Expanded View Figures

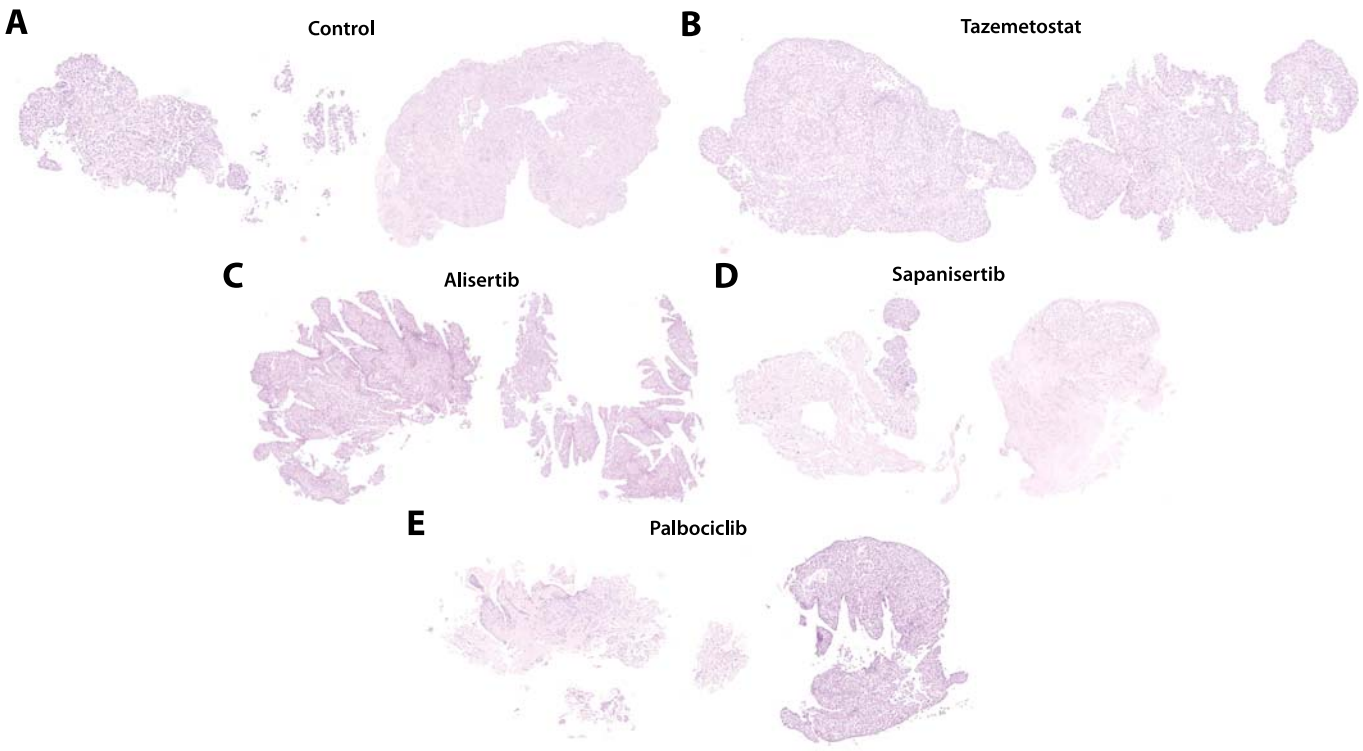

Figure EV1. Hematoxylin and eosin (H&E) staining of patient-derived tissue slice cultures under different treatment conditions.

(**A**) Control slices treated with the maximum equimolar concentration of DMSO. One of the control slices is also shown in Fig. 3B. (**B**) Tazemetostat-treated slices. (**C**) Alisertib-treated slices. (**D**) Sapanisertib-treated slices, showing extensive tumor necrosis in the lower portion of the tissue. One of the control slices is also shown in Fig. 3E. (**E**) Palbociclib-treated slices.

