CHARACTERISING THE TUMOUR MICROENVIRONMENT IN MELANOMA PATIENTS TREATED WITH COMBINATION ANTI-TIGIT + ANTI-PD-1 IMMUNOTHERAPIES

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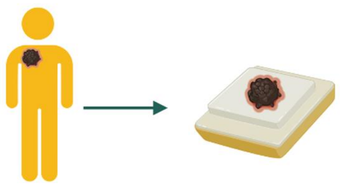
Background

- T-cell immunoreceptor with Ig and ITIM domains (TIGIT) suppresses T-cell and NK-cell activity and modulates anti-tumour immune responses[1].
- Early studies in melanoma suggested that dual TIGIT and programmed cell death receptor-1 (PD-1) blockade could enhance anti-tumour immunity[2]; however, subsequent clinical trials demonstrated minimal benefit over PD-1 inhibition alone[3,4].
- Despite this, variability in patient outcomes indicates that a subset may still benefit.

Objectives

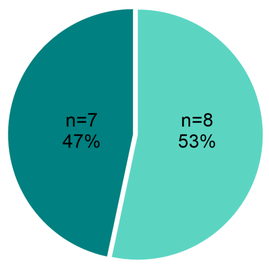
- To determine whether features of the pre-treatment tumour microenvironment are associated with differential clinical outcomes in patients with metastatic melanoma treated with anti-TIGIT immunotherapy
- To evaluate the relationship between pre-treatment tumour microenvironment characteristics and response to neoadjuvant anti-TIGIT-based immunotherapy in melanoma

Methods



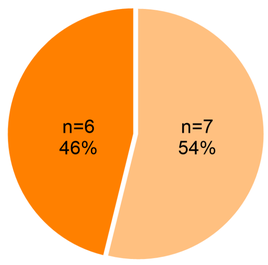
Pre-treatment FFPE biopsies
Resectable stage III melanoma N=15
Unresectable stage III/IV melanoma N=13

Neoadjuvant cohort

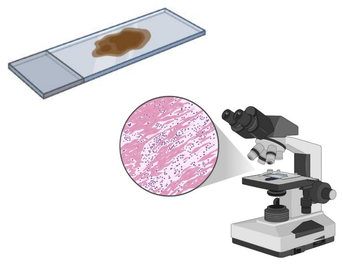


MPR: Major pathological response (CR, near-pCR)
non-MPR: pPR, pNR

Advanced cohort



Responder: PFS ≥ 6 months
Non-responder: PFS < 6 months

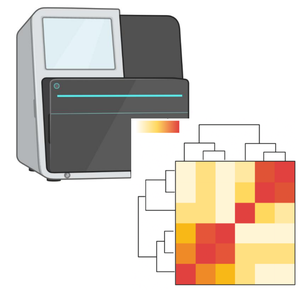


Chromogenic IHC for **TIGIT** (BLR047F)

Tumour-immune profiling



Multiplex immunofluorescence (**LAG-3, HLA-ABC, PD-1, PD-L1**)



Gene expression profiling (NanoString)

