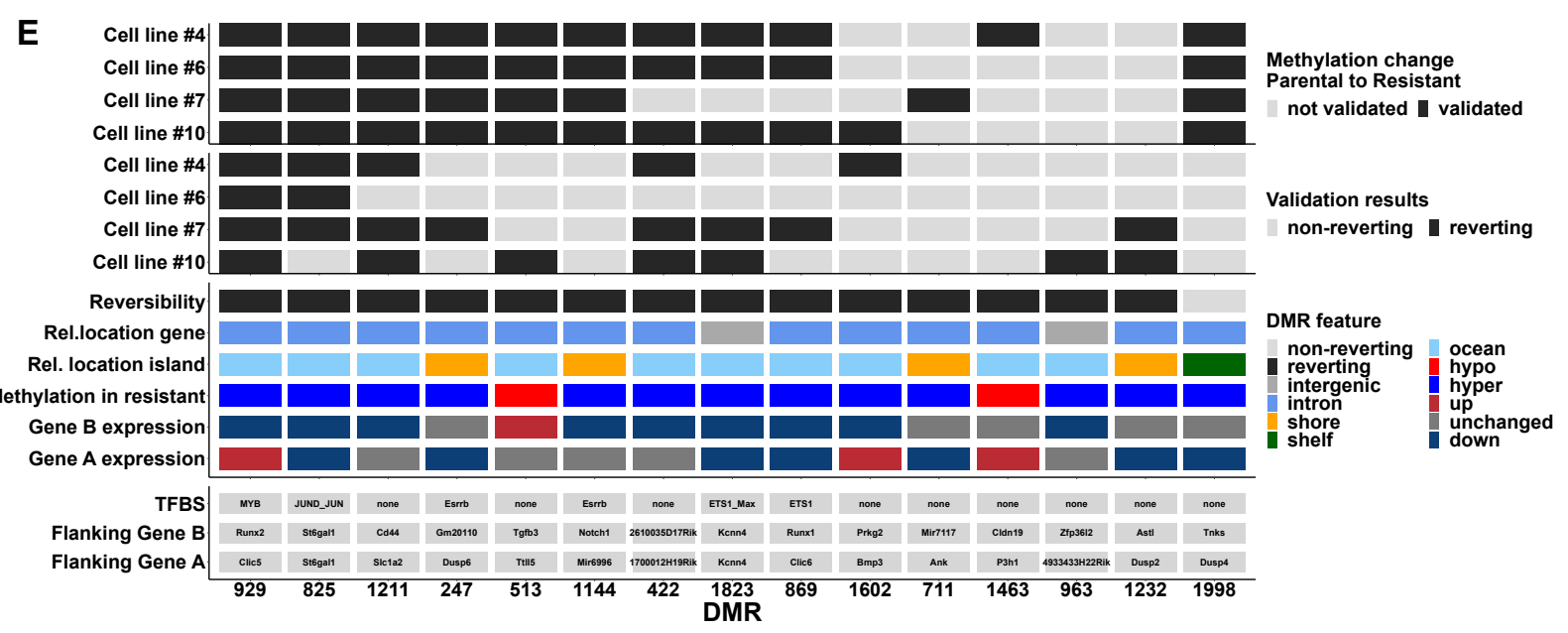
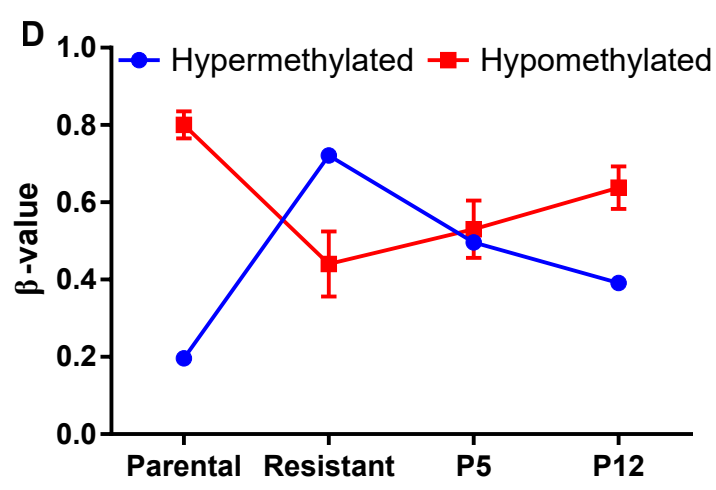
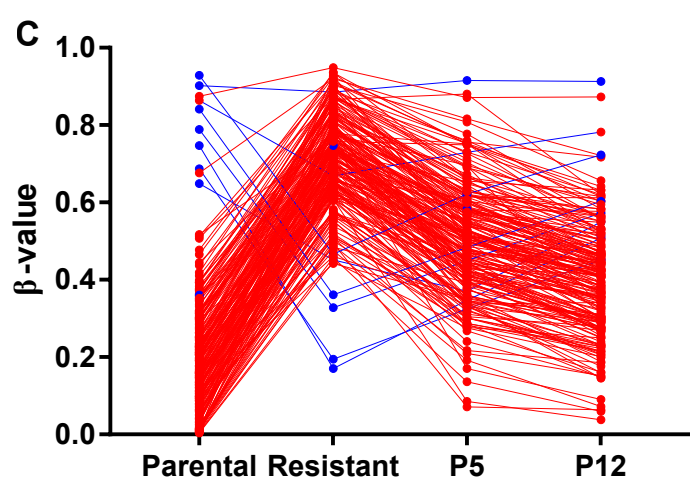
