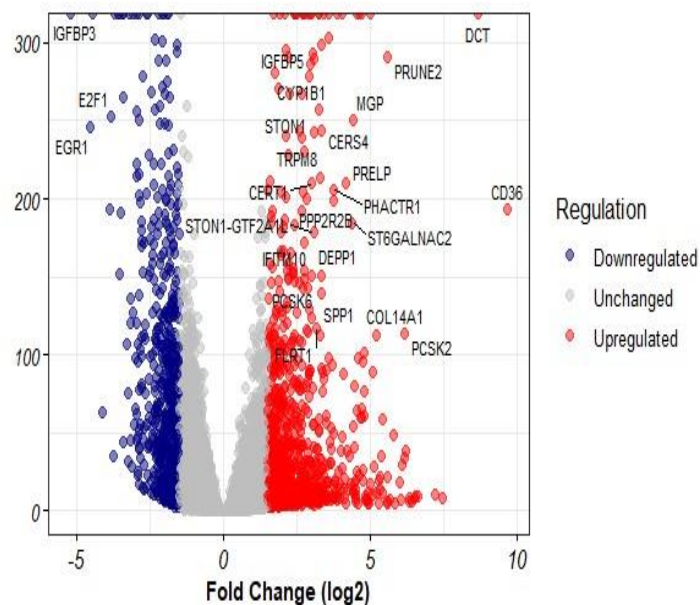
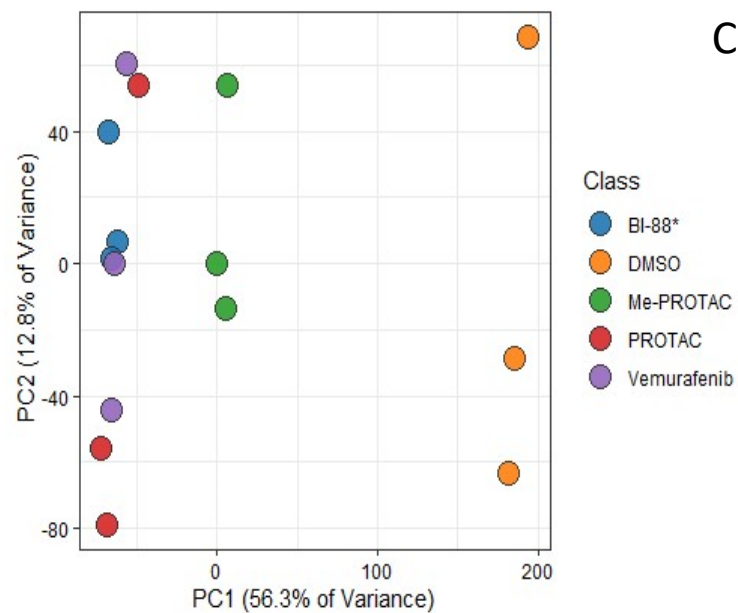


Me-PROTAC vs DMSO (DEGs = 839)

