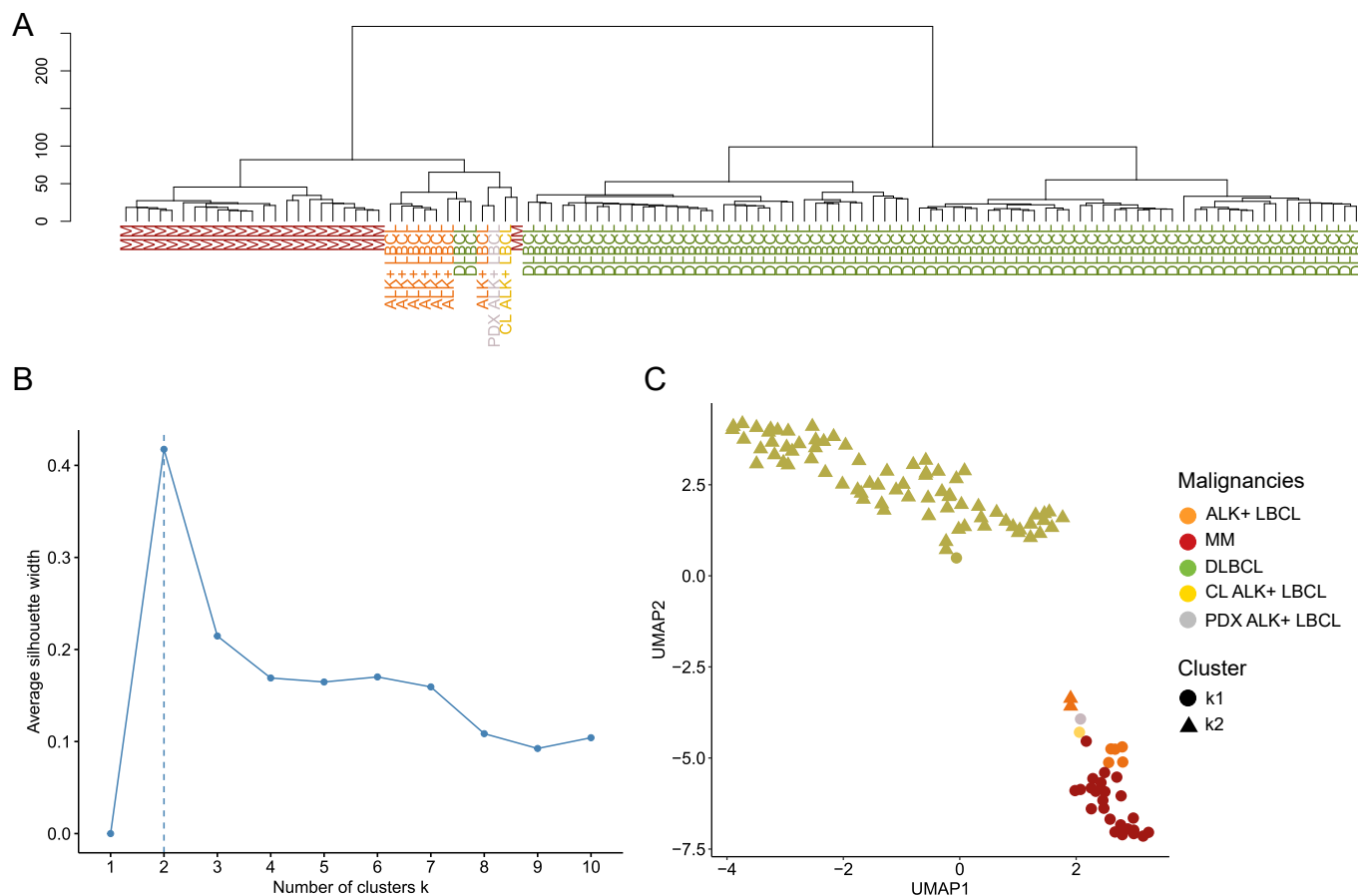
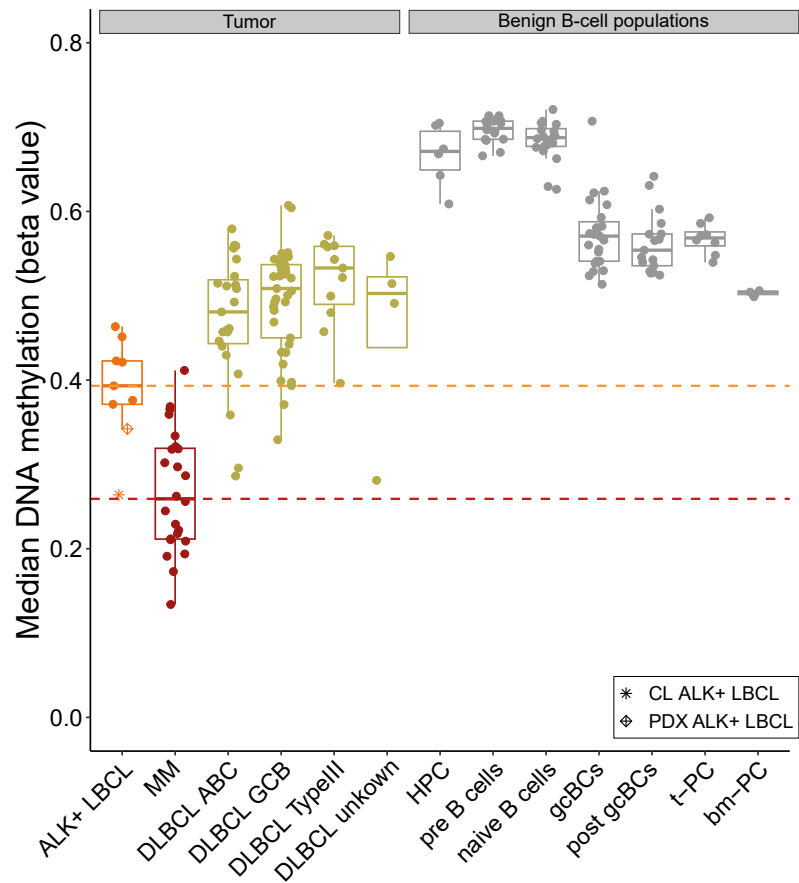


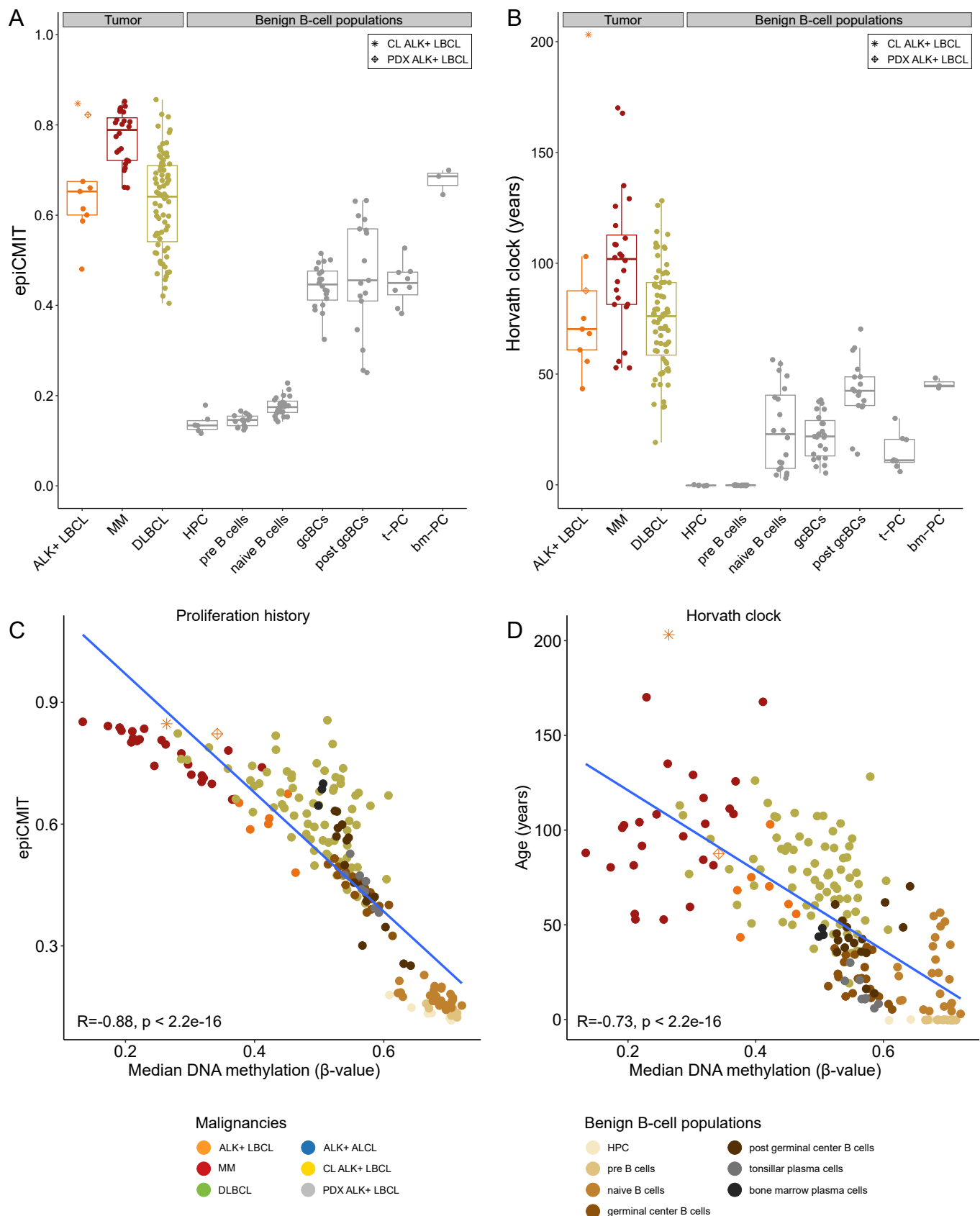
Supplemental Figure S1: UMAP analysis of T- and B-cell malignancies. UMAP analysis (20 neighbors) was performed using all 441,870 CpGs including ALK-positive LBCL (n=7), DLBCLs (n=75), MM (n=24) and ALK-positive ALCLs (n=12).



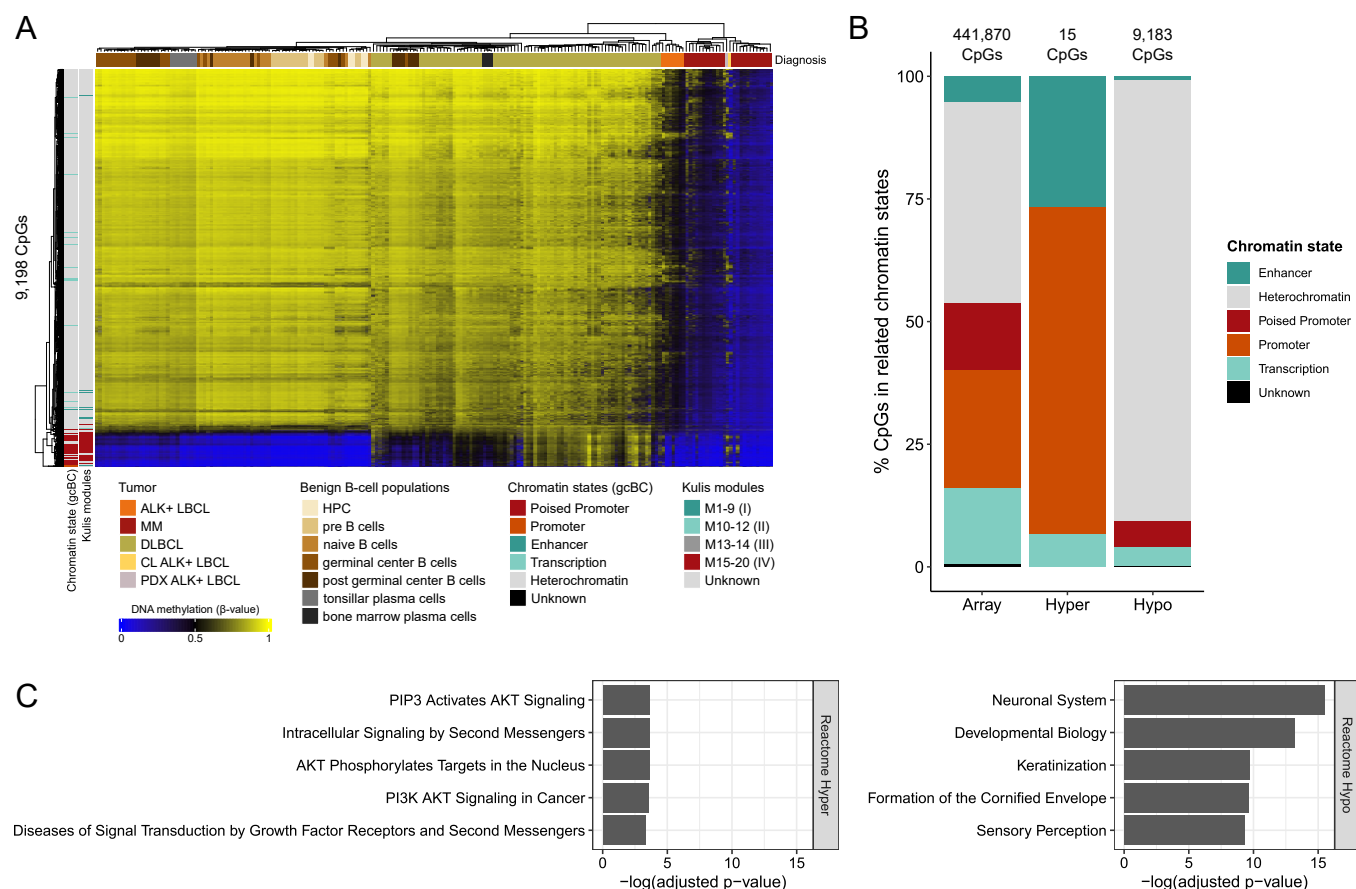
Supplemental Figure S2: Clustering based on the 10,000 most variable CpGs (ALK-positive LBCL, MM, DLBCL). (A) Hierarchical clustering (ward.d2) dendrogram of the 10,000 most variable CpGs. Cluster relationships highlight the epigenetic similarities and differences across these samples. (B) Calculation of the optimal number of k-means clusters using the 10,000 most variable CpGs (R package cluster). Dashed