Figure S1. Mononuclear phagocyte landscape in human CLM by scRNA-seq. (**A**) Schematic representation of tissue sampling, normal adjacent and invasive margin regions, from 3 CLM patients. (**B**) Flow cytometry gating strategy to isolate CD45$^+$ cells and MP from CLM. (**C**) Violin plots showing mean nUMI and number of detected genes in NA and IM datasets. (**D**) Pie charts showing proportions of cell clusters of 3 CLM patients. (**E**) Expression heatmap of significant top ten genes per cluster. Selected genes are labelled. Rows represent marker genes. Columns represent individual cells. (**F**) Dot plot showing expression of relevant genes across clusters. Circle size represents the proportion of cells expressing each gene; color represents average gene expression in each cluster. (**G**) Volcano plot showing differentially expressed genes between KC(1-2) and TAM. Exemplar genes are labelled. Colored dots represent genes with log2(fold change)≥0.5 and adjusted P-value<0.05. (**H**) Barplot showing the number of cells expressing *GPNMB* in each cluster, as percentage. (**I**) Violin plots showing the expression of *GPNMB* across all MP clusters.

Figure S2. Transcriptional features of MoMϕ and clinical relevance of MP clusters in human CLM. (**A**) Monocle pseudotemporal trajectory of monocytes CD14$^+$ and MoMϕ(1-3) clusters in a two-dimensional state-space. Cells are colored by cluster identity. (**B**) Heatmap of branchpoint analysis showing differentially expressed genes along the pseudotemporal trajectory from Mono CD14$^+$ to MoMϕ(1) or to MoMϕ(2-3). Exemplary genes are labelled. (**C**) Barplot showing the number of cells expressing *SERPINB2* in each cluster, as percentage. (**D**) Violin plots showing the expression of *SERPINB2* across all MP clusters. (**E**) Representative images of the main steps of mf-IHC analysis workflow. Shown in (1) is the manual annotation of the tumor core and its expansion to define the invasive margin; (2) identification of individual nuclei and cell segmentation; (3) assignment of immune phenotype, based on presence or absence of markers (CD68, GPNMB, SERPINB2, LAMP3). Scale bar: 800μm. (**F**) Representative mf-IHC images showing the distribution of CD68$^+$ cells (green) and LAMP3$^+$ cells (yellow) in the IM, where high cell density regions are outlined in red. Scale bar

300μm. (**G**) Quantification of the propensity of MP clusters to localize in high cell density areas, expressed as Δρ(%). ****, P<0.0001 by paired t-test.

Figure S3. Spatial transcriptomics on human CLM. (**A**) Spatial feature plots showing gene expression of signature genes for adjacent liver (*APOC3*), stromal (*COL1A2*) and tumor (*EPCAM*) areas. (**B**) Principal component (PC) analysis projections on the first two PCs, referred to Figure 4F, showing similarities of the manually annotated zones (N1-N8, T1-T7) across patients. (**C**) Heatmap showing hierarchical clustering of the manually annotated zones (N1-N8, T1-T7) on the first five PCs of the PC analysis. (**D**) Spatial feature plots showing expression of *GPNMB*. (**E**) Genes with highest Pearson correlation coefficient with *SERPINB2* in scRNA-seq data from MP. (**F**) Spatial feature plots showing expression of *S100A12*.

Figure S4. scRNA-seq of CD45+ cells from human CLM and reclustering of MP. (**A**) UMAP plots of the 20 clusters of CD45+ cells color-coded by selected marker gene expression. (**B**) UMAP plot of CD45+ cells as in Fig. 5A. Major cell lineages are labelled (left panel). Arrow shows clusters considered for reclustering of myeloid cells to obtain 13 MP clusters (UMAP plot in right panel), color-coded by cluster assignment. (**C**) UMAP plots of the 13 clusters of reclustered MP, color-coded by selected marker gene expression. (**D**) Circle plot showing the number of ligand-receptor pairs, identified by CellPhoneDB, between selected MP phagocyte clusters re-clustered from CD45+ dataset (larger circles, color-coded by cluster) and other CD45+ clusters (smaller circles, light blue). Line thickness is proportional to number of ligand-receptor pairs. (**E**) Heatmap showing the number of bidirectional ligand-receptor pairs among reclustered MP and other CD45+ cell clusters. MP clusters derived from reclustering are labelled in red.