Results

TIGIT expression in pre-treatment melanoma specimens

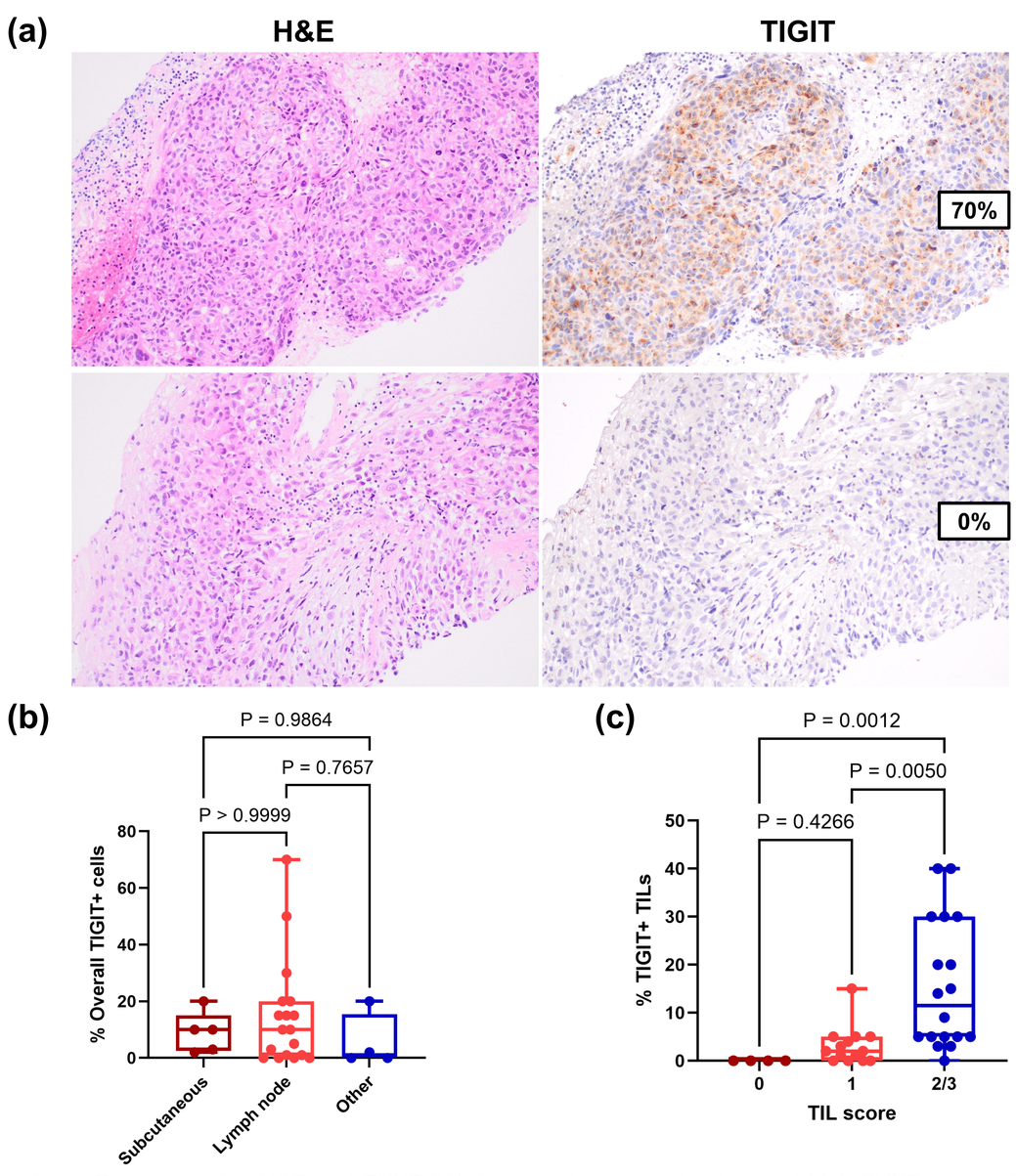


Figure 1: (a) Representative H&E and TIGIT IHC images demonstrating low and high TIGIT expression. **(b)** Box plots showing TIGIT expression across different metastatic sites. **(c)** Box plots showing TIGIT expression in tumour-infiltrating lymphocytes (TILs) according to TIL grade.