line represents suggested optimal number of k-means clusters. (C) UMAP plot based on Figure 1B additionally shaped according to the suggested clusters by k-means (k1-2). CL: cell line, PDX: patient-derived xenograft model, LBCL: large B-cell lymphoma, MM: multiple myeloma, DLBCL: diffuse large B-cell lymphoma.



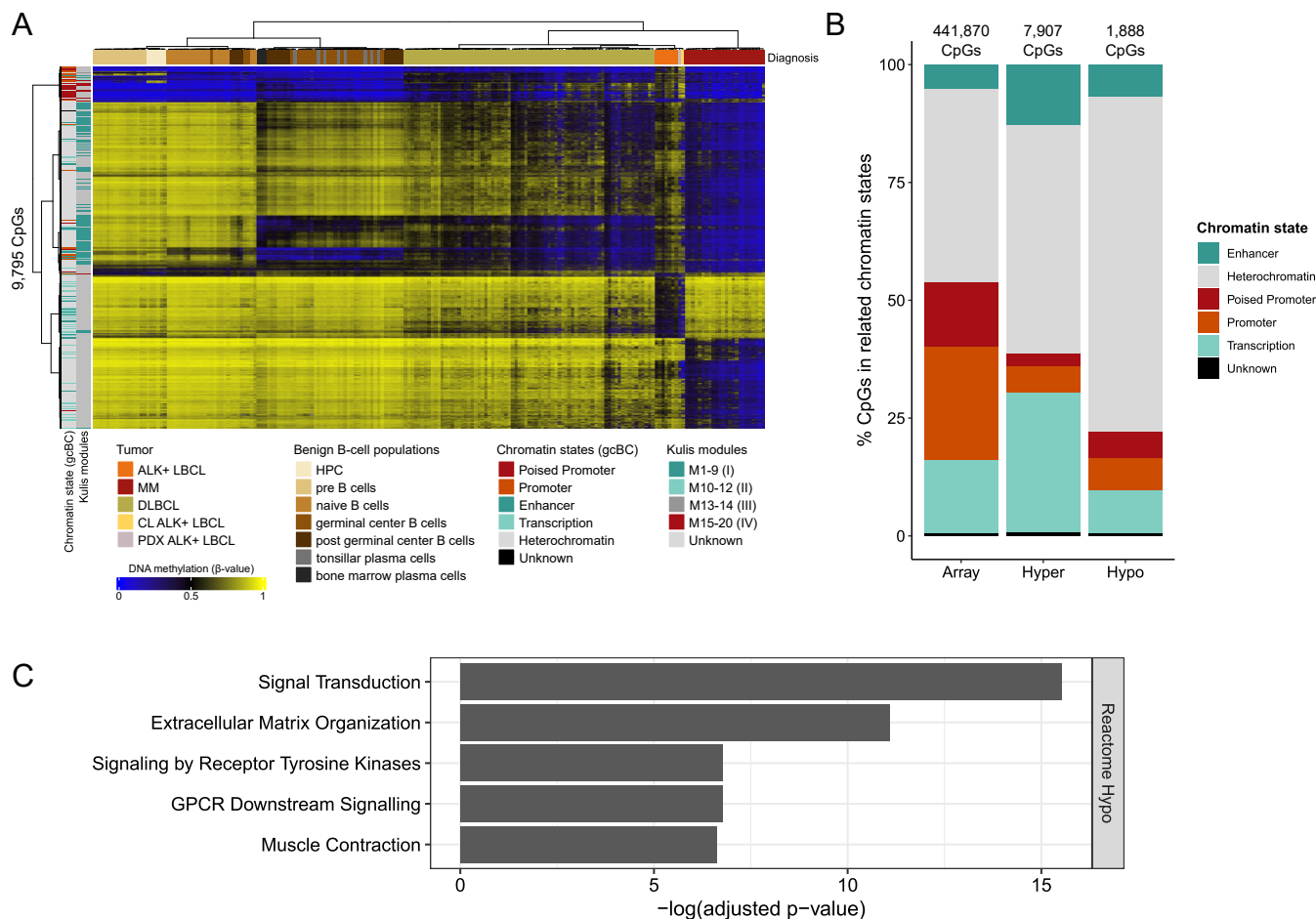
Supplemental Figure S3: Median DNA methylation of various B-cell lymphomas and benign B-cell populations across the 441,870 CpGs. LBCL: large B-cell lymphoma, ABC: activated B-cell-like: GCB: germinal center B-cell-like, MM: multiple myeloma, DLBCL: diffuse large B-cell lymphoma, HPC: hematopoietic stem cells, t-PC: plasma cells from tonsils, bm-PC: plasma cells from bone marrow, CL: cell line.



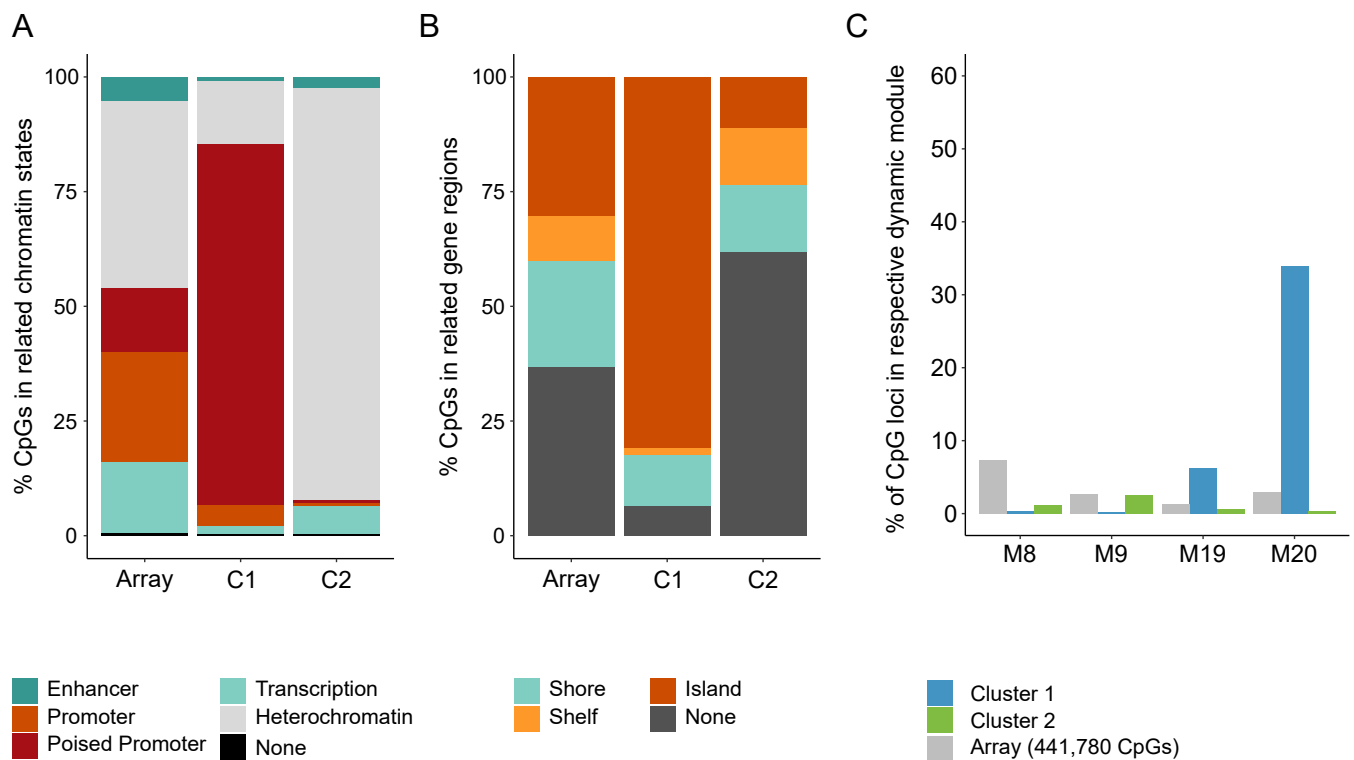
