Supp. Figure 1

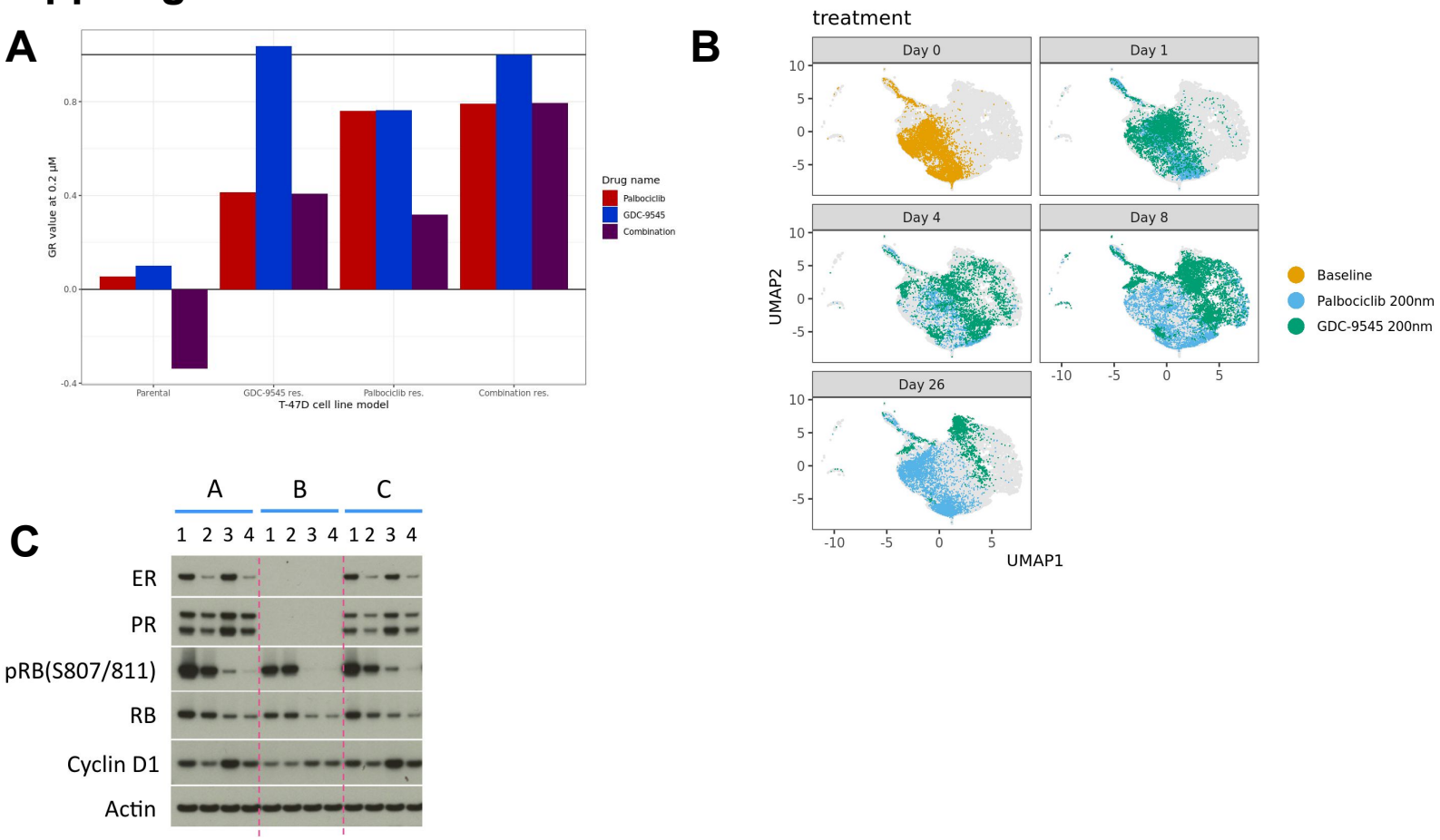

Figure S1. (A) GR value for parental T-47D, giredestrant-treated PS population, or palbociclib-treated PS population, or combination-treated PS population treated for 7 days with either 0.2μM of giredestrant, 0.2μM of palbociclib, or their combination. (B) Transcriptomic changes are observed in palbociclib treated cells (blue), but return to a baseline (orange) state, while giredestrant-treated cells (green) have remained changed. (C) Western Blot of parental T-47D [A], giredestrant-treated PS population [B], or palbociclib-treated PS population [C], treated for 24 hours with either DMSO [1], giredestrant [2], palbociclib [3], or their combination [4].