Baseline TIGIT expression does not differ between treatment settings

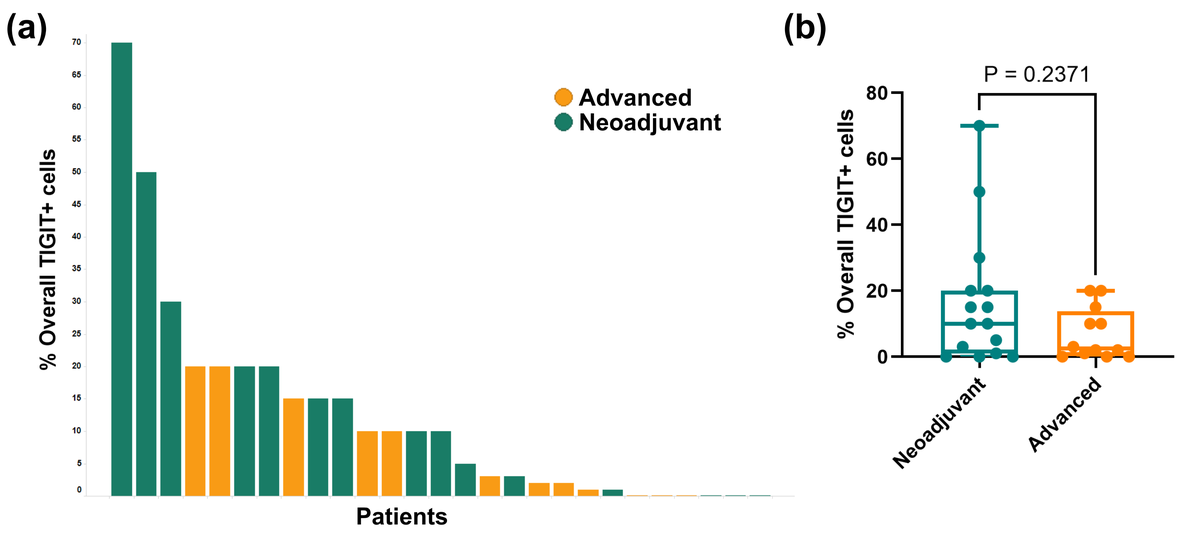


Figure 2: (a) Overall TIGIT expression in individual patients from the neoadjuvant (green) and advanced melanoma (orange) cohorts. **(b)** Comparison of overall TIGIT expression between the neoadjuvant and advanced melanoma cohorts.

TIGIT expression is not associated with response to anti-TIGIT therapy

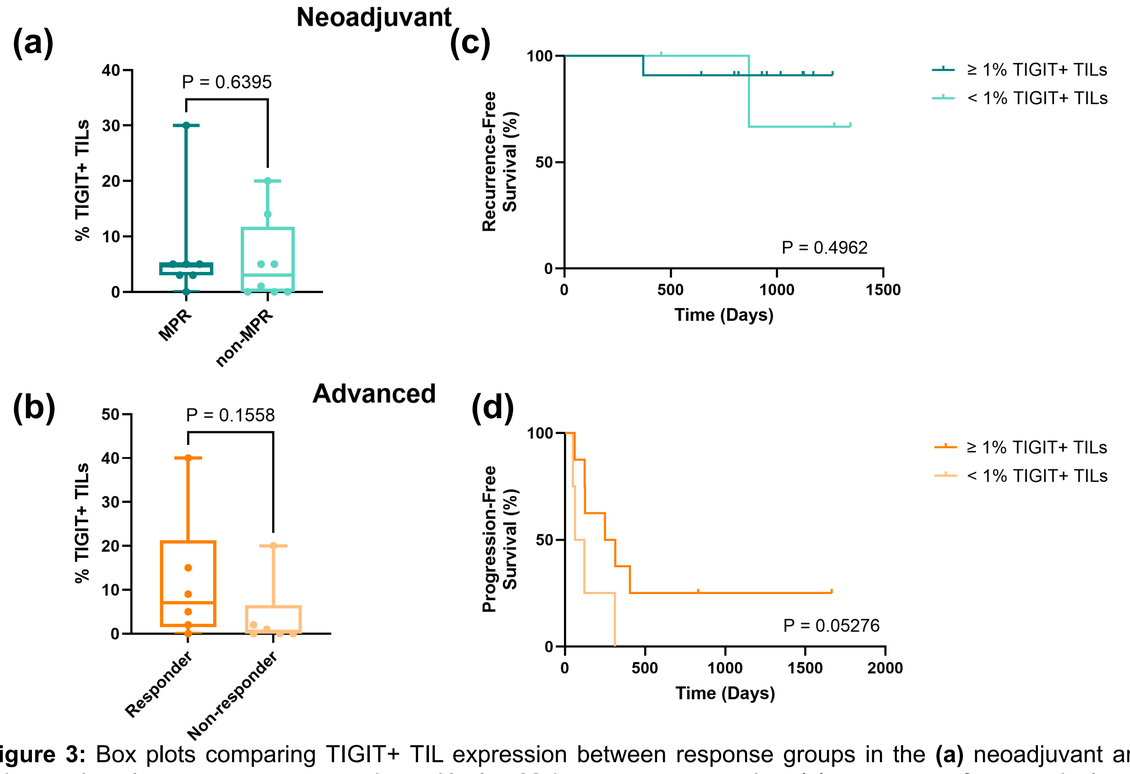


Figure 3: Box plots comparing TIGIT+ TIL expression between response groups in the **(a)** neoadjuvant and **(b)** advanced melanoma treatment settings. Kaplan-Meier curves comparing **(c)** recurrence-free survival and **(d)** progression-free survival in patients with ≥1% versus <1% TIGIT+ TILs.

