

Supplementary Figure S2. Establishment of spatial transcriptional signatures for TMEs with distinct immune profiles.

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- **A)** Volcano plot of the DEGs comparing the spatial TME2 to the spatial TME1 AOIs. Blue and yellow dots represent genes significantly expressed in spatial TME1 and in spatial TME2 AOIs, respectively.
- **B)** Table summarizing the establishment of the spatial signatures.
- **C)** Violin plots of the spatial Stroma DEG signature (232 genes) enrichment in tumor and stroma AOIs. Horizontal bars indicate the mean. P-value was calculated by unpaired two-sided Student's *t* test. *** p< 0.001.
- **D)** PCA plot of the spatial Stroma DEG signature (232 genes) in individual stroma AOIs.
- **E)** Ranked individual AOIs according to their enrichment for the spatial TME1 (STME1) and spatial TME2 (STME2) signatures (left). Dotted lines indicate upper quartile (25%) with the highest enrichment. Specificity of spatial signatures assessed by the representation of tumors AOIs, TME1 and TME2 AOIs in the 25% most enriched AOIs (right). Positive and negative values indicate over- and under-representation respectively compared to expectations (fold change), based on the cumulative distribution function of the hypergeometric distribution. * p<0.05.
- **F)** Bar plot showing the GO biological processes enriched in STME1 and STME2 signatures respectively.