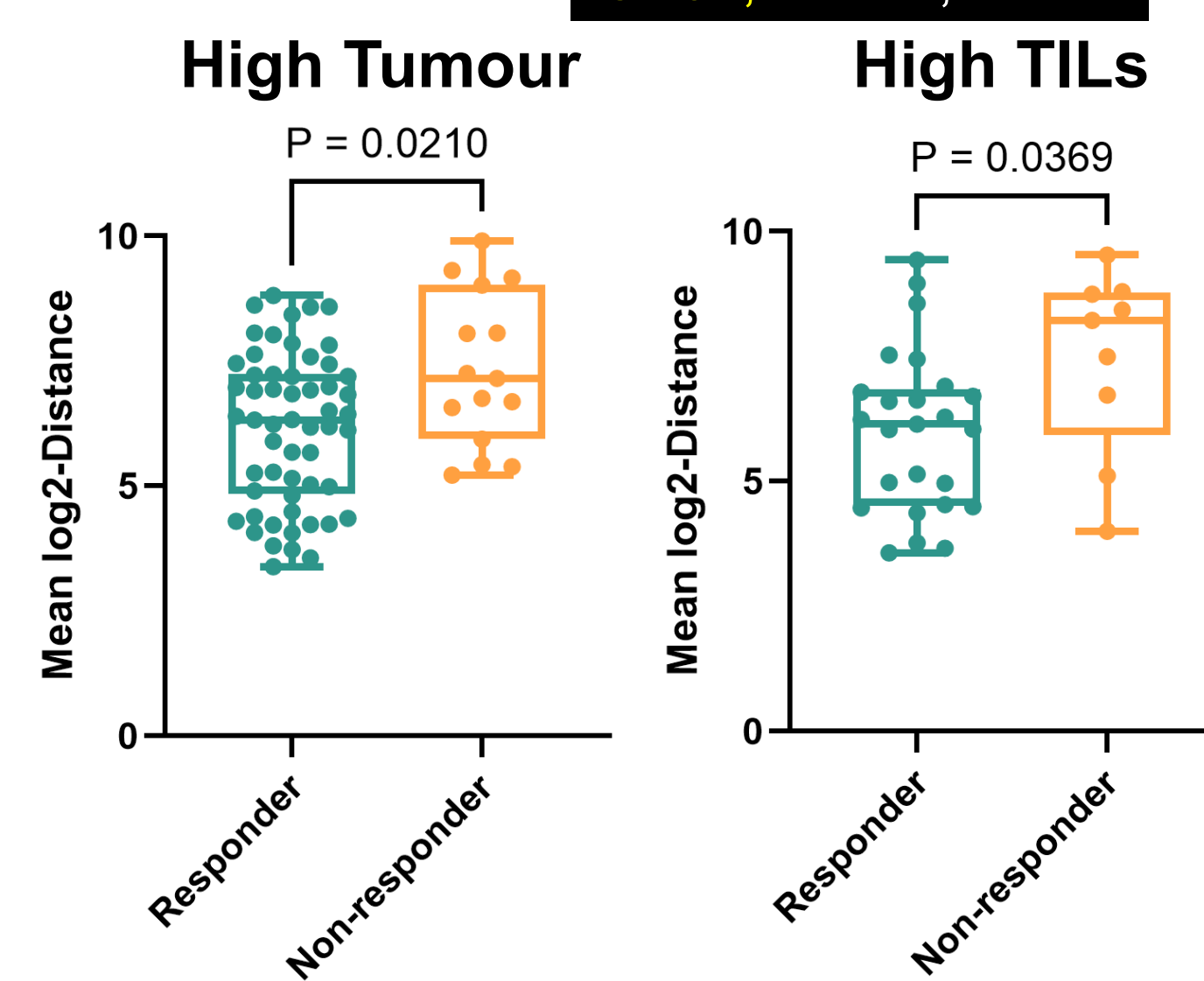
