

Neoadjuvant pembrolizumab plus lenvatinib in resectable stage III melanoma patients (NeoPele): analysis of the tumor microenvironment (TME) and of the peripheral immune profile correlated to pathological response.

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Background & Objectives

- Neoadjuvant immunotherapy (NeoIT) with anti-PD-1 (PD1) alone or in combination with anti-CTLA-4 is associated with better event-free survival (EFS) compared with adjuvant PD1 for patients with resectable clinical stage III melanoma^{1,2}.
- Patients with major pathological response (MPR, $\leq 10\%$ viable cells in the tumor bed) with NeoIT rarely recur; while non-MPR patients are at higher risk of recurrence³.

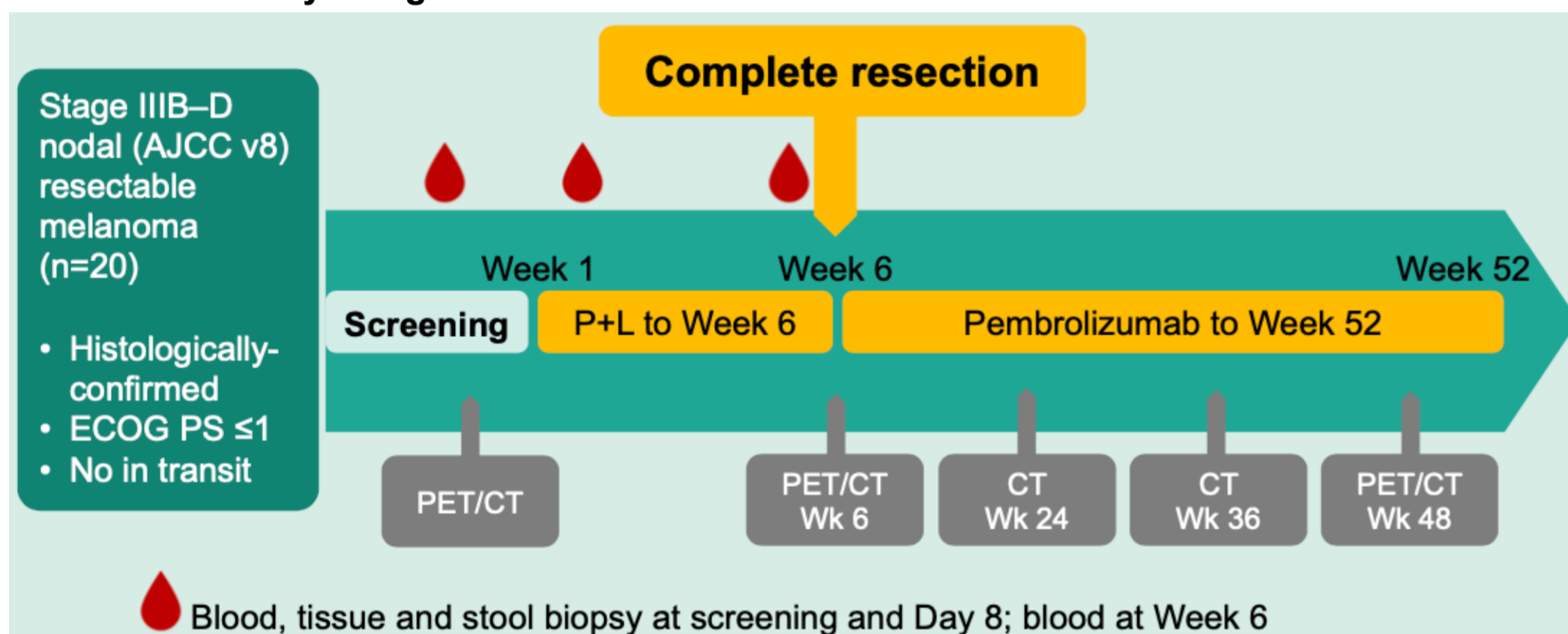
We sought to characterize the TME and the peripheral immune profile before and after NeoIT (PD1 + lenvatinib) in MPR vs. non-MPR patients.

Methods

- Patients with stage IIIB-D melanoma treated with 6 weeks of PD1-based neoIT (PD1 + lenvatinib) were included (NCT04207086).
- Multiplex immunofluorescence (mIF) and pathway enrichment analyses (PEA; RNAseq) were performed on baseline (BL) and 6 weeks post-treatment (post-Tx) tissue samples.
- Cytometry by time of flight (CYTOF; 39-marker panel) was performed on peripheral blood mononuclear cells (PBMCs) at BL and 6 weeks post-Tx, prior to surgery.