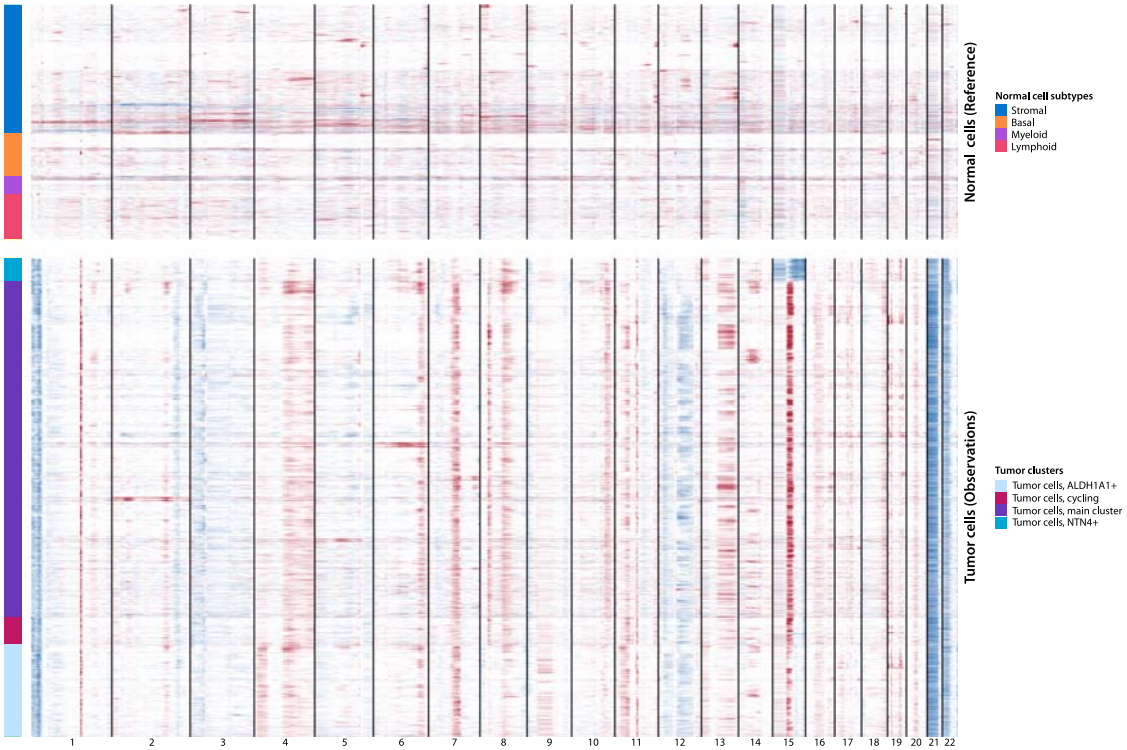

Figure EV2. Heatmap of single-cell copy number profiles inferred from single-nucleus RNA sequencing data.

Notably, loss of chromosome 15 is exclusively found in the NTN4+ tumor cell cluster.

