Distinct effect of neoadjuvant PD1 alone, PD1+IPI and PD1+Lenvatinib in the peripheral immune profile of melanoma patients (pts) and correlation with pathological (path) response.

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Background

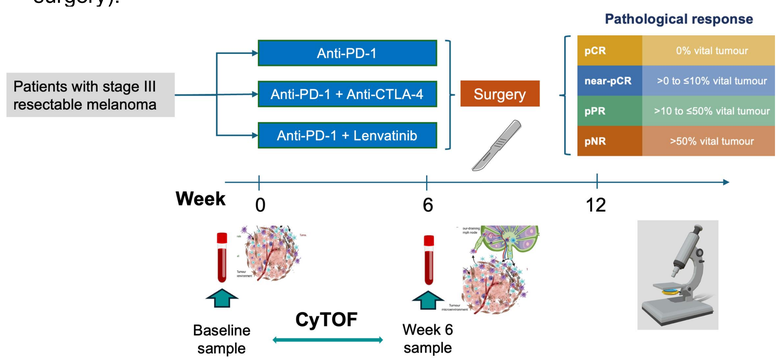
- Neoadjuvant immunotherapy (NeoIT) has significantly improved clinical outcomes for patients with macroscopic stage III resectable melanoma and is the current standard of care for these patients[1,2].
- Pathological response (at week 6) correlates well with recurrence-free survival; patients who achieve a major pathological response (≤ 10% of viable tumour cells]) rarely recur, while those not achieving a MPR (>10% of viable tumour cells) are at higher risk of recurrence[3].

Objectives

We sought to analyse the longitudinal peripheral immune profiles and their correlation with pathological response (MPR *versus.* non-MPR) for 3 different PD1-based NeoIT regimens.

Methods

- Patients with macroscopic stage III resectable melanoma treated with neoadjuvant PD1-based regimens (PD1 alone, PD1+IPI and PD1+Lenvatinib) for 6 weeks, followed by surgery, were included.
- Cytometry by time-of-flight (CYTOF; 39-marker panel) was performed on peripheral blood mononuclear cells (PBMCs) at baseline and week 6 (pre-surgery).



	PD1	PD1 + IPI	PD1 + Lenvatinib
MPR	7	20	12
Non-MPR	10	6	9

Figure 1. Schematic representation of the cohort and PBMCs analysed in this study.

Results

Figure 2. Statistically significant treatment effects (from baseline to week 6), overall and based on pathological response (MPR *versus.* non-MPR), in patients treated with PD1 alone, PD1+IPI and PD1+Lenvatinib. *Red, increase in the expression. Blue, decrease in the expression. Light, $p < 0.05$. Dark, $p < 0.01$.*

	Anti-PD1			Anti-PD1 + Anti-CTLA4			Anti-PD1 + Lenvatinib		
Baselise → Week 6	**Entire cohort**	**MPR**	**Non-MPR**	**Entire cohort**	**MPR**	**Non-MPR**	**Entire cohort**	**MPR**	**Non-MPR**
CD8+ T effector memory [Tem] cells									
TIM3+ CD4+ & CD8+ T cells									
GZM+ CD4+ & CD8+ T cells									
Stem-like [TCF7+] CD4+ & CD8+ T cells									
Activated [ICOS+ / LAG3+ / TIGIT+] CD4+ T cells									
KI67+ ICOS+ CD4+ T cells									
Th1									
Th17									
Tregs									
OX40+ / ICOS+ Tregs									
Double negative [DN; CD27- IgD-] B cells									
Non-classical [CD14low+CD16++] monocytes									
HLA-DR+ non-classical monocytes									
Cytotoxic [CD56dim CD16+] NK cells									

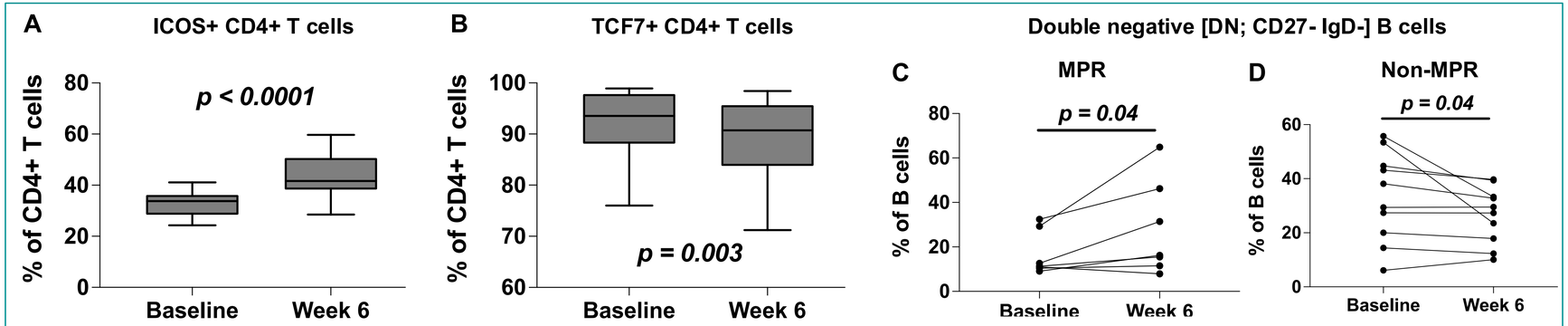


Figure 3. Representative comparisons of immune cell populations between baseline and week 6. Treatment effect (PD1+IPI-treated cohort) in the percentage of ICOS+ CD4+ T cells **(A)** and of TCF7+ CD4+ T cells **(B)**. Different treatment effect (PD1-treated cohort) in MPR **(C)** *versus.* non-MPR **(D)** (Double negative [DN; CD27- IgD-] B cells).

Conclusions

- IPI+PD1 and PD1+Lenvatinib induced stronger peripheral blood immune activation compared with PD1 alone, irrespective of pathological response.
- There were differences in the treatment effect in the MPR *versus.* non-MPR patients, particularly for PD1 alone.
- A more in-depth analysis of the effects of these PD1-based regimens and their association with recurrence is underway to identify key immune cell types/phenotypes associated with response & resistance to NeoIT.

References

1. Patel SP, *et al*. NEJM 2023.
2. Blank C, *et al*. NEJM 2024.
3. Menzies AM, *et al*. Nat Med 2021.

Acknowledgements

All patients and their families
Melanoma Institute Australia

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