Supp. Figure 2

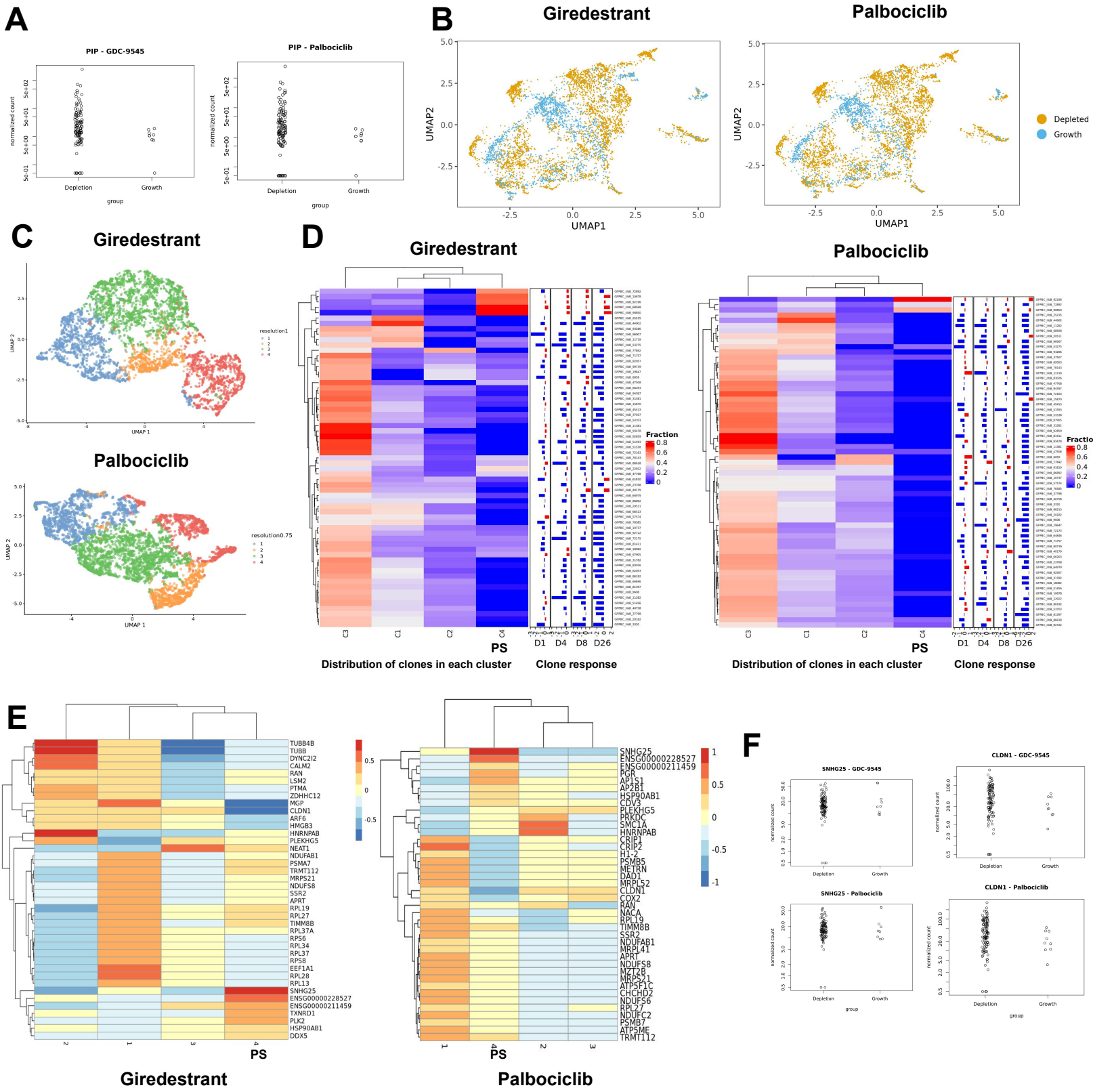

Figure S2. The PIP gene is differentially expressed in PS clones compared to NS clones in giredestrant and palbociclib (A). PS clones (blue) are not separated from NS clones (orange) when PCA dimension reduction is used to create a UMAP projection (B). Clustering results produced from the PLSR approach are plotted for giredestrant and palbociclib-treated cells (C). Heatmaps depict the fraction of clones (y-axis) within a given PLSR cluster (x-axis), where cluster 4 is the PS cluster in both giredestrant and palbociclib treatment. The barplots on the right side show the increase (in red) or decrease (in blue) in the clonal population at days 1, 4, 8, and 26 after treatment (D). Genes found to be differentially expressed via findMarkers are plotted relative to the expression in the PS cluster 4 (E). Genes found through the PLSR approach, SNHG25 and CLDN1, were not shown to be differentially expressed when comparing PS clones to NS clones (F).

