Supplementary data

Supplementary Figure 1: Neither genetic melanoma subtype, brain metastasis status nor response to ICI therapy translate into global DNA methylation patterns in ICI treated stage IV melanoma patients.

(A) Principal component analyses and (B) plotting of group-wise average DNA methylation values for CpG sites of 65 melanoma patients based on *BRAF* mutation status, *NRAS* mutation status, presence or absence of brain metastases and the response status to ICI therapy defined as progressive disease (PD) or disease control (DC). (B) Differentially methylated regions according to a p-value below 1x10-5 are marked in red.

Supplementary Figure 2: Parameter selection for MeDeCom analysis in the total cohort (TCGA + ICI cohort).

(A) Cross validation error plotted against the number of LMCs k. Cross validation error tends to decrease with more components being included and we selected k=8 as the value where the error starts to level out. (B) Selection of the regularization parameter λ for k=8. We selected λ=0.001 as the point where the cross-validation error is still low, while the objective function tends to increase.

Supplementary Figure 3: Reference-based tumor deconvolution of the DNA methylome by LUMP and MethylCIBERSORT indicates a microenvironmental signature of a particular LMC-based cluster of the TCGA cohort and no major differences in the LMC-based clusters of the ICI cohort.

Tumor deconvolution of the TCGA melanoma cohort (A, B) and the ICI cohort (C, D), respectively, was performed by the reference-based (A, C) LUMP and (B, D) MethylCIBERSORT algorithm. The LUMP estimate ratio and proportions (in percent) of the

respective cell type were compared between patients belonging to the distinct LMC-based clusters 1 and 2 using the non-parametric Wilcoxon's test (significant p-values in bold italics, number of patients in parentheses).

Supplementary Figure 4: Reference-based tumor deconvolution of the DNA methylome shows no major differences in cellular composition with regard to sample collection before or after onset of ICI treatment.

DNA methylome-based tumor deconvolution was performed by the reference-based algorithms (A) LUMP and (B) MethylCIBERSORT. The LUMP estimate ratio and the proportions (in percent) of the respective cell type were compared in tissue prior (pre-ICI) and after (post-ICI) onset of ICI treatment using the non-parametric Wilcoxon's test (significant p-values in bold italics, number of patients in parentheses).