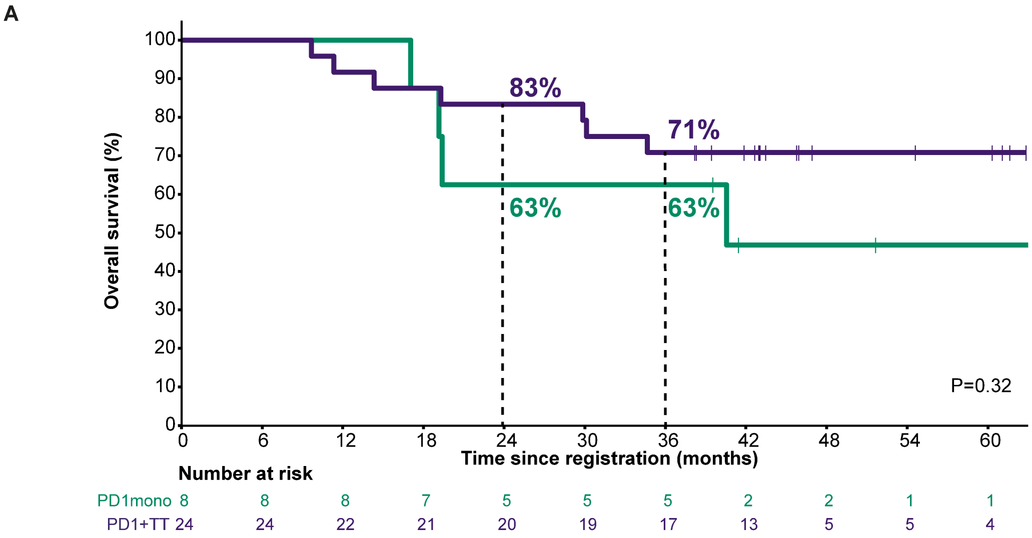
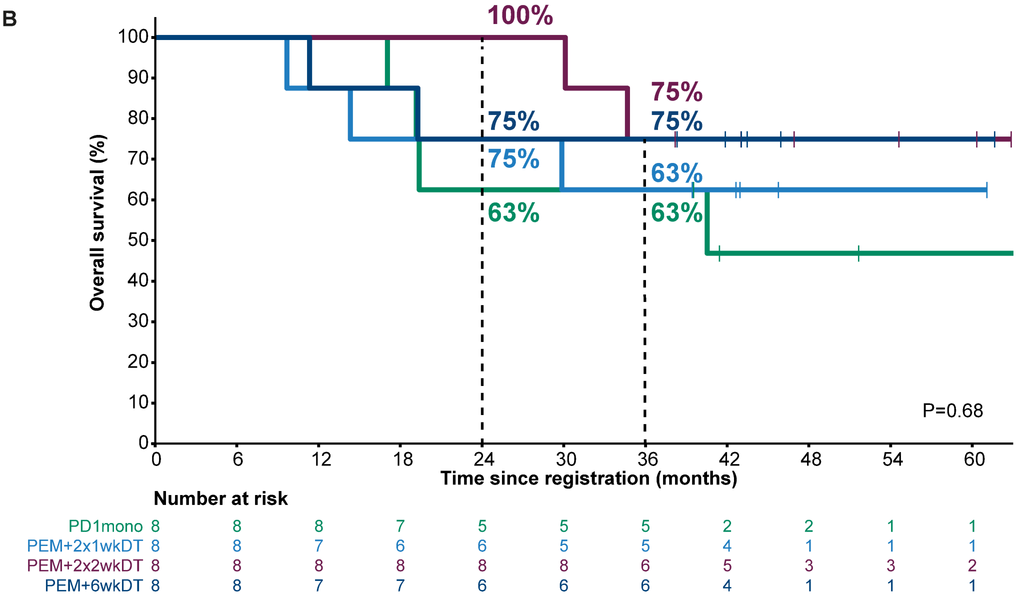
Supplemental Materials

Supplement to: 'The IMPemBra trial, a phase 2 study comparing pembrolizumab with intermittent/short-term dual MAPK pathway inhibition plus pembrolizumab in melanoma patients harboring the BRAFV600 mutation'