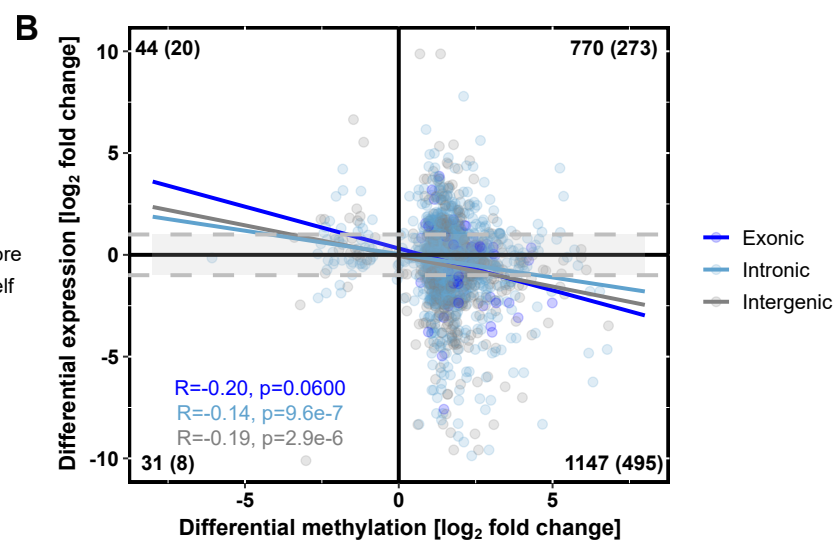
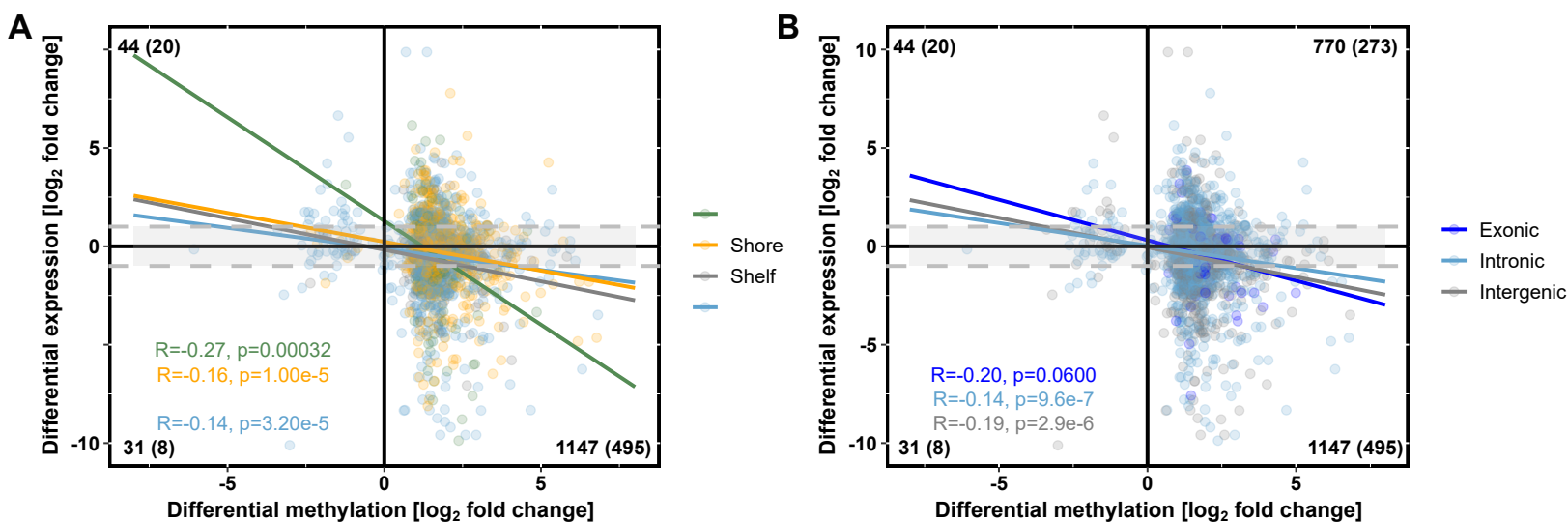