Supplementary Figure 3

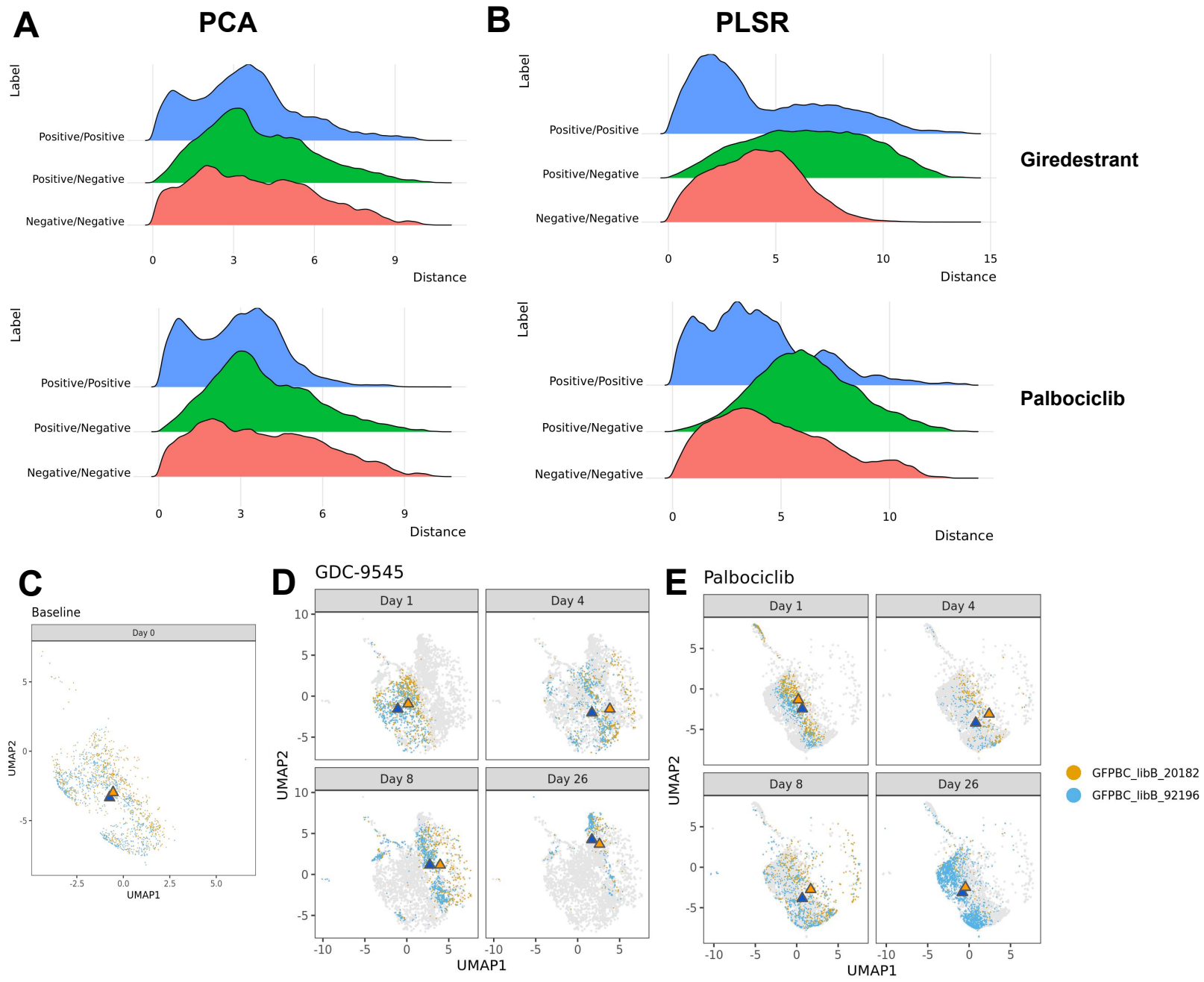

Figure S3. Ridge plots depict the pairwise distance between two PS cells (blue), two NS cells (red), and one PS cell and one NS cell (green) when PCA dimension reduction is used (A). The distance between PS to PS cells and NS to NS cells is reduced, while PS and NS cells are more separated with PLSR (B). The transcriptomes of a NS clone (orange) and PS clone (blue) and their centroids (triangles) are plotted together pre-treatment, showing they are not separated (C). When treated with giredestrant (D) or palbociclib (E) the transcriptomes of these clones change throughout treatment, but the clone centroids remain together and are not separated by treatment.

