

Background

- Neoadjuvant immunotherapy (NeoIT) has demonstrated impressive efficacy in stage III melanoma; patients who achieve a major pathological response (MPR; <10% viable tumour) rarely recur^{1,2,3}.
- However, it remains unclear how different PD1 based combinations modulate the tumour immune microenvironment (TME) and contribute to therapeutic response.
- Lenvatinib, a multi-tyrosine kinase inhibitor with anti-angiogenic and immunomodulatory effects, may synergise with PD1 blockade by altering immune infiltration and tumour proliferation.

Objectives

To characterise and compare the tumour immune microenvironment in patients treated with neoadjuvant PD1 alone versus PD1+Lenvatinib, and to identify immune features associated with pathological response.

Methods

- Patients with stage III melanoma treated with 6 weeks of PD1+Lenvatinib (NeoPele - NCT04207086) or PD1 alone (NeoTrio-NCT0285921) were included.
- Multiplex immunohistochemistry (mIHC) and RNA sequencing (RNA-seq) analysis were performed on tumour samples collected at baseline (pre-treatment) and at week 6 post-treatment.

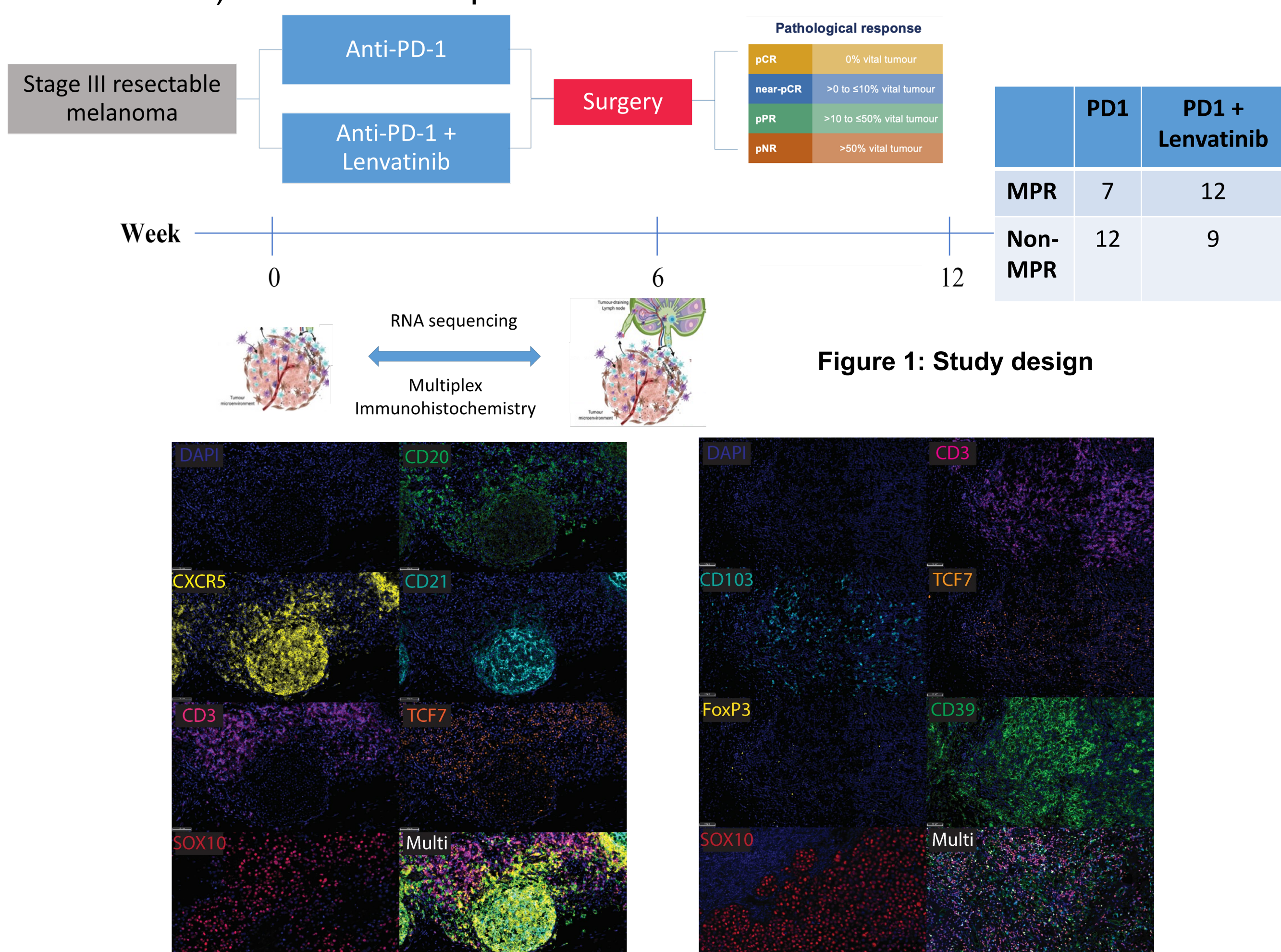


Figure 1: Study design

Figure 2: Multiplex IHC showing A) B-cell panel and B) T-cell panel

Results

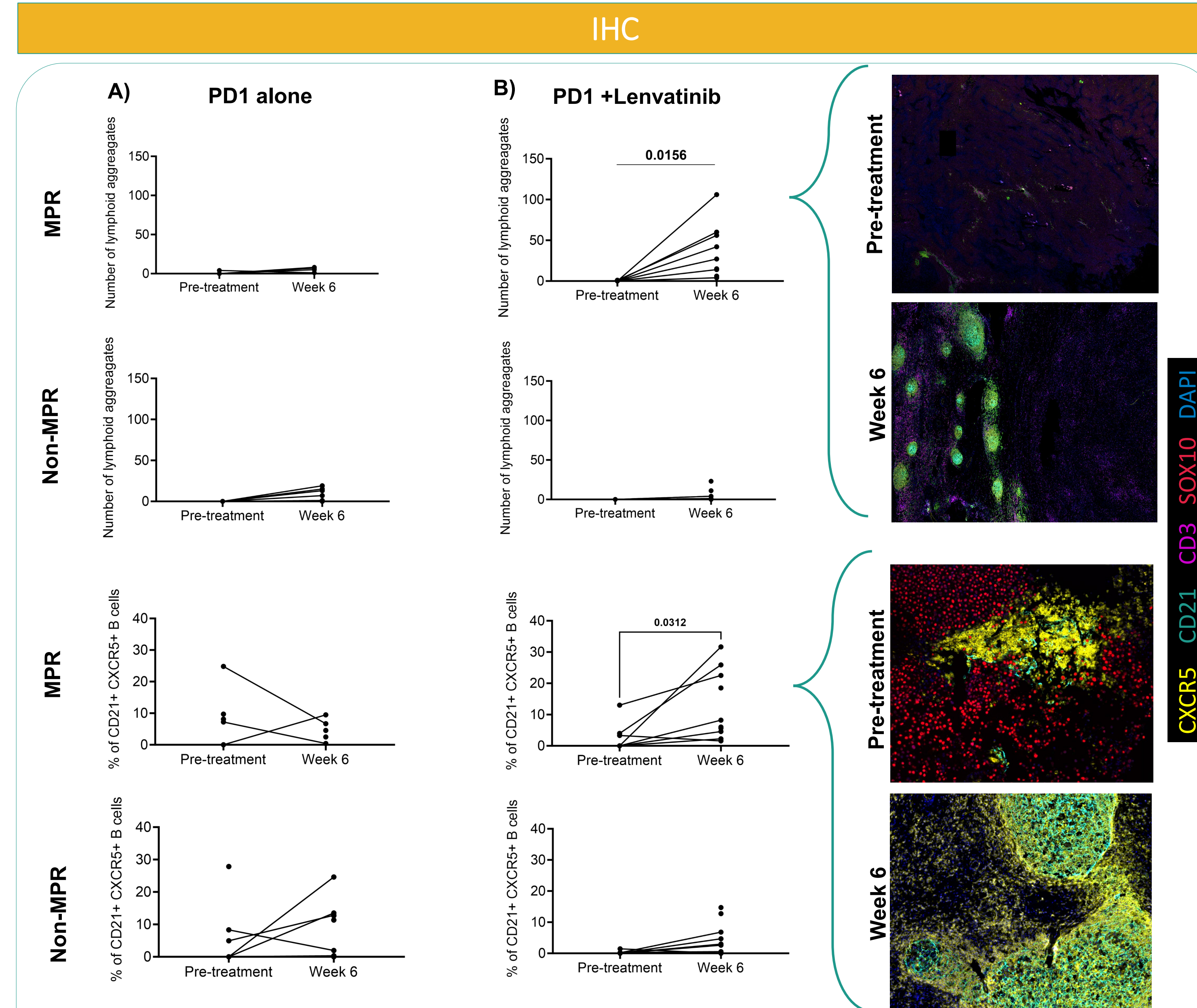


Figure 3: B-cell compartment showing changes pre-treatment to week 6 by path response in A) PD1 alone and B) PD1 +Lenvatinib treated patients