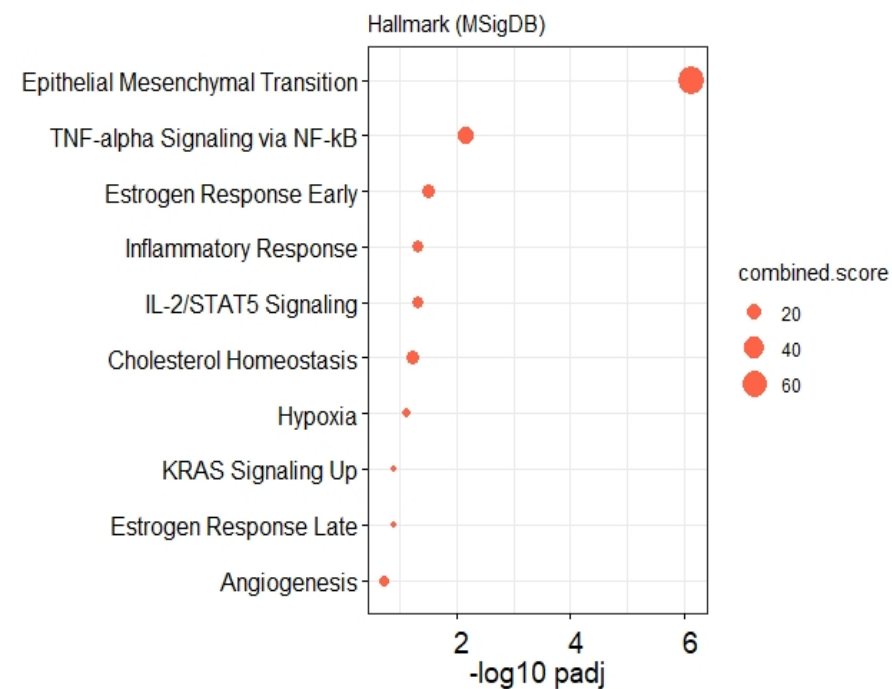
A



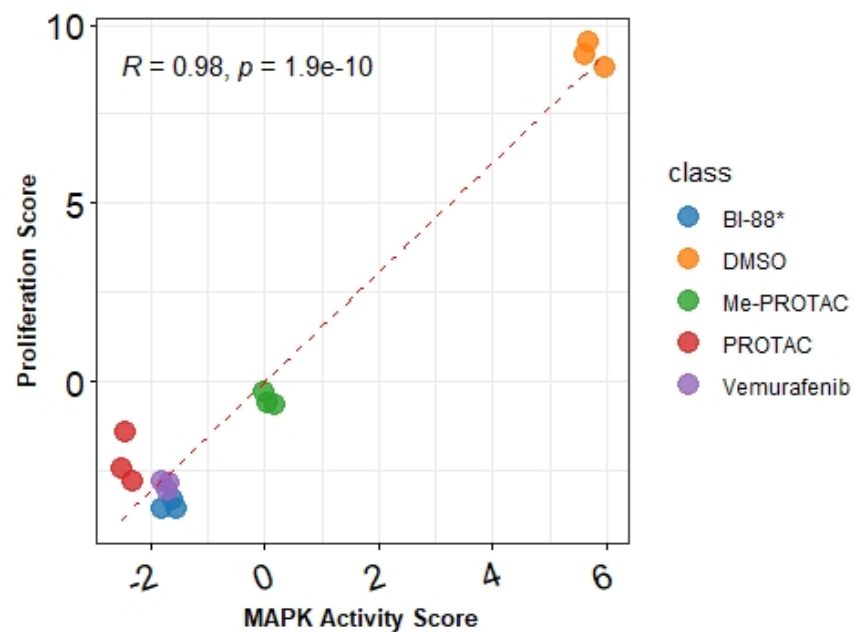
B



C

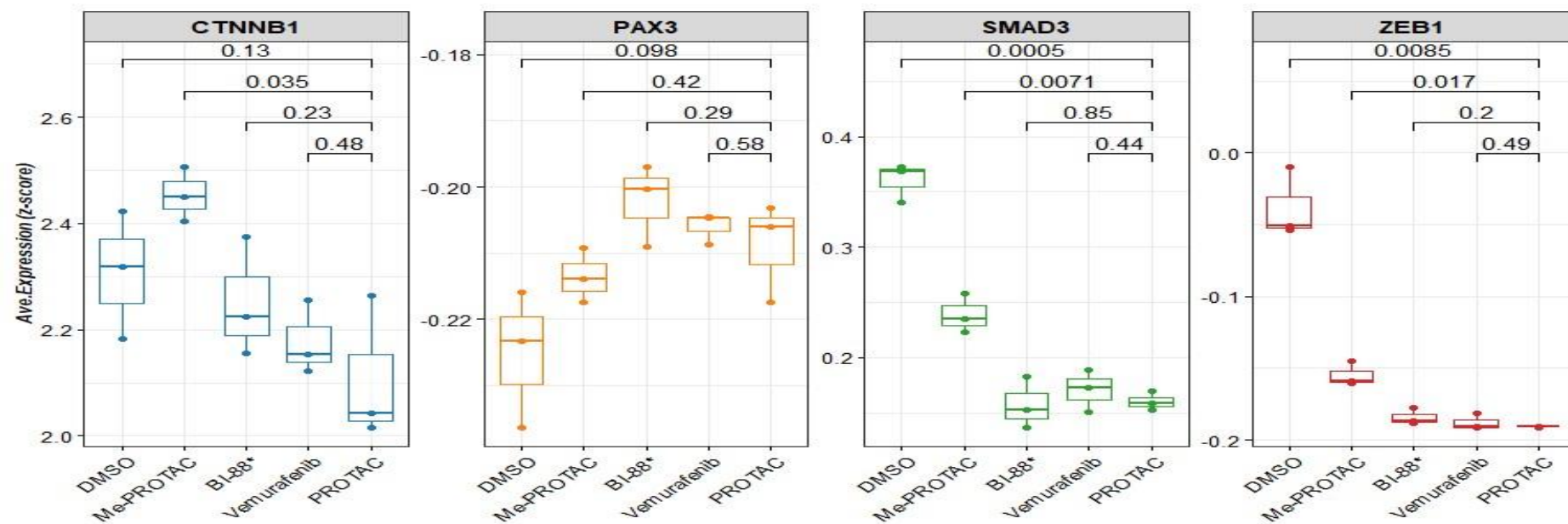


D

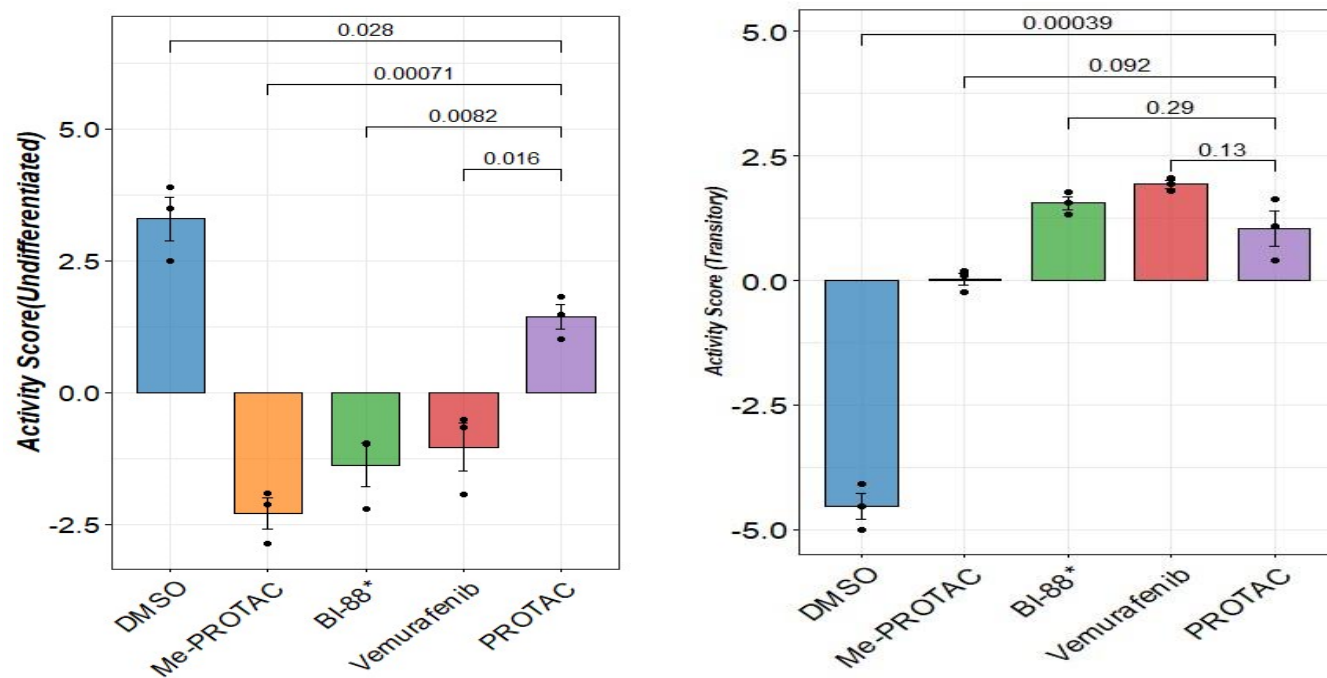


**Figure S1:** **(A)** Differentially expressed genes in A375 cell treated with methylated analog of PROTAC. **(B)** Principal Component analysis of A375 cells treated with PROTAC and inhibitors. Projections of the first two principal components (PC1 and PC2) are shown with percentage of variances explained by each is indicated. **(C)** Significantly enriched (adjusted  $p < 0.05$ ) gene ontology (Hallmark) terms genes differentially expressed common to both inhibitors and PROTAC **(D)** Scatterplot of proliferation scores and MAPK activity scores.

A



B



**Figure S2:** **(A)** Average expression of key transcription factors effecting a differentiation program in melanoma cells. Expression is derived from z-score normalized value of each gene. **(B)** Activity of genes defining an undifferentiated and transitory state phenotype in melanoma in PROTAC, and inhibitor treated cells. Subtype signatures are obtained from Tsoi et al., 2018. Error bars: Mean  $\pm$  SE of biological replicates