Supplementary Figure 4

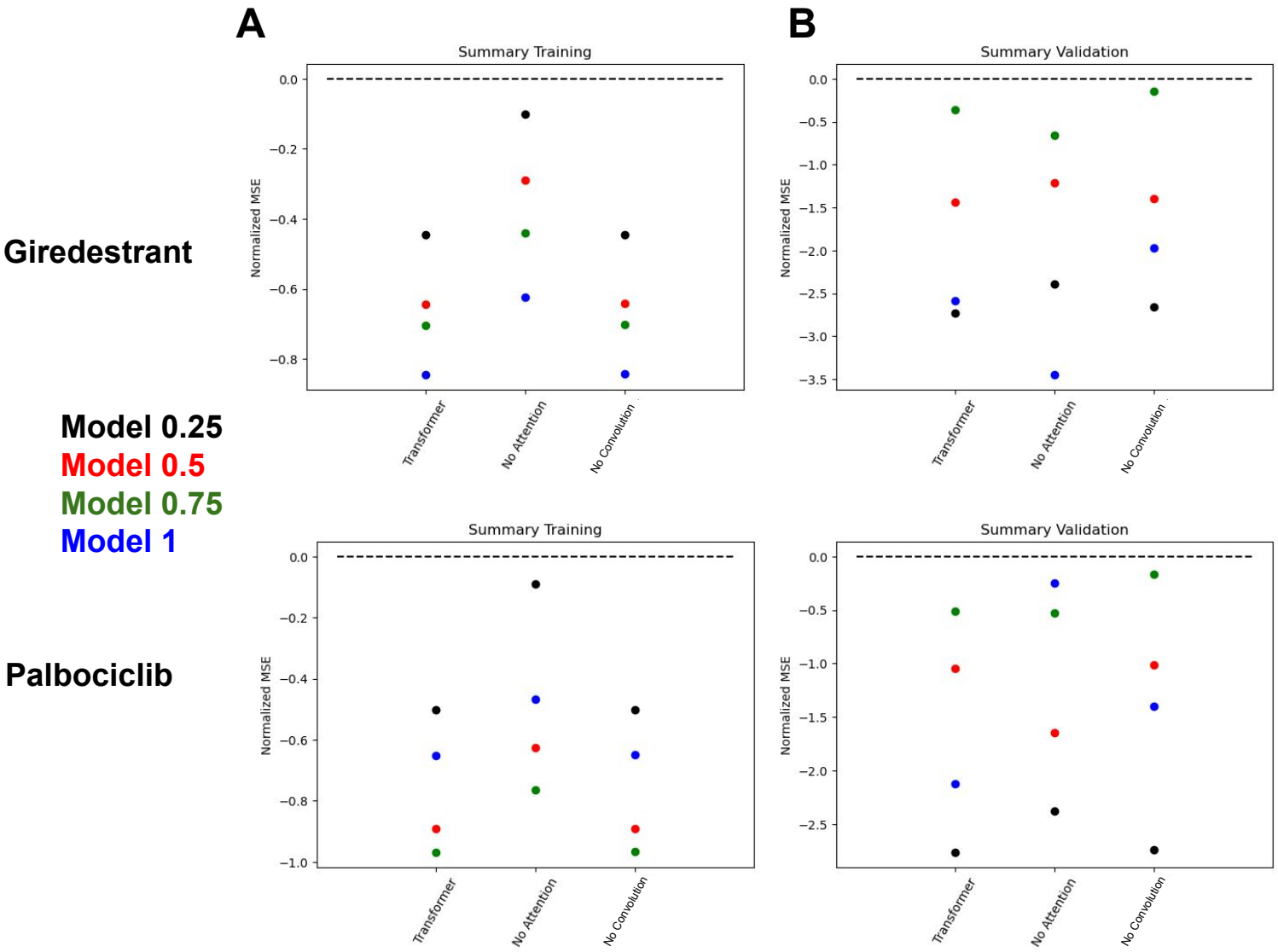

Figure S4. The model error in training is plotted relative to multivariate regression (dashed line) for modeling up till each of the four testing increments at 0.25 (black), 0.5 (red), 0.75 (green), and the full fraction of the clonal data (blue). Error is represented as the mean error for the modeled barcodes for the full TraCSED model (left), TraCSED without the attention layers (middle), and TraCSED without the convolutional layers (right) for both giredestrant and palbociclib (A). The model error is then also plotted in the same way for the validation data (B).

