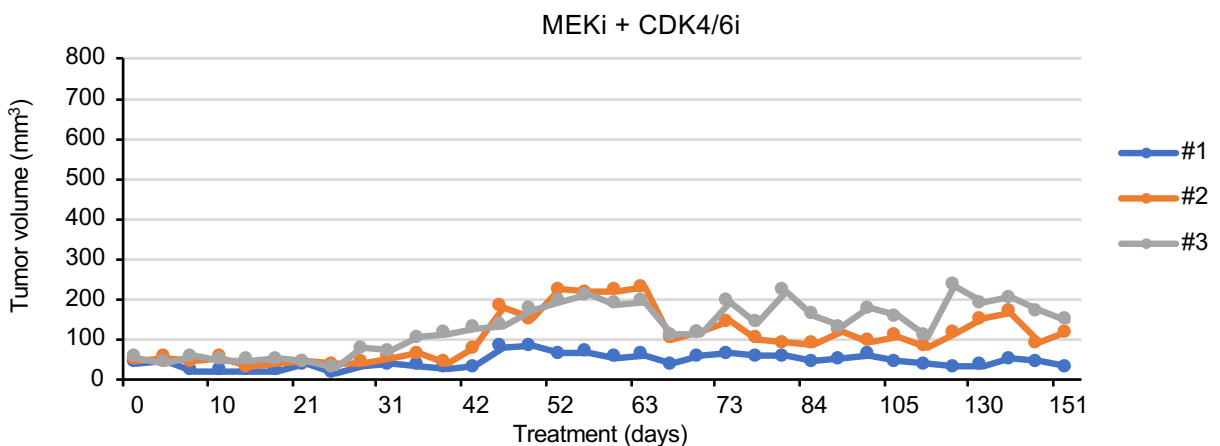
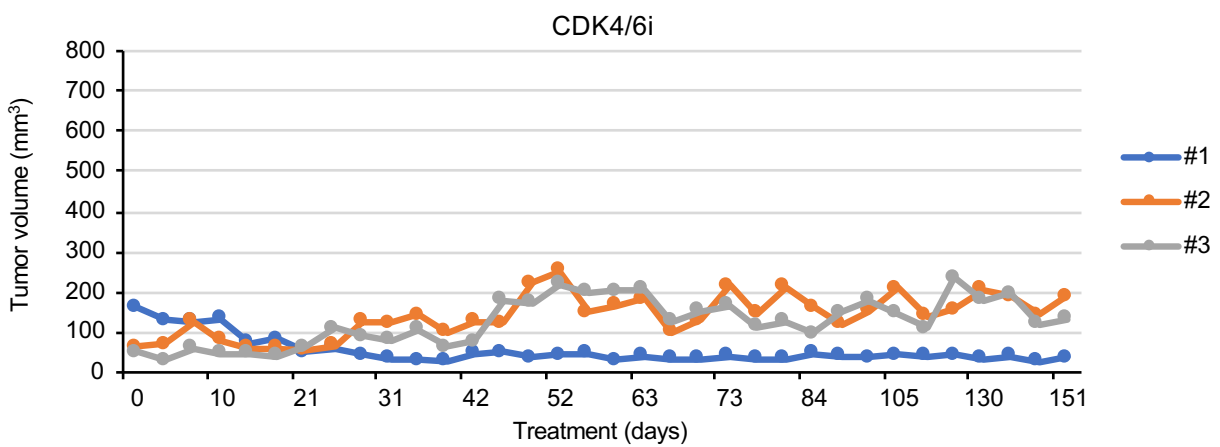
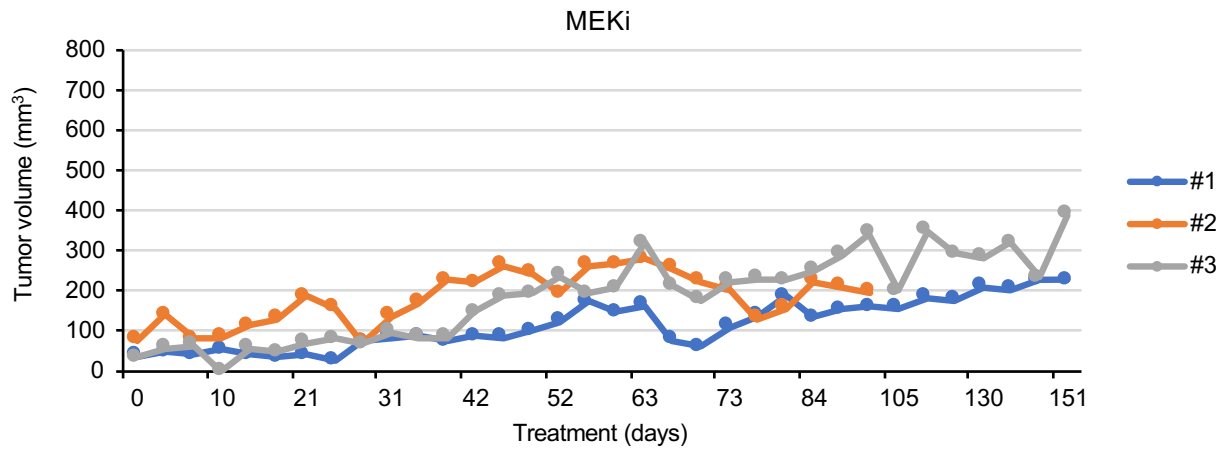