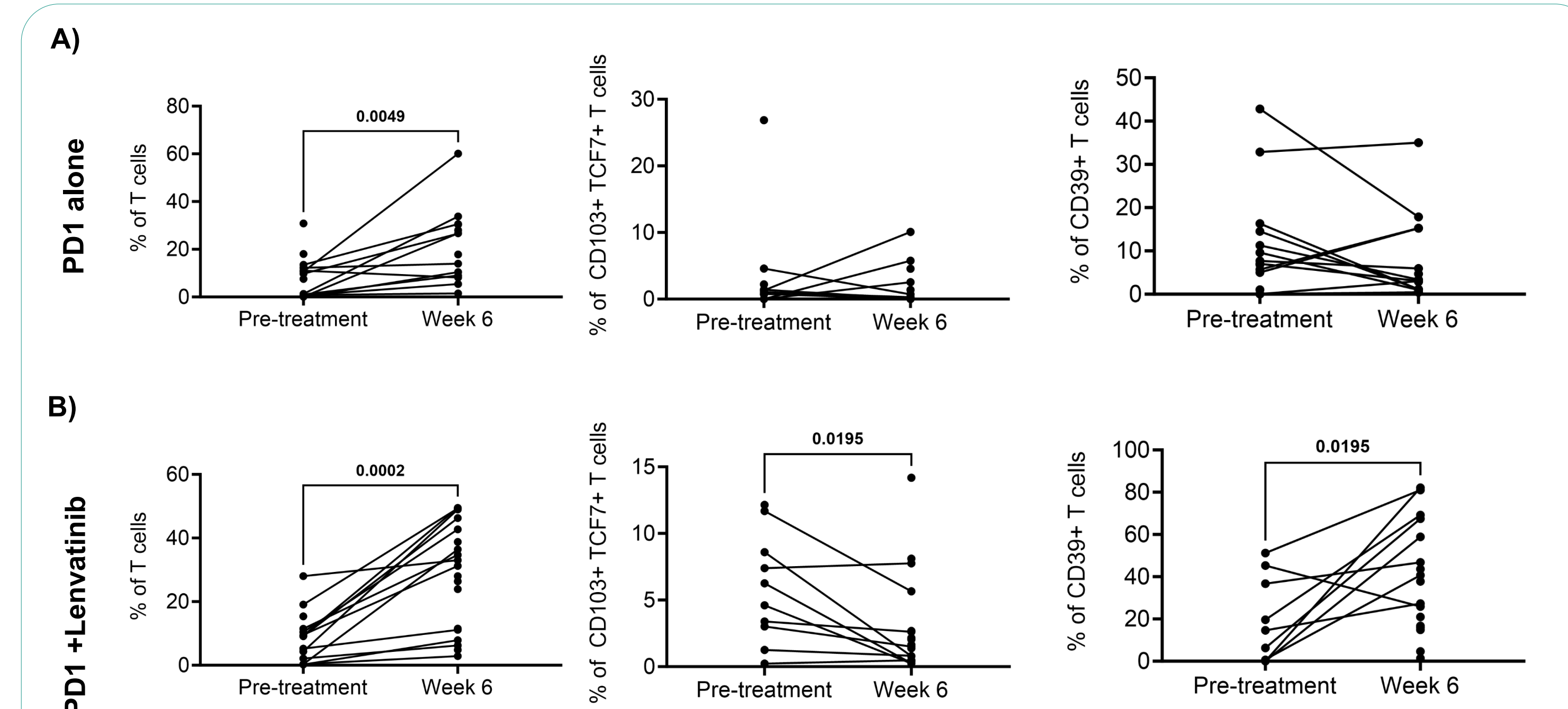


Figure 4: T-cell compartment showing changes pre-treatment to week 6 in A) PD1 alone and B) PD1 +Lenvatinib treated patients, regardless of pathological response