Supplemental Figure S4: Analysis of epigenetic age and relative proliferative history. (A) Relative proliferative history, as determined by the epigenetically-derived cumulative mitotic clock (epiCMIT), and (B) epigenetic age, calculated using the Horvath clock, were assessed for various malignancies (ALK+ LBCL, MM, DLBCL) and benign B-cell populations. (C) Pearson correlation of median DNA methylation levels with relative proliferative history and (D) with epigenetic age. LBCL: large B-cell lymphoma, MM: multiple myeloma, DLBCL: diffuse large B-cell lymphoma, HPC: hematopoietic stem cells. CL: cell line.



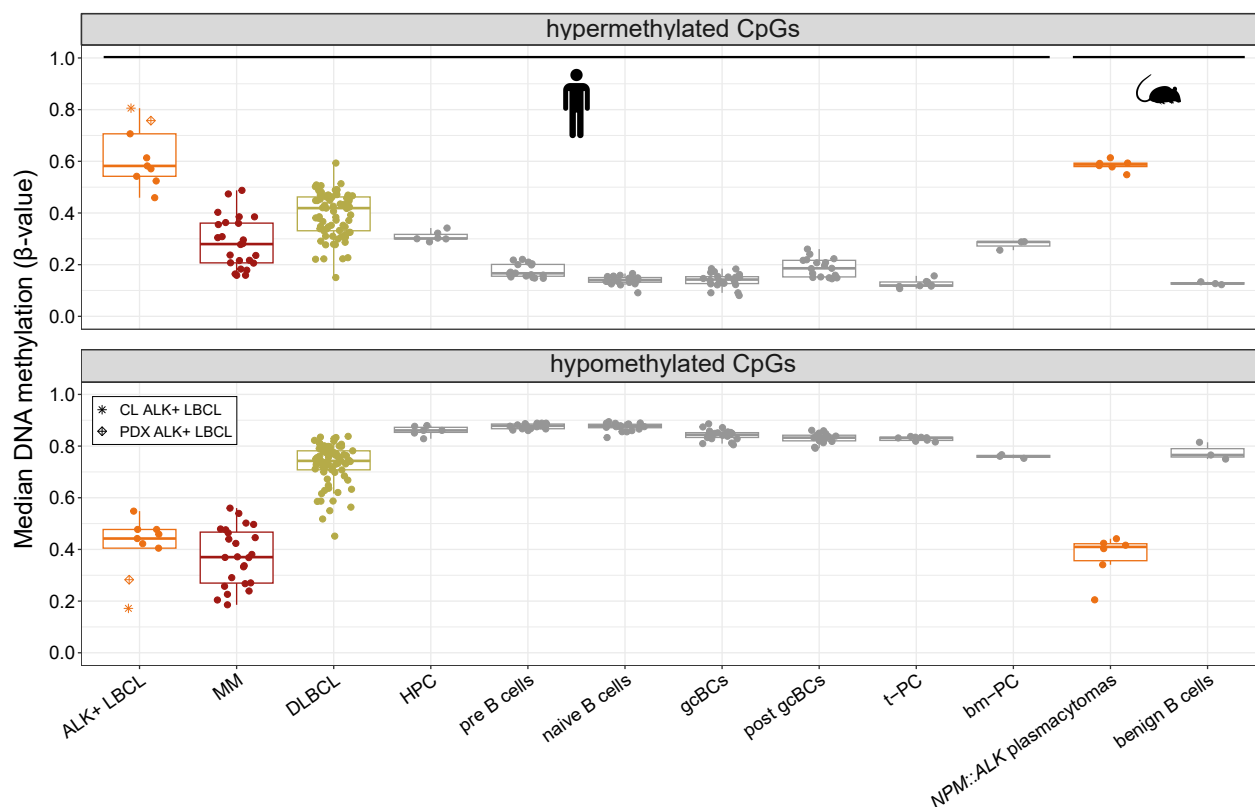
Supplemental Figure S5: Differential DNA methylation analysis of ALK-positive LBCL and MM versus DLBCL. Differential DNA methylation