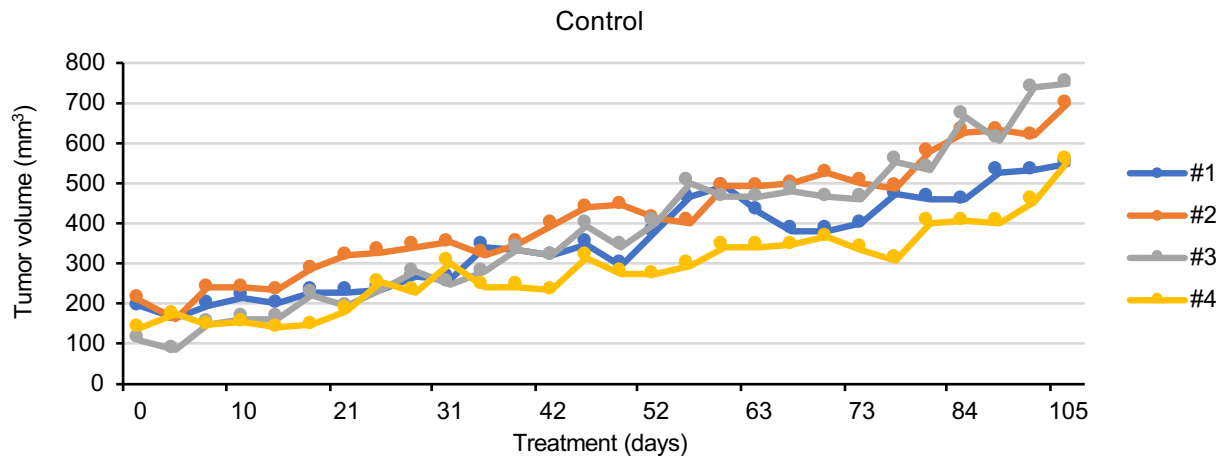
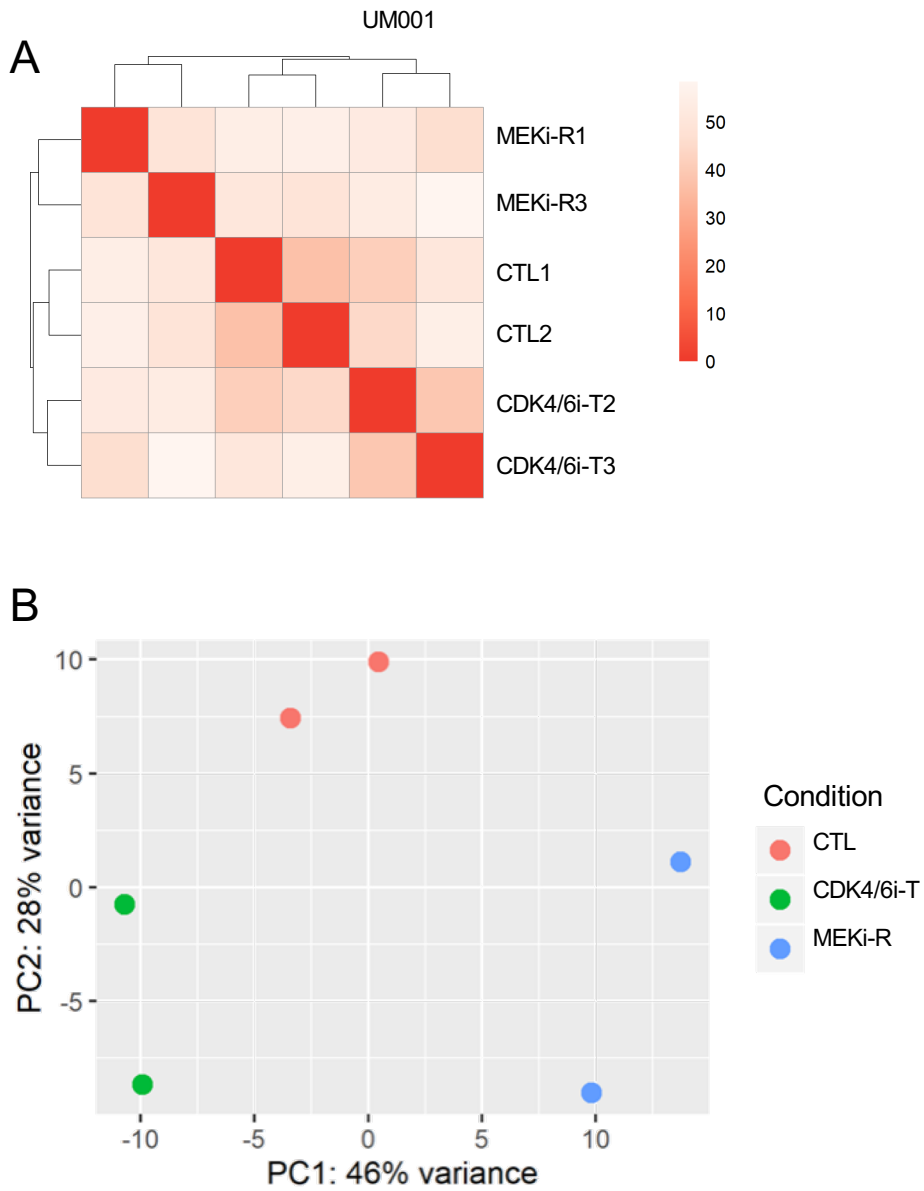