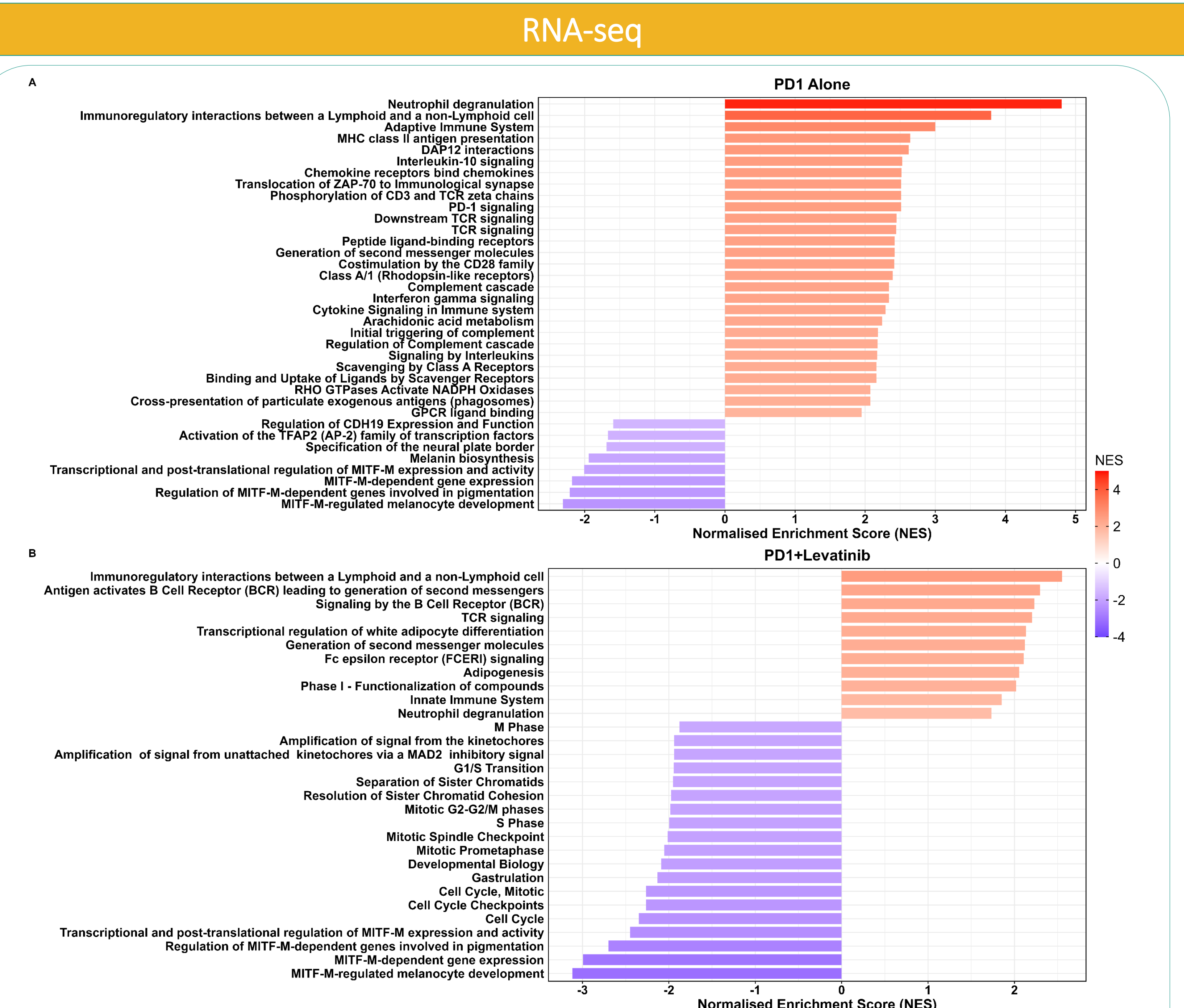


Figure 5: Reactome pathways upregulated (red) or downregulated (blue) from pre-treatment to week 6 in patients treated with A) PD1 alone and B) PD1+Lenvatinib