analysis revealed 9,198 CpG sites (FDR < 0.001, mean $|\Delta\beta| > 0.4$), of which 15 were hypermethylated and 9,183 hypomethylated in ALK-positive LBCL and MM compared to DLBCL. **(A)** Heatmap representing DNA methylation levels of the 9,198 CpGs. Samples are listed per column, CpGs per row. CpGs are further annotated according to chromatin states in germinal center B cells and Kulis modules. **(B)** Chromatin state annotation (based on germinal center B cells) of the differentially methylated CpGs. **(C)** Gene ontology enrichment analysis (top five according to adjusted p-value) of the genes affected by hypermethylated (left; 14 genes) and hypomethylated (right; 2,066 genes) CpGs. LBCL: large B-cell lymphoma, MM: multiple myeloma, DLBCL: diffuse large B-cell lymphoma, HPC: hematopoietic stem cells.



Supplemental Figure S6: Differential DNA methylation analysis of ALK-positive LBCL and MM versus DLBCL. Differential DNA methylation analysis revealed 9,795 CpG sites (FDR < 0.01, mean $|\Delta\beta| > 0.3$), of which 7,907 were hypermethylated and 1,888 hypomethylated in ALK-positive LBCL compared to MM. **(A)** Heatmap representing DNA methylation levels of the 9,795 CpGs. Samples are listed per column, CpGs per row. CpGs are further annotated according to chromatin states in germinal center B cells and Kulis modules. **(B)** Chromatin state annotation (based on germinal center B cells) of the differentially methylated CpGs. **(C)** Gene ontology enrichment analysis (top five according to adjusted p-value) of the genes affected by hypermethylated (2,425 