Five tumour-immunity clusters (TICs) predict response and guide resistance after neoadjuvant immunotherapy (NeoIT) in melanoma

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Background

- Neoadjuvant anti-PD-1-based immunotherapy (NeoIT) achieves high pathological response rates in stage III melanoma, yet patients without a major pathological response (MPR) remain at high risk of recurrence.
- Tumour-immune interaction comprises multiple phases that together determine NeoIT response; single biomarkers fail to capture this complexity.
- The immunogram integrates seven tumour-immune phases from RNA-seq into a single profile per tumour.[1]

Objectives

- Analyse pre- and post-treatment tumour-immunity clusters (TICs) in melanoma patients receiving anti-PD-1-based NeoIT.
- Identify resistance phenotypes associated with pathological response and recurrence-free survival (RFS).
- Identify therapeutic opportunities for patients who do not respond.

Methods

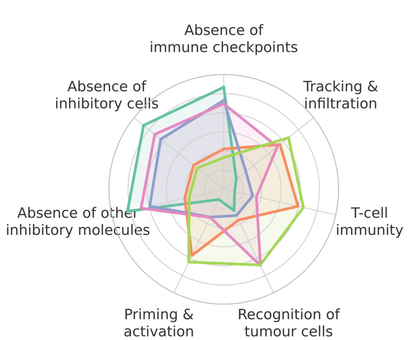
1 Cohort 91 stage III pts anti-PD-1-based NeoIT → **2 Bulk RNA-seq** Pre-treatment & post-treatment (week 6) → **3 ssGSEA** NES z-scores for 7 tumour–immune phases → **4 Clustering** Unsupervised consensus clustering → 5 TICs

- **Seven phases:** tumour recognition; priming/activation; trafficking/infiltration; T-cell immunity; absence of inhibitory cells; (absence of) checkpoints; (absence of) inhibitory molecules.[1]
- **Clustering:** unsupervised clustering of ssGSEA normalised enrichment score (NES) z-scores identified five TICs.
- **Comparisons across TICs:** KEGG pathway activity, pathological response (MPR vs non-MPR) and RFS (Kaplan–Meier, log-rank).

91 stage III pts | **44** MPR (48%) | **47** non-MPR (52%) | **25** recurred (27%)

Results

A Five tumour-immunity clusters (TICs)



C1 — Immune Desert
Absent checkpoints / inhibitory cells; minimal priming, tracking & T-cell immunity

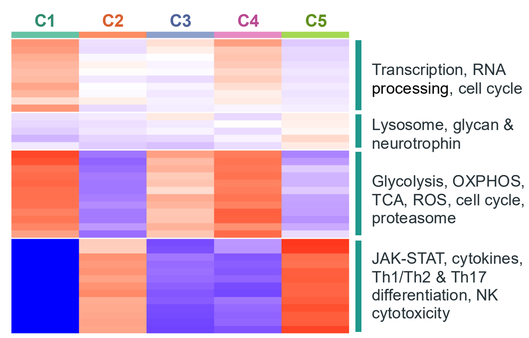
C2 — Immune Primed
High T-cell immunity & priming; moderate–high tracking / infiltration; lower tumour recognition

C3 — Stalled Immunity
Low recognition, T-cell immunity, tracking & priming; high checkpoints / inhibitors

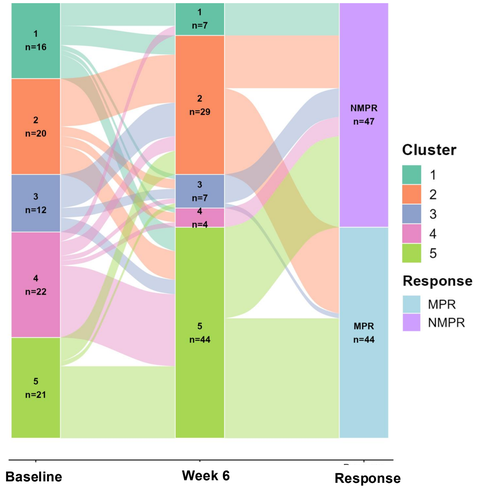
C4 — Recognition without Ignition
Moderate–high tracking / infiltration & antigen recognition; low T-cell immunity / priming

C5 — Immune Rich
High tracking / infiltration; good T-cell immunity & priming

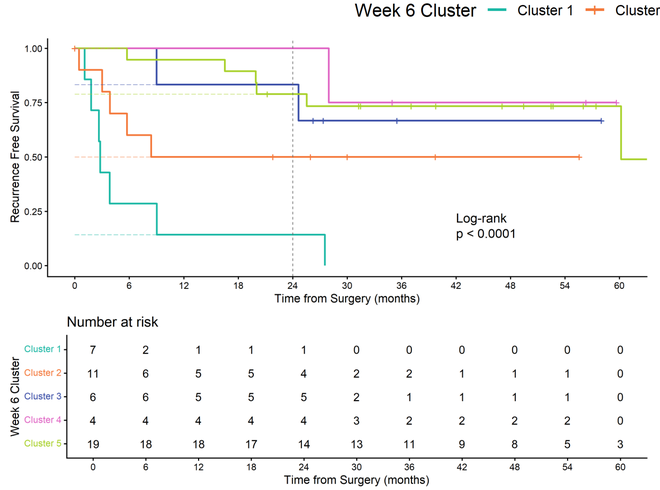
B KEGG pathway activity (GSVA)



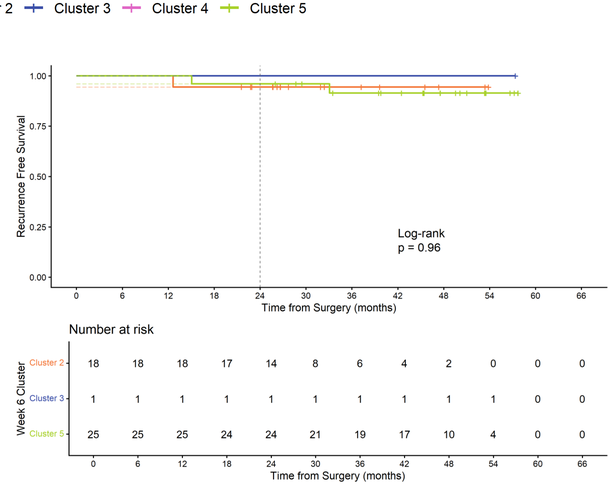
C Cluster transitions & response



D RFS by post-treatment TIC: non-MPR



E RFS by post-treatment TIC: MPR



Conclusions

- Post-treatment TICs stratify RFS after anti-PD-1-based NeoIT in melanoma; most strongly in non-MPR pts (24-mo RFS 14% in C1 vs 79–100% in C3–C5).
- MPR patients are almost exclusively Immune Rich (C5) or Immune Primed (C2) after treatment, with excellent 24-mo RFS (94–100%).
- Distinct TICs could guide salvage therapy: non-MPR C1 (immune desert) may benefit from TIL therapy; non-MPR C2 (immune primed, high immunity but low tumour recognition) may benefit from a personalised vaccine.

References

1. Long GV, et al. Five-year survival with neoadjuvant therapy in melanoma: updated pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). Nat Med. 2026.
2. Karasaki T, et al. An immunogram for the cancer-immunity cycle: towards personalized immunotherapy of lung cancer. J Thorac Oncol 2017.

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