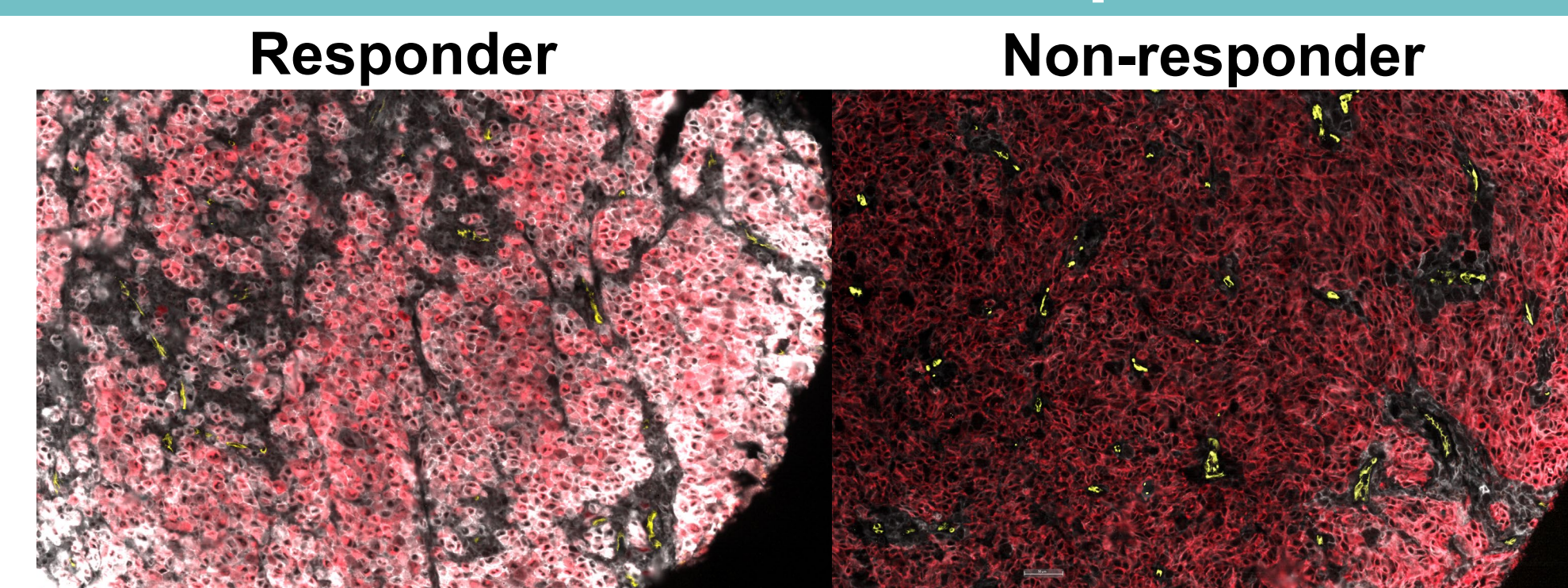