Distinct gene expression profiles differentiate responders and non-responders in advanced melanoma

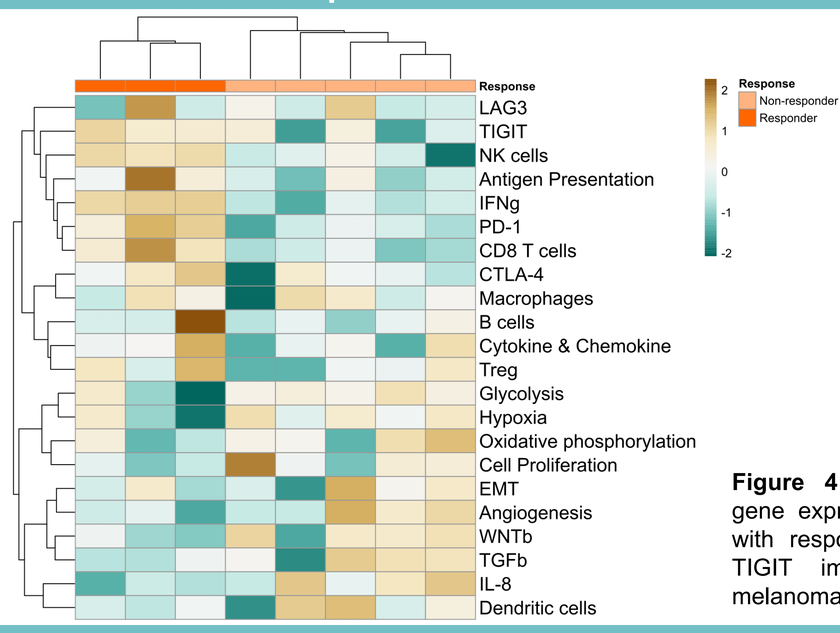


Figure 4: Heatmap showing distinct gene expression signatures associated with response and resistance to anti-TIGIT immunotherapy in advanced melanoma.

Multiplex immunofluorescence profiling of immune checkpoints

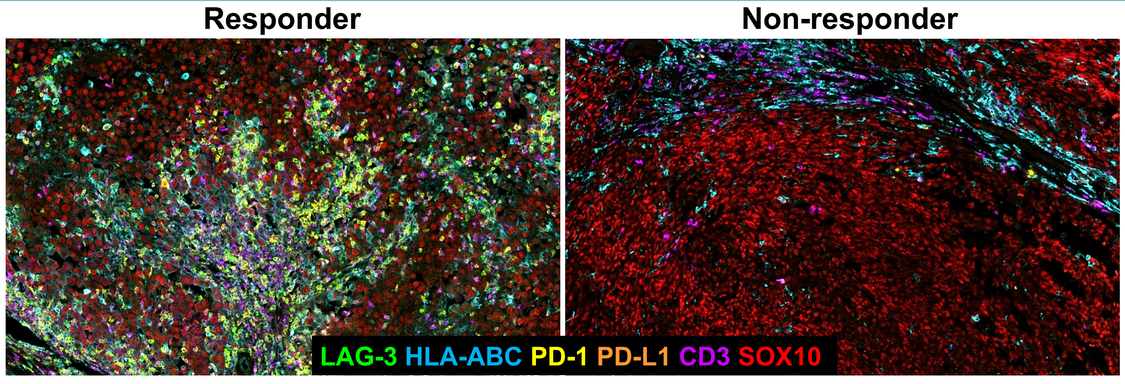


Figure 5: Representative multiplex immunofluorescence images of a responder and non-responder showing staining of LAG-3 and its ligand HLA-ABC, PD-1 and its ligand PD-L1, the pan T-cell marker CD3, and the melanoma marker SOX10.

Conclusions and Future Directions

- TIGIT expression was comparable at baseline between neoadjuvant and advanced anti-TIGIT treatment cohorts and was not associated with response.
- In advanced melanoma, ≥1% TIGIT+ TILs showed a trend towards improved PFS, although no association was observed for RFS.
- Responders demonstrated enrichment of immune-related pathways, while non-responders exhibited increased metabolic and immunosuppressive pathway activity.
- Multiplex immunofluorescence analysis is underway to assess whether PD-1, LAG-3 and their ligands are associated with response to anti-TIGIT immunotherapy.

References

1. Tang, W., et al. *Cell Death Dis.* 2023
2. Chauvin, JM., et al. *J Clin Invest.* 2015
3. Dummer, R., et al. *Lancet Oncol.* 2026
4. Dummer, R., et al. *Nat Med.* 2025

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