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

FIGURE 1. Study design⁴.



Baseline \rightarrow Post NeoIT (PD1 + Lenvatinib): IHC

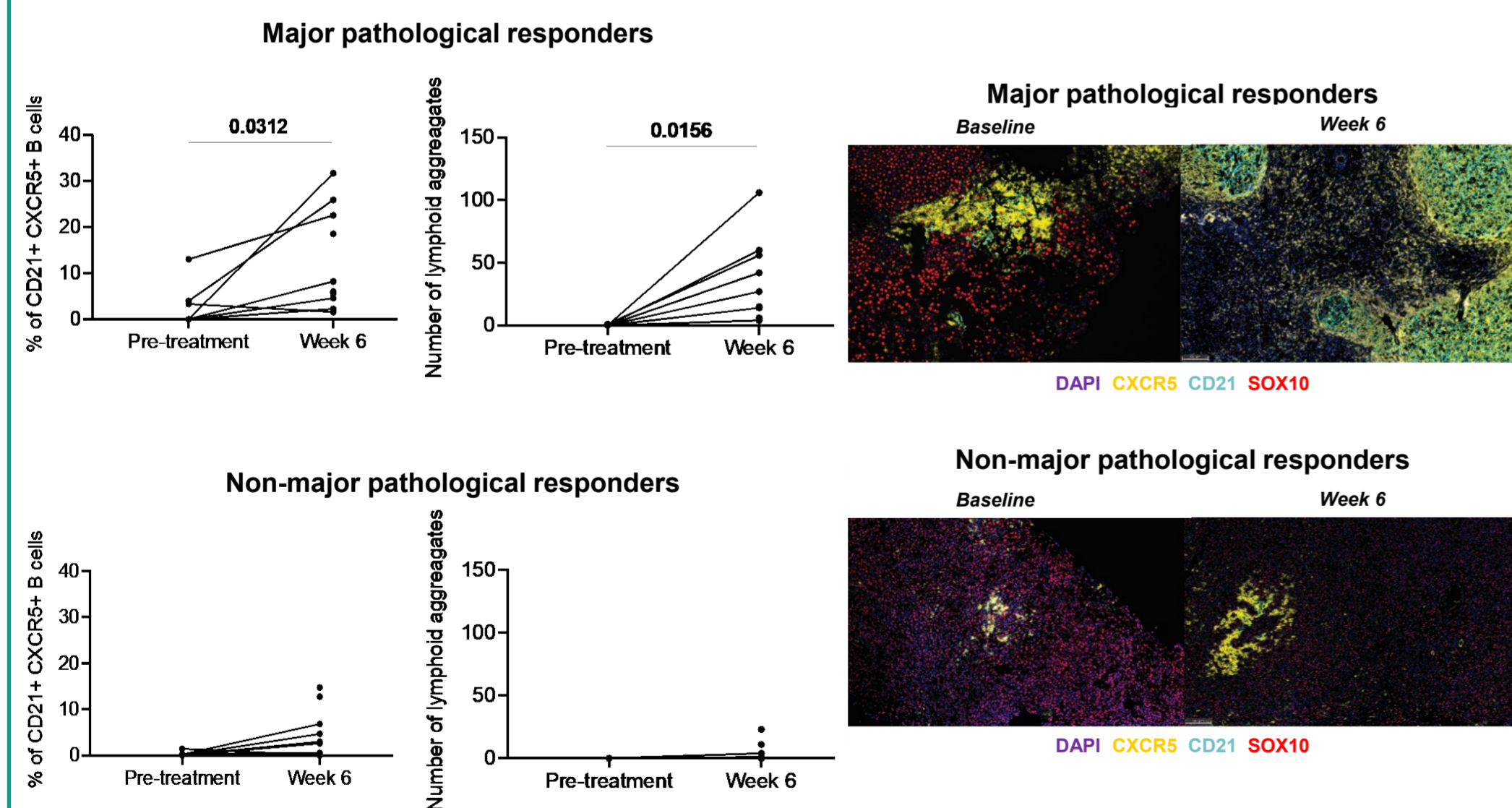


FIGURE 2. Effect of neoIT on the TME (IHC) in MPR versus non-MPR; analysis of the B cell compartment and of the lymphoid aggregates.