Supplemental figure S1



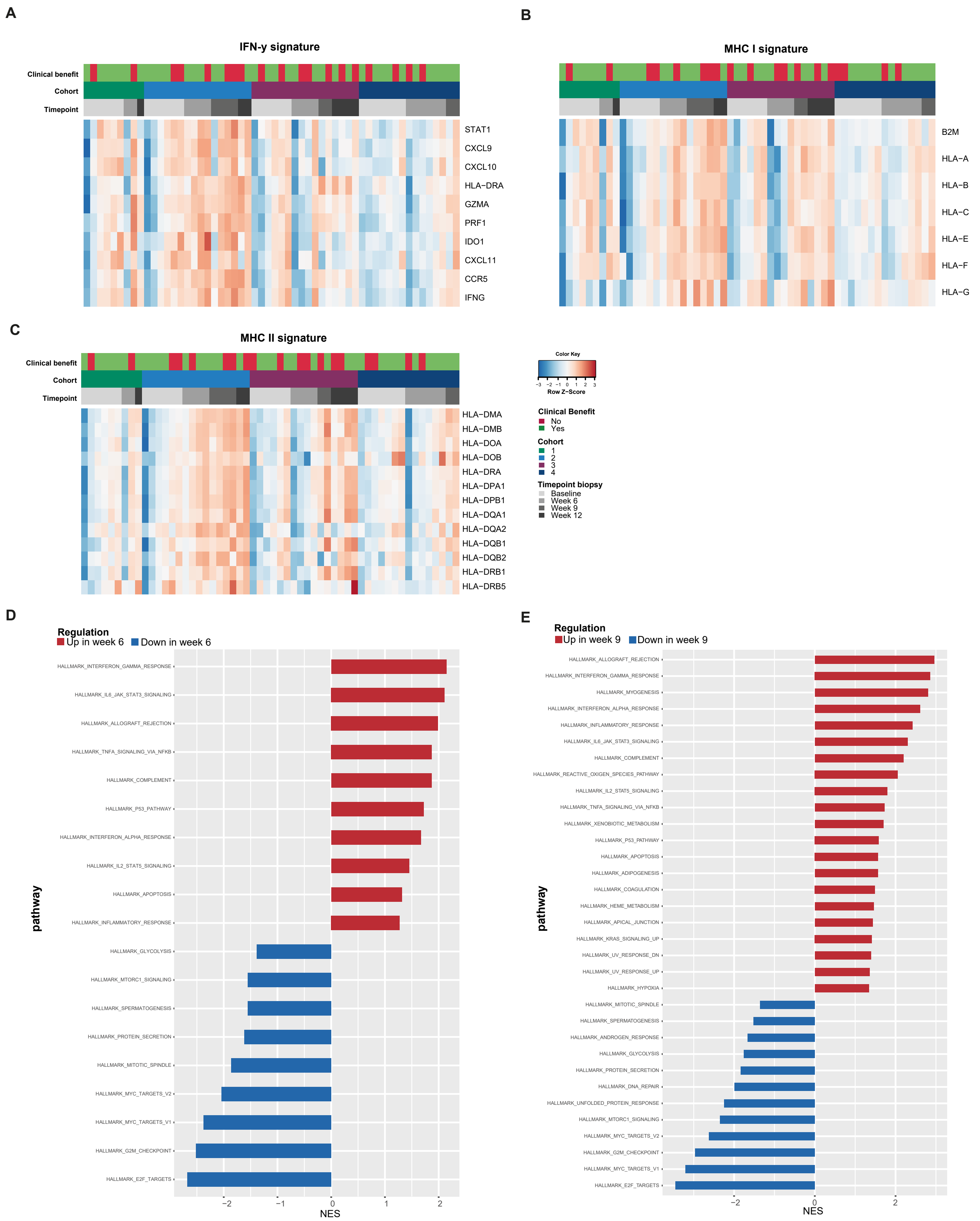


Supplemental Figure S1

A. Overall-survival curves, comparing patients treated with pembrolizumab only (green) to patients who received pembrolizumab with short-term dabrafenib plus trametinib (purple).

B. Overall survival curves of all individual cohorts.

Supplemental figure S2



Supplemental Figure S2

Heatmap of the IFN-γ RNA signature[1] (**A),** MHC I signature (**B**) and MHC II signature (**C**) as previously described[2], ordered according average z-score of all genes, per cohort and time point. Z-scores were calculated based on the gene expression counts normalized by DESeq2. Each column represents a different biopsy. For every biopsy it is indicated on which time point it was taken (greyscale), in which cohort the corresponding patients was treated (dark green: cohort 1, light blue: cohort 2, indigo: cohort 3, dark blue: cohort 4) and whether the patient had clinical benefit (light green: clinical benefit, red: no clinical benefit). Positive values (red) indicate higher expression and negative values (blue) indicate lower expression. **D.** Gene set enrichment analysis (GSEA) displaying hallmark gene sets that are significantly enriched in week 6 (red) or downregulated in week 6 (blue) as compared to baseline. Pathways are ordered according to the normalized enrichment scores (NES). NES were computed as previously described[3]. **E**. GSEA displaying hallmark gene sets that are significantly enriched in week 9 (red) or downregulated in week 9 (blue) as compared to week 6, only in patients in cohort 2-4 whom were treated with additional targeted therapy during those weeks. Pathways are ordered according to the normalized enrichment scores (NES). NES were computed as previously described[3]

References

1. Ayers M, Lunceford J, Nebozhyn M, et al. IFN-gamma-related mRNA profile predicts clinical response to PD-1 blockade. *The Journal of clinical investigation* 2017;127(8):2930-40. doi: 10.1172/JCI91190
2. Ribas A, Lawrence D, Atkinson V, et al. Combined BRAF and MEK inhibition with PD-1 blockade immunotherapy in BRAF-mutant melanoma. *Nature medicine* 2019;25(6):936-40. doi: 10.1038/s41591-019-0476-5 [published Online First: 2019/06/07]
3. Subramanian A, Tamayo P, Mootha VK, et al. Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles. *Proceedings of the National Academy of Sciences* 2005;102(43):15545-50. doi: 10.1073/pnas.0506580102