Supplementary Figure 5

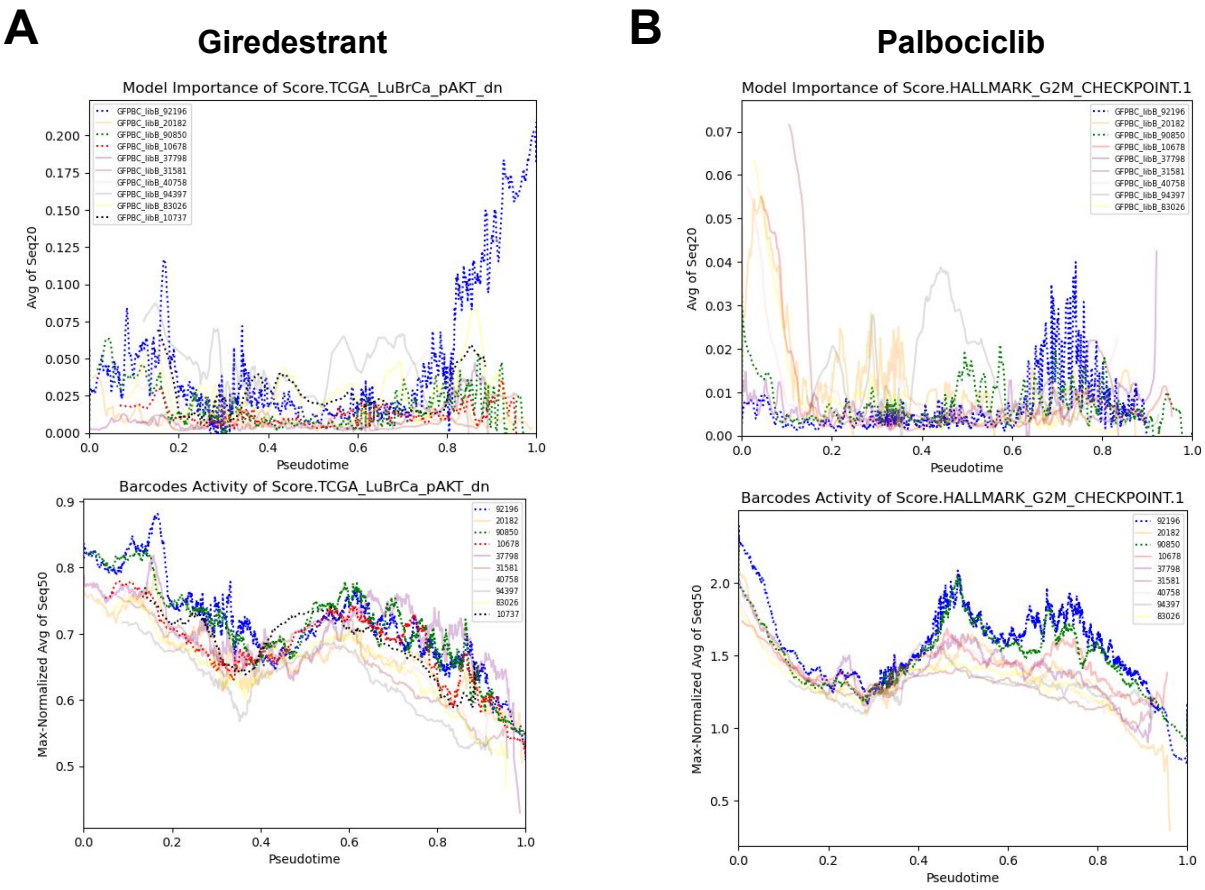

Figure S5. Smoothed model importance (averaging 20 adjacent cells) was plotted for PS clones (bold, dashed lines) and NS clones (faint, solid lines) for the AKT pathway in giredestrant treatment (upper panel). Smoothed pathway activity (averaging 50 adjacent cells) was also plotted (lower panel, A). Similarly, the smoothed model importance (upper panel) and pathway activity (lower panel) were plotted for the G2M checkpoint pathway in palbociclib treatment (B).