Baseline \rightarrow Post NeoIT (PD1 + Lenvatinib): RNAseq

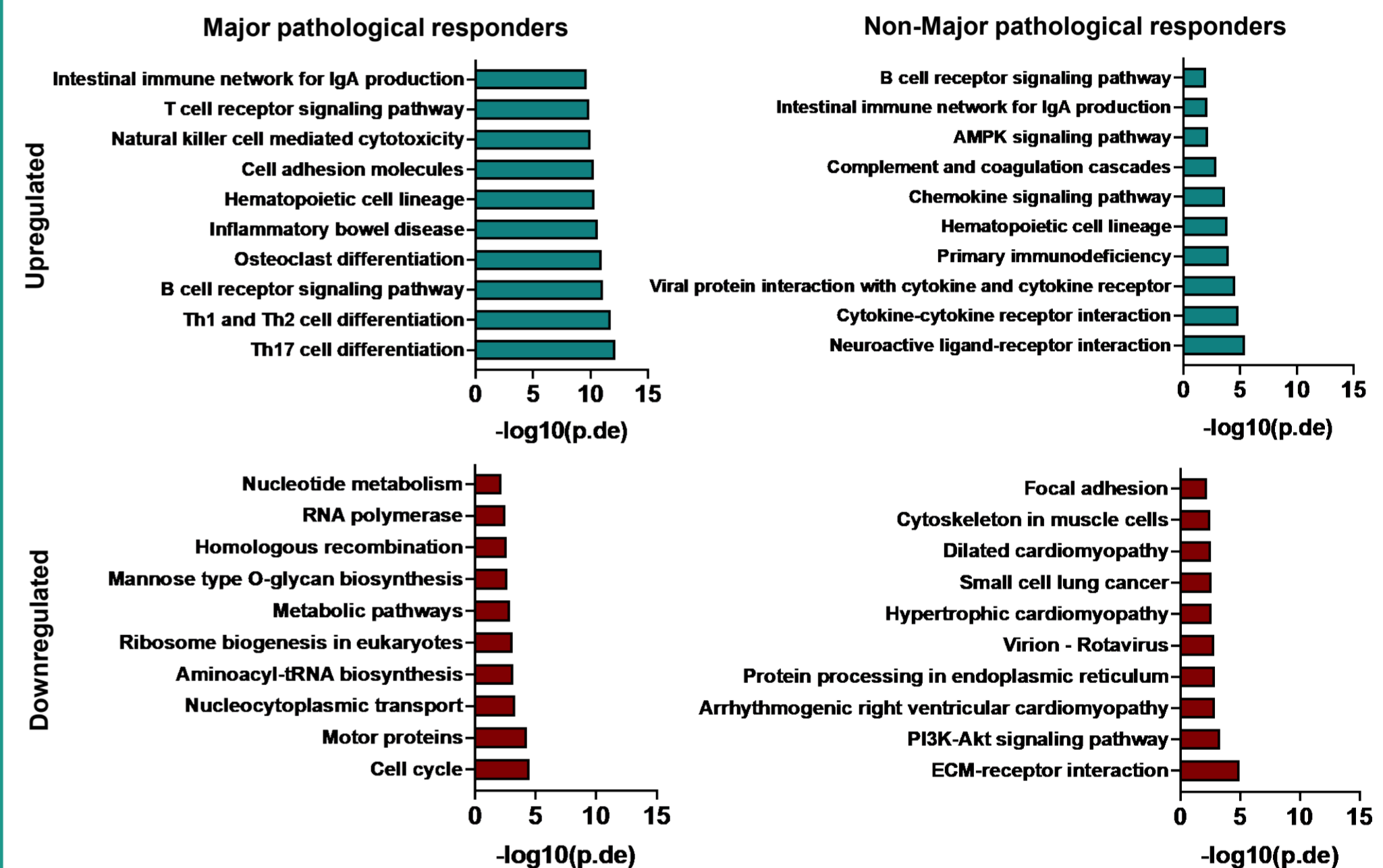


FIGURE 3. Effect of neoIT on the TME (RNAseq - PEA) in MPR versus non-MPR; top 10 pathways upregulated and downregulated in MPR versus non-MPR patients.

Baseline \rightarrow Post NeoIT (PD1 + Lenvatinib): CyTOF

TABLE 1. Peripheral immune responses from baseline (pre-NeoIT) to week 6 (post-NeoIT) that differed between MPR versus non-MPR patients.

Cell type (baseline \rightarrow 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		↓

Conclusions

- Baseline differences were observed in the TME and PBMCs from MPR versus non-MPR patients, and could help predicting response to NeoIT.
- NeoIT induces a stronger local and peripheral anti-tumor response in MPR vs. non-MPR patients, which may contribute to the better EFS observed in MPR patients.

References

- Patel SP, et al. NEJM 2023.
- Blank CU, et al. NEJM 2024.
- Menzies AM, et al. Nature Medicine 2021.
- Long GV, et al. ESMO 2022, Abstract #3819.

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