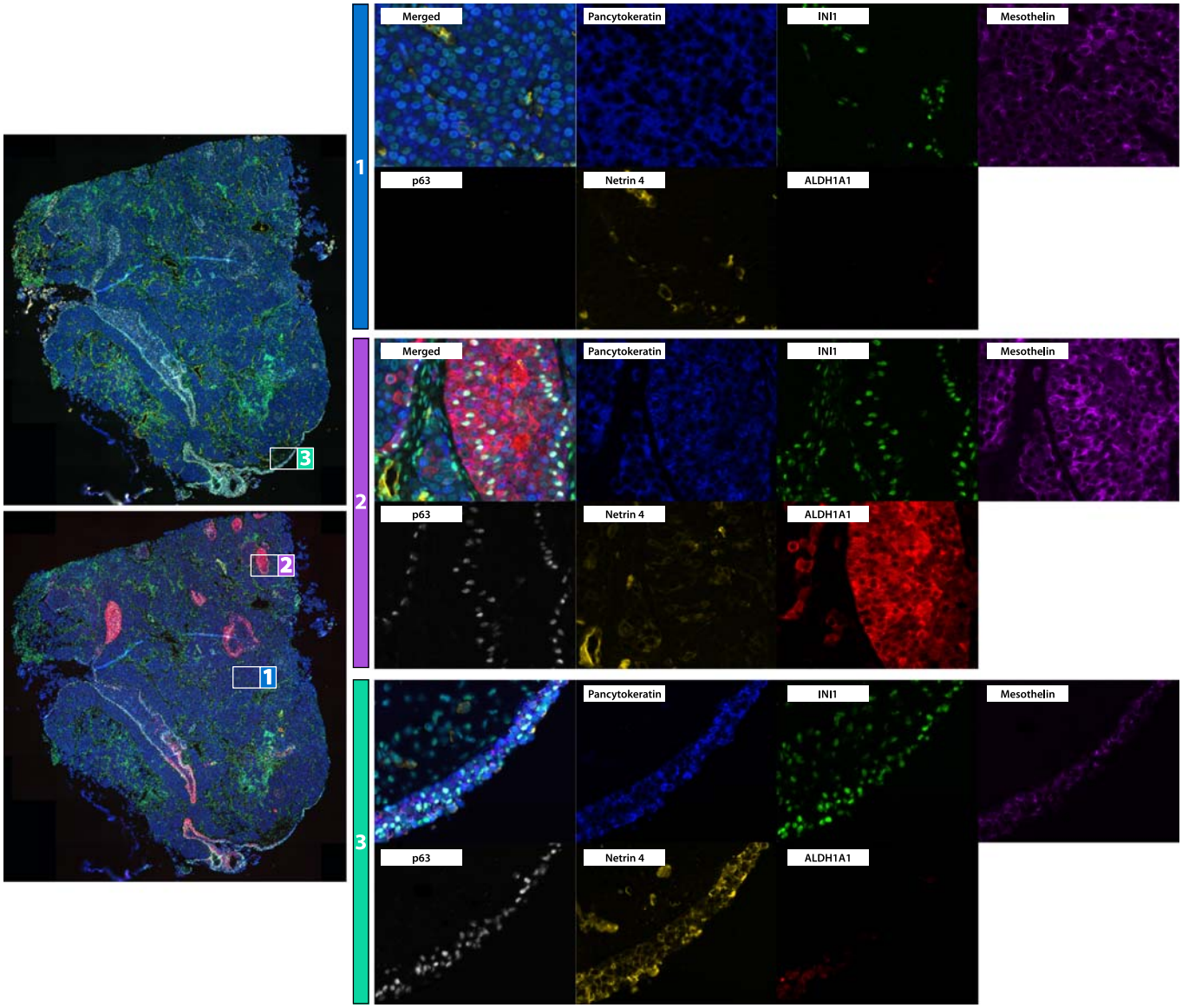

Figure EV3. Validation of tumor niches identified by spatial transcriptomics on the protein level.

Overview and high-magnification sequential immunofluorescence images of a cultured, untreated tissue slice culture recapitulate the three spatial tumor niches defined by spatial transcriptomic analysis. Niche 1 represents the main tumor compartment, characterized by an absence of p63-positive basal cells. NTN4 expression is confined predominantly to endothelial cells lining blood vessels, with only rare expression in tumor cells, and ALDH1A1 is absent. Niche 2 is composed of ALDH1A1-high tumor cells intermingled with p63-positive basal epithelial cells. Netrin 4 again localizes mainly to endothelial cells, retaining nuclear INI1 expression, while tumor cell staining is infrequent. Niche 3 illustrates pagetoid spread of INI1-negative, pancytokeratin-positive tumor cells within the surface epithelium, showing strong Netrin 4 expression and complete absence of ALDH1A1.