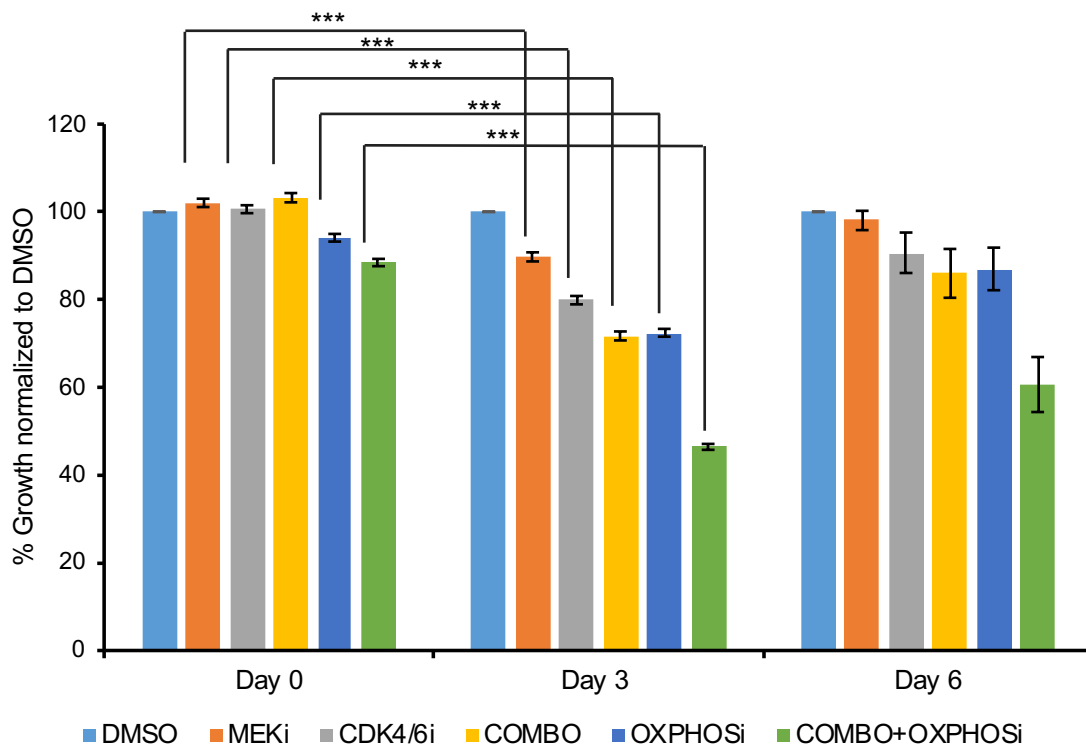
**Supplemental Figure 1. CDK4/6i + MEKi treatment does not modulate proteins within the apoptotic signaling pathway.** Heatmap of median centered log<sub>2</sub>-transformed average expression RPPA data for antibodies with corresponding proteins present in the apoptotic signaling pathway gene set from the Gene Ontology database.