Figure 3: Comparison of distance between HLA+ melanoma and CD34+ vessels in responders vs non-responders for high tumour and high TIL regions

Results

Melanoma cells and immune cells have distinct metabolic profiles

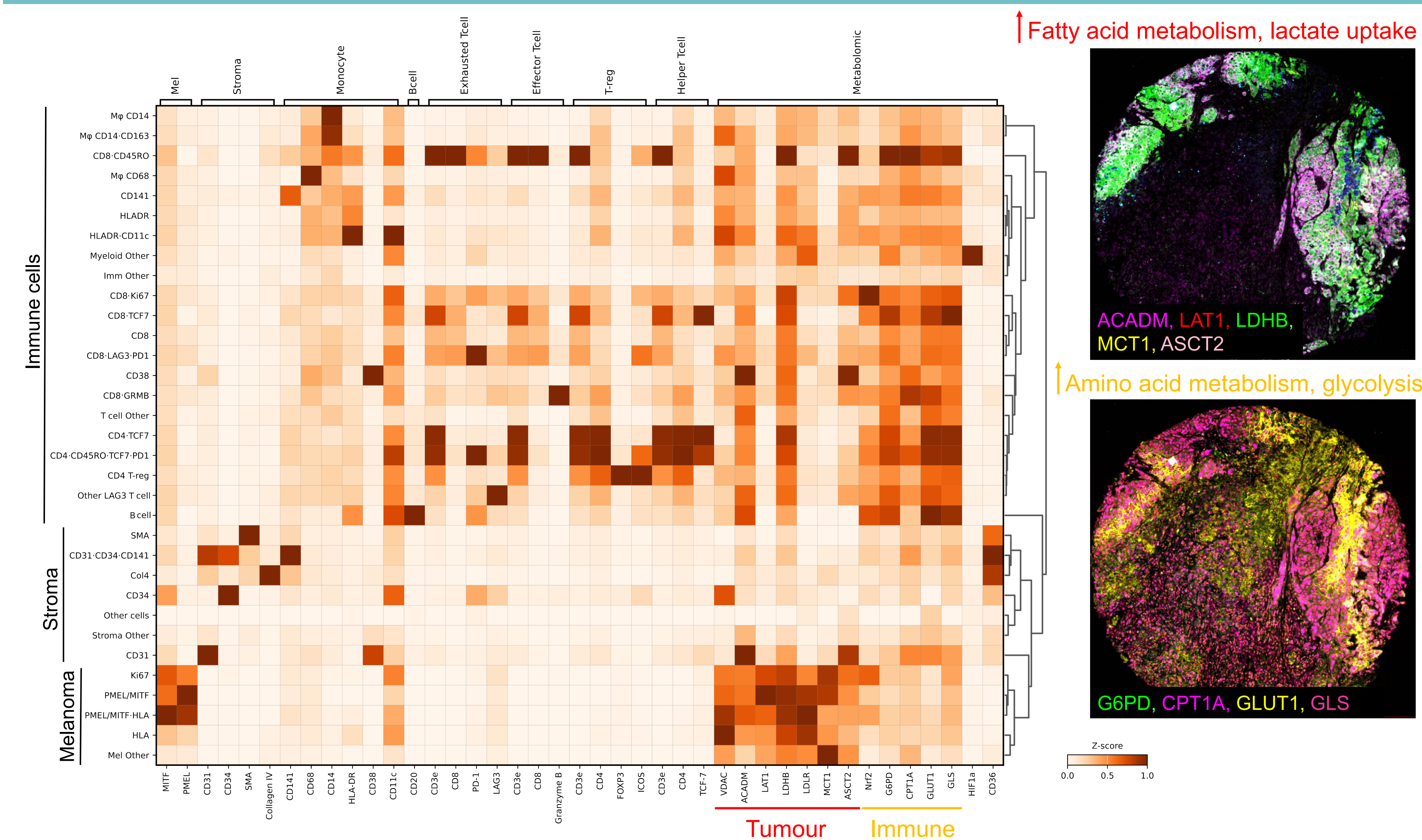


Figure 4: Heatmap and representative multiplex images showing metabolic profiles of various melanoma and immune populations