genes) CpGs. LBCL: large B-cell lymphoma, MM: multiple myeloma, DLBCL: diffuse large B-cell lymphoma, HPC: hematopoietic stem cells.



Supplemental Figure S7: Investigation of the 10,000 most variable CpGs between ALK-positive LBCL, multiple myeloma and DLBCL. **A:** Mapping of the 10,000 CpGs according to the two clusters (C1: cluster 1 with 4,861 CpGs, C2: cluster 2 with 5,139 CpGs) to chromatin states defined in germinal center B cells. For background comparison the 441,870 cpGs are displayed (array). **B:** Mapping of the 10,000 CpGs according their related gene position (Shore: ~2 kb from CpG Island, Shelf: ~4 kb from CpG Island). **C:** CpGs within the two CpG clusters were mapped to the Kulis modules (M1-M20), representing different B-cell differentiation states. Only those with the highest enrichments for the two clusters are displayed.



Supplemental Figure S8: Median DNA methylation of differentially methylated CpGs in human and murine ALK-positive B-cell neoplasms. Box plot displaying median DNA methylation levels of differentially methylated CpGs in human and murine ALK-positive B-cell neoplasms compared to germinal center B cells. Differentially methylated CpGs are categorized into hypermethylated (top) and hypomethylated (bottom) groups. In human ALK-positive B-cell neoplasms, 4,544 CpGs are hypermethylated and 49,426 CpGs are hypomethylated, while in murine ALK-positive B-cell neoplasms, 2,498 CpGs are hypermethylated and 51,909 CpGs are hypomethylated. gcBC: germinal center B cells; t-PC: plasma cells from tonsils; bm-PC: plasma cells from bone marrow.