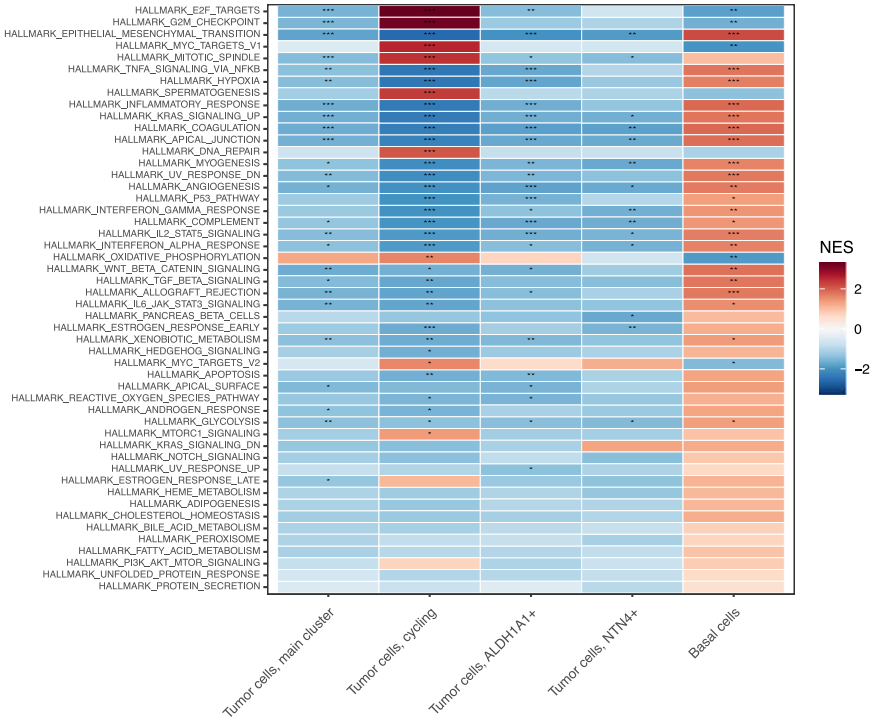

Figure EV4. Heatmap of baseline Hallmark pathway activity score differences between basal and tumor cells in untreated, uncultured control samples.

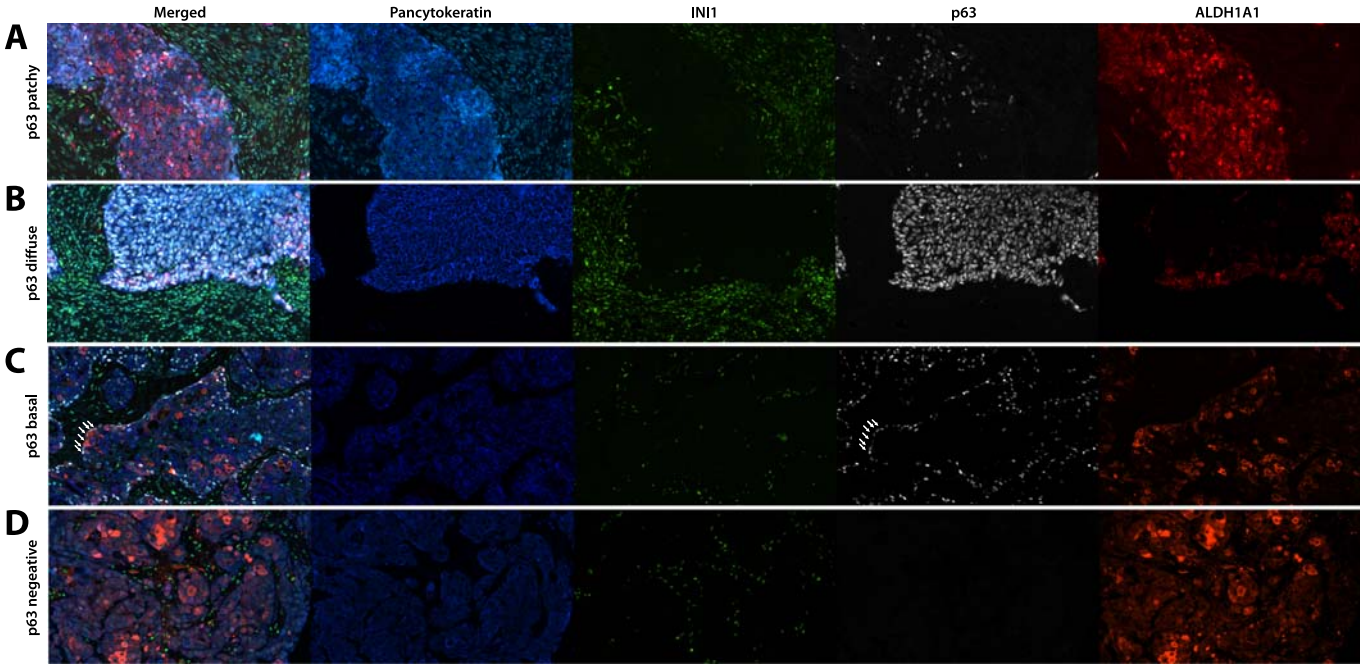

Figure EV5. Representative staining patterns of p63 in the retrospective cohort.

(**A**) Patchy expression of p63 in tumor cells (loss of nuclear INI1). (**B**) Diffuse p63 expression in almost all tumor cells. A similar region of the same sample is also shown in Fig. 4B. (**C**) Predominant expression of p63 in tumor cells at the basal (near stroma; white arrows) layer. (**D**) No p63 expression in tumor cells.