G6PD expression on CD4+ Tregs is higher in Non-responders

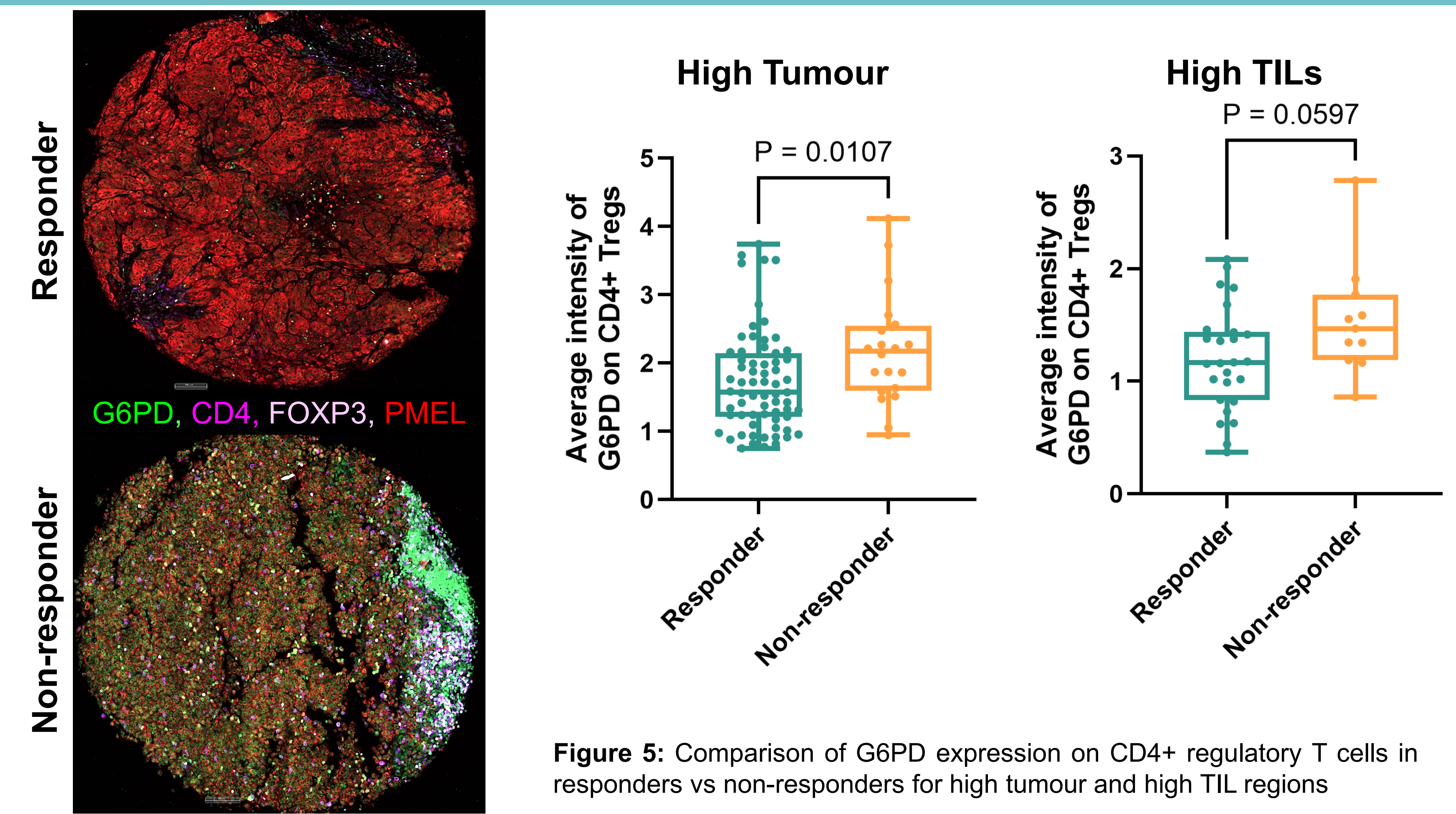


Figure 5: Comparison of G6PD expression on CD4+ regulatory T cells in responders vs non-responders for high tumour and high TIL regions

Conclusions

- HLA+ melanoma cells are higher in responders, and are located in closer proximity to blood vessels compared to non-responders
- Tumour and high TILs regions show distinct metabolic profiles:
 - > Tumour: Increased fatty acid metabolism and lactate uptake
 - > TILs: Amino acid metabolism and glycolysis
- Non-responders have higher expression of G6PD on CD4+ regulatory T cells

References

- Wolchok, J., et al. NEJM 2024.
- Carlino, M.S., et al. Lancet 2021.
- Kouidhi S., et al. Front Immunol 2017.
- Ricci, J. Cell Reports 2025.

Acknowledgements



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