

Background

- Neoadjuvant immunotherapy (NeoIT) with anti-PD-1 (PD1) alone or in combination with anti-CTLA-4 (IPI+PD1) is associated with better event-free survival compared with adjuvant PD1 for patients with resectable stage IIIB-D melanoma, and patients with major pathological response (MPR, $\leq 10\%$ viable cells in the tumour bed) have a very low risk of recurrence^{1,2}.
- We have previously reported patients achieving MPR with NeoIT with PD1 and lenvatinib had a significant increase in CD21+ CXCR5+ B cells and number of lymphoid structures in the tumour microenvironment compared to non-MPR patients³.

Objectives

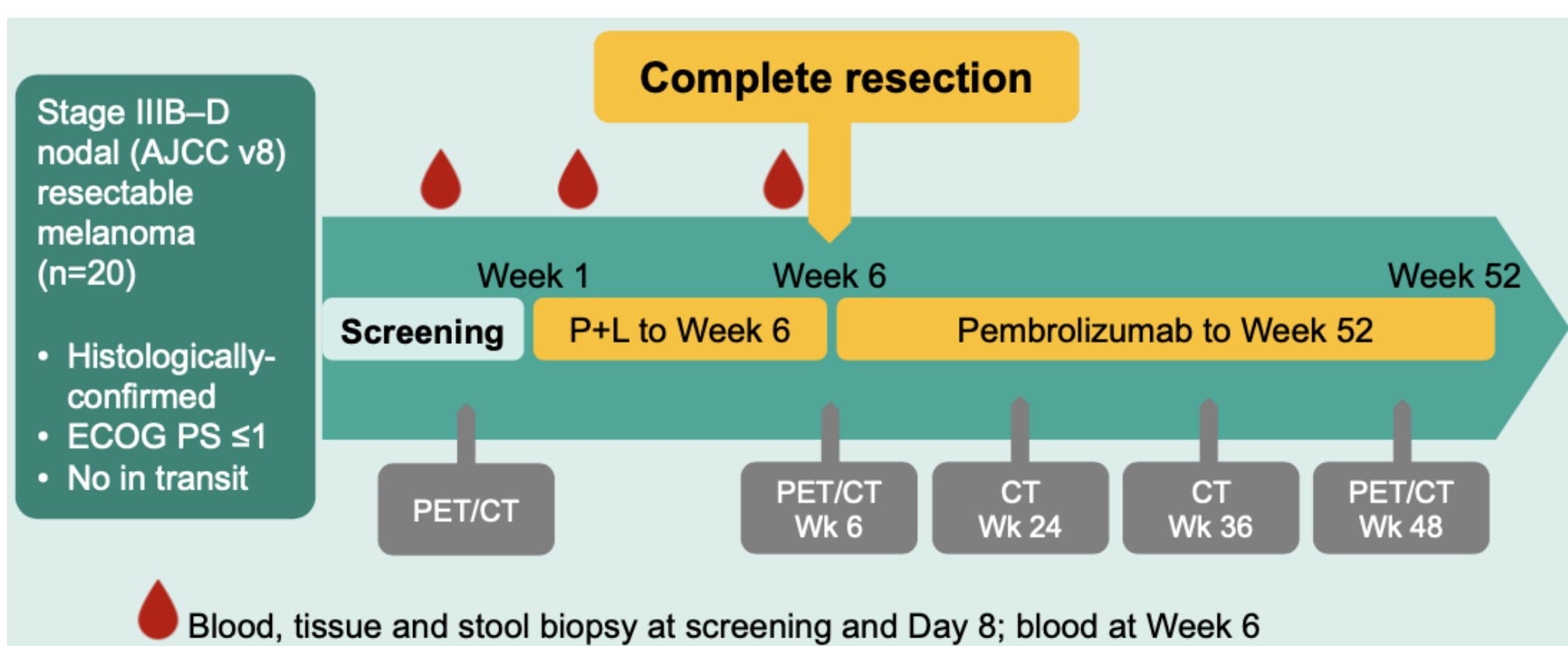
We sought to analyse the effect of NeoIT (PD1 + lenvatinib) in peripheral immune profiles from MPR versus. Non-MPR patients.