**Supplemental Figure 2. Growth of UM001 xenografts treated with MEKi and/or CDK4/6i.** Tumor volumes were monitored up to 151 days of treatment with control, MEKi (PD0325901), CDK4/6i (palbociclib) or the combination of MEKi and CDK4/6i.

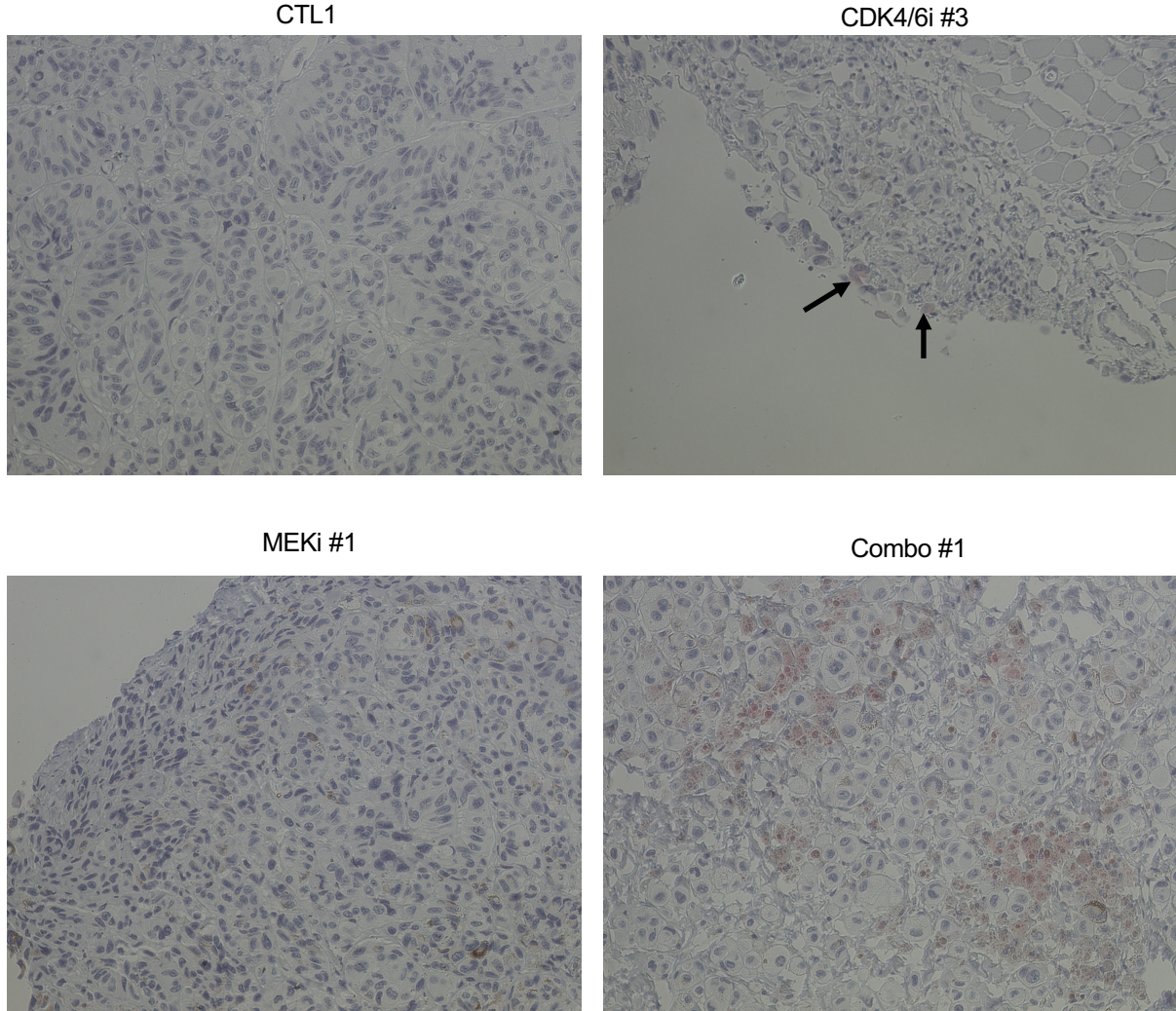


**Supplemental Figure 3. RNA-seq samples cluster based treatment. A** Heatmap of unsupervised hierarchical clustering of Euclidean distances between samples data. **B** PCA plot of samples colored by treatment condition.



**Supplemental Figure 4. MEKi, CDK4/6i, and OxPhosi have reversible effects.** IncuCyte analysis of UM001 cell line treated with control (DMSO), MEKi (PD0325901, 5 nM), CDK4/6i (palbociclib, 0.5  $\mu$ M), OxPhosi (IACS-010759, 50 nM), MEKi + CDK4/6i (combo) or MEKi + CDK4/6i + OxPhosi (combo + OxPhosi). Cells were treated for 3 days. Medium was renewed with normal growth media (drug-free) at day 3 and cells were allowed to grow until day 6. (n=4).

**Cleaved caspase 3**



**Supplemental Figure 5. Cleaved caspase 3 staining in UM001 xenograft tumors.** UM001 xenografts treated with MEKi, CDK4/6i or combo were stained for cleaved caspase 3 by immunohistochemistry. Positive staining was observed in the CDK4/6i-treated sample (very few cells, indicated by arrows) and in the combo-treated sample.