Supplementary Figure 6

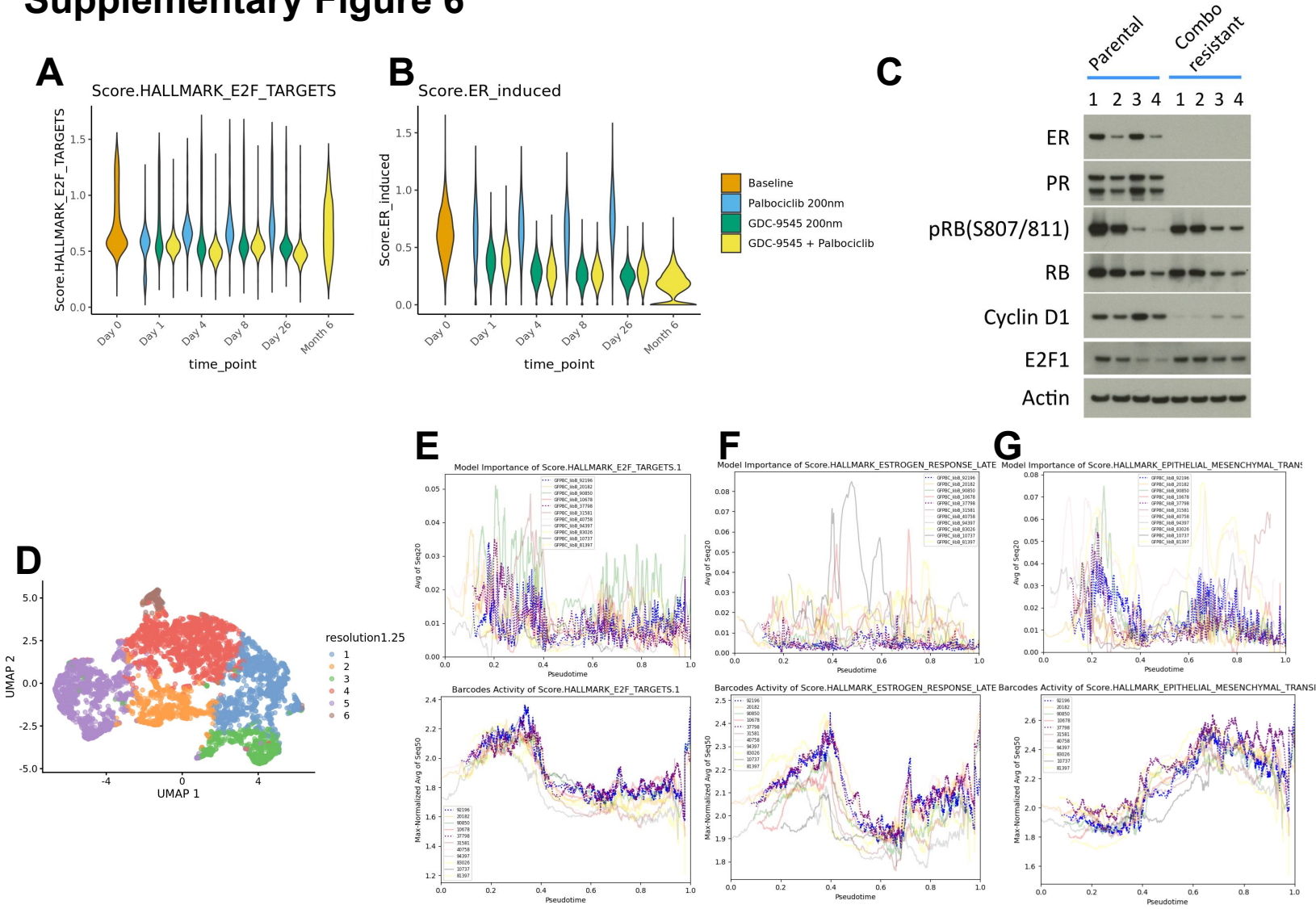

Figure S6. Pathway scores for E2F targets (A) and ER induced activity (B) is plotted across pre-treatment (orange) and for the duration of treatment with palbociclib (blue), giredestrant (green), and the giredestrant-palbociclib combination therapy (yellow). The cluster results from the PLSR approach are plotted for the giredestrant and palbociclib combination treatment (C). Smoothed model importance (averaging 20 adjacent cells) was plotted