Methods

- Patients with stage III melanoma treated with 6 weeks of PD1-based neoIT (PD1 + lenvatinib) were included (NeoPele clinical trial; NCT04207086).
- Cytometry by time of flight (CYTOF; 39-marker panel), was performed on peripheral blood mononuclear cells (PBMCs) at baseline (pre-NeoIT) and 6 weeks post NeoIT, prior to surgery (week 6).

Results

FIGURE 1. Study design⁴.



Conclusions

NeoIT induces a stronger peripheral anti-tumour immune response in MPR versus. non-MPR patients, including an increased pool of T effector memory cells, which may contribute to the better recurrence-free survival observed in MPR compared to non-MPR patients.

Results: MPR (n=11, 55%) versus non-MPR (n=9, 45%)

1. Baseline

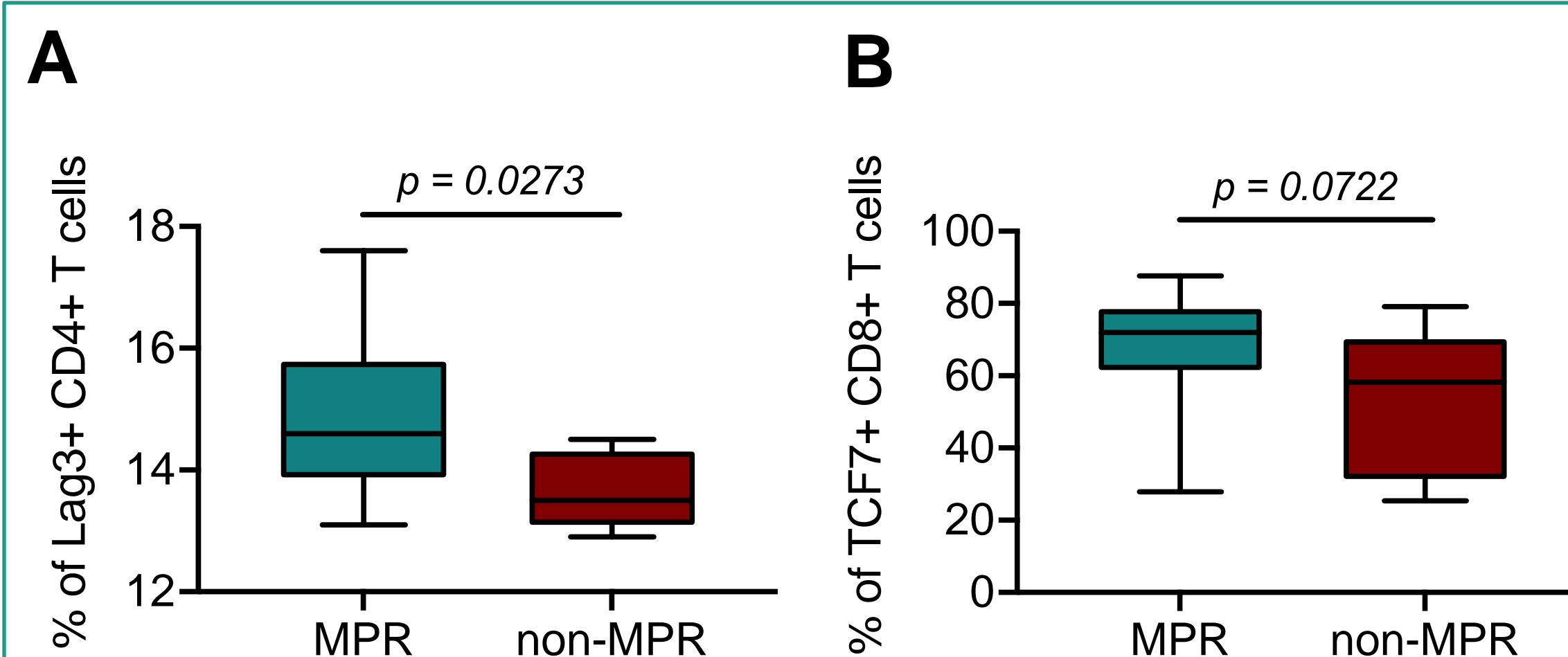


FIGURE 2. Differences in the peripheral immune profile between MPR versus non-MPR patients at baseline. At baseline MPR patients have higher peripheral levels of Lag3+ CD4+ T cells (A) and of TCF7+ CD8+ T cells (B) compared to non-MPR patients.