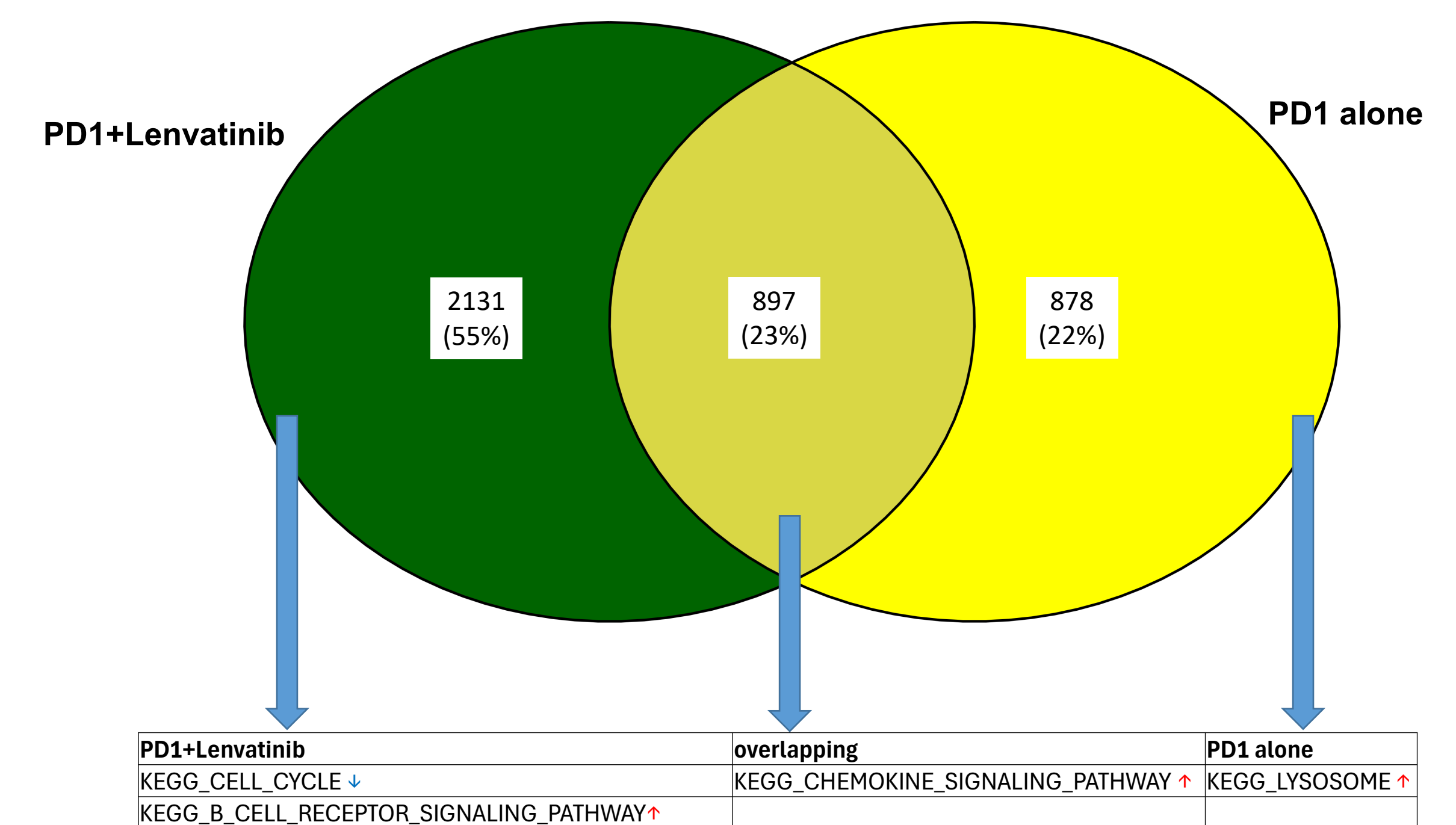


Figure 6: Number of treatment unique and overlapping genes up or down regulated from pre-treatment to week 6 and associated KEGG pathways in MPR patients treated with PD1 alone or PD1+Lenvatinib

Conclusions

- PD1 + Lenvatinib induces distinct immune activation in the tumour microenvironment compared to PD1 alone, particularly via an increase in B-cell activity and suppression of cell proliferation pathways.
- These features were strongly associated with a major pathological response, suggesting a unique mechanism of action with potential translational relevance for biomarker development that should also be further tested functionally to understand the mechanisms of lenvatinib.
- Further analysis of peripheral immune responses are also underway.

References

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

Acknowledgments

All patients and their families
Melanoma Institute Australia