for PS clones (bold, dashed lines) and NS clones (faint, solid lines)(upper panel). Smoothed pathway activity (averaging 50 adjacent cells) was also plotted (lower panel). This was done for the E2F targets pathway (C), Estrogen Response Late (D), and EMT pathway (E).

Supplementary Figure 7

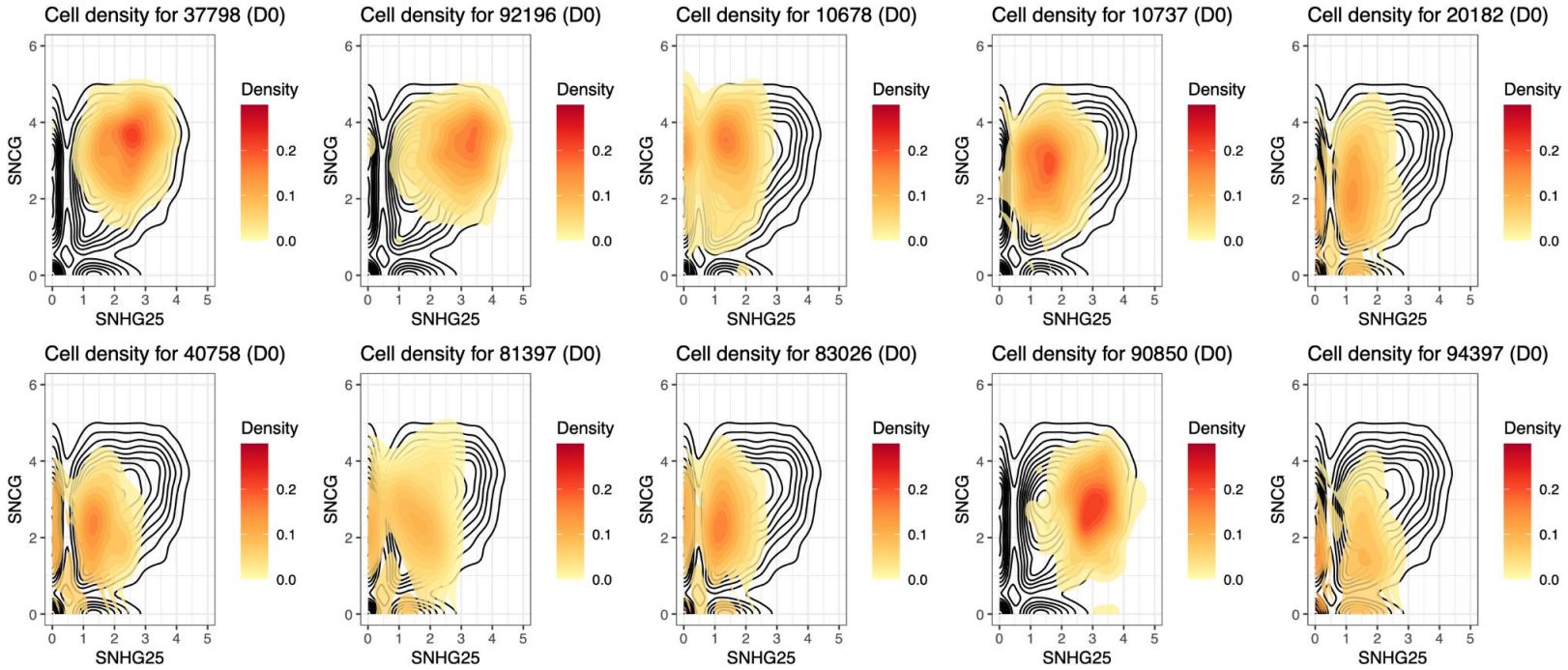

Figure S7. Distribution of cells at baseline based on the expression of SNHG25 and SNCG. Black outline shows all cells; color density shows cells from each clone individually.