2. Baseline → Post NeoIT (PD1 + Lenvatinib): whole cohort

Increase % of:

- TEMRA CD8+ T cells
- CD4+ Th1, Th17 and Tregs
- CD8+ & CD4+ T cells expressing Lag-3, Tim-3 or TIGIT
- Naïve and mature double negative (CD27- IgD-) B cells
- Classical (CD14+ CD16-) monocytes

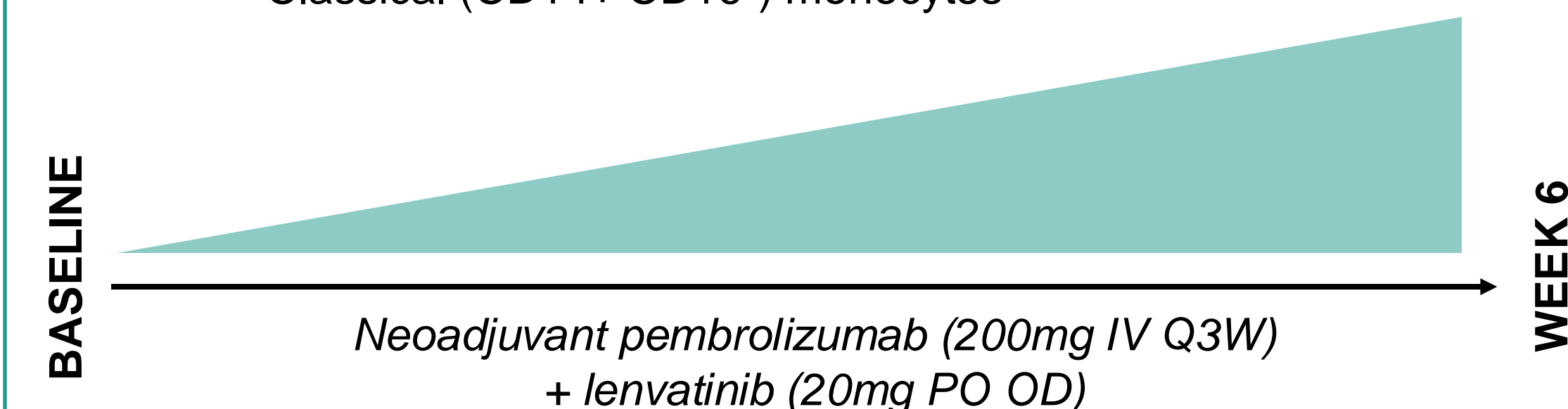


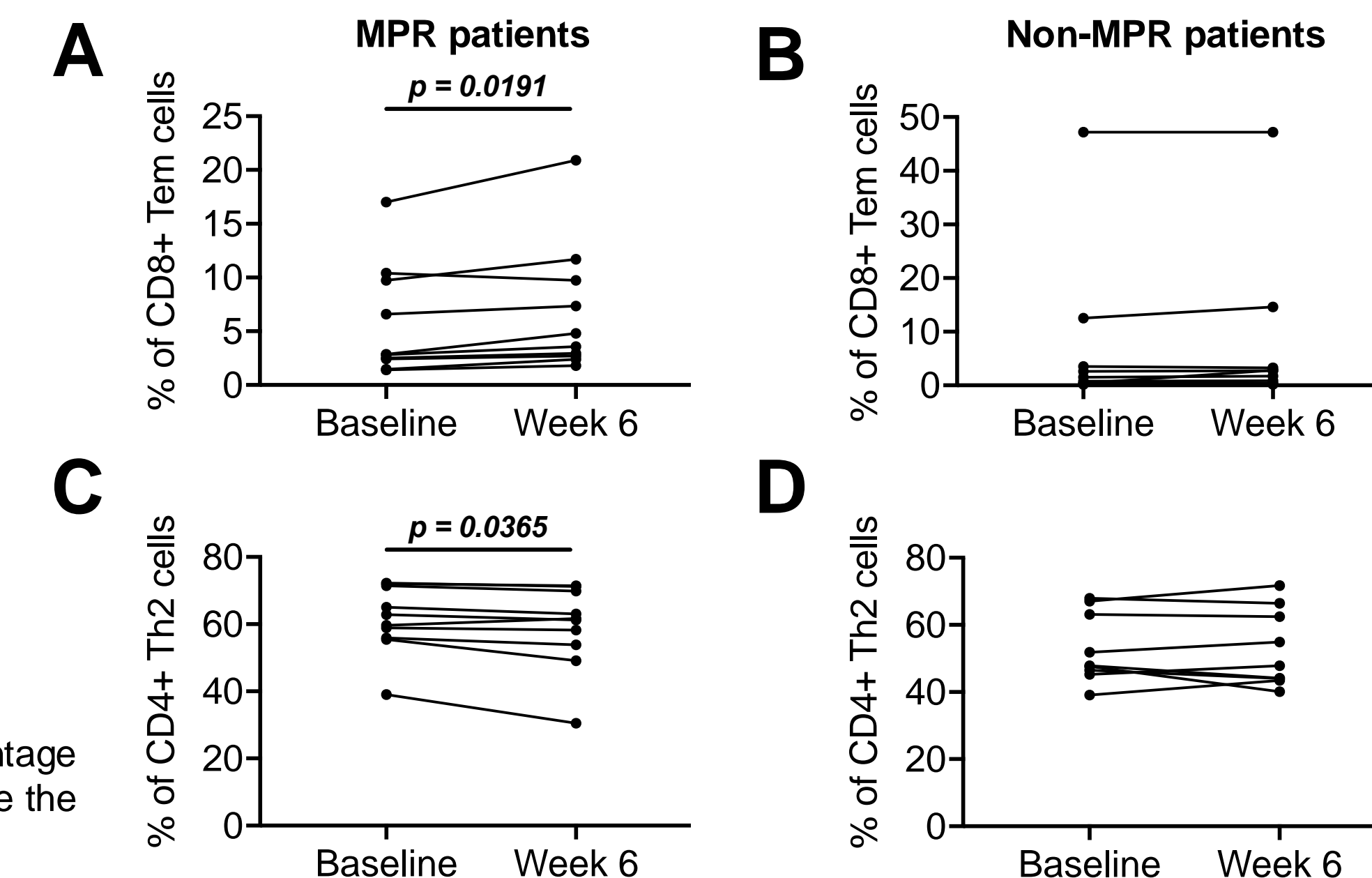
FIGURE 3. Effect of 6 weeks of neoadjuvant pembrolizumab + lenvatinib in the peripheral immune profile, independent of the pathological response.

3. Baseline → Post NeoIT (PD1 + Lenvatinib): MPR versus non-MPR

TABLE 1. Summary table of the peripheral immune responses from baseline (pre-NeoIT) to week 6 (post-NeoIT) that differed between MPR versus. non-MPR patients.

Cell type (baseline → week 6)	MPR	Non-MPR
Effector memory CD8 T cells (CD8+ Tem): CD3+ CD8+ CD45RA- CCR7- CD45RO+ CD27-	↑	
Effector memory CD4 T cells (CD4+ Tem): CD3+ CD4+ CD45RA- CCR7- CD45RO+ CD27-	↑	
CD4+ Th2 (CD3+ CD4+ GATA3+)	↓	
Cytotoxic (CD56dim CD16+) NK cells	↑	
Cytokine producers (CD56bright CD16-) NK cells		↓

FIGURE 4. Effect of neoIT on the peripheral immune profile in MPR versus non-MPR patients. Percentage of CD8+ Tem increases at week 6 (from baseline) MPR patients (A), but not in non-MPR patients (B); while the % of CD4+ Th2 decreases at week (from baseline) in MPR patients (C), but not in non-MPR patients (D).



References

- Patel SP, et al. NEJM 2023.
- Blank CU, et al. NEJM 2024.
- Pires da Silva I, et al. Presented at ASCO 2024; Abstract #9566.
- Long GV, et al. Presented at ESMO 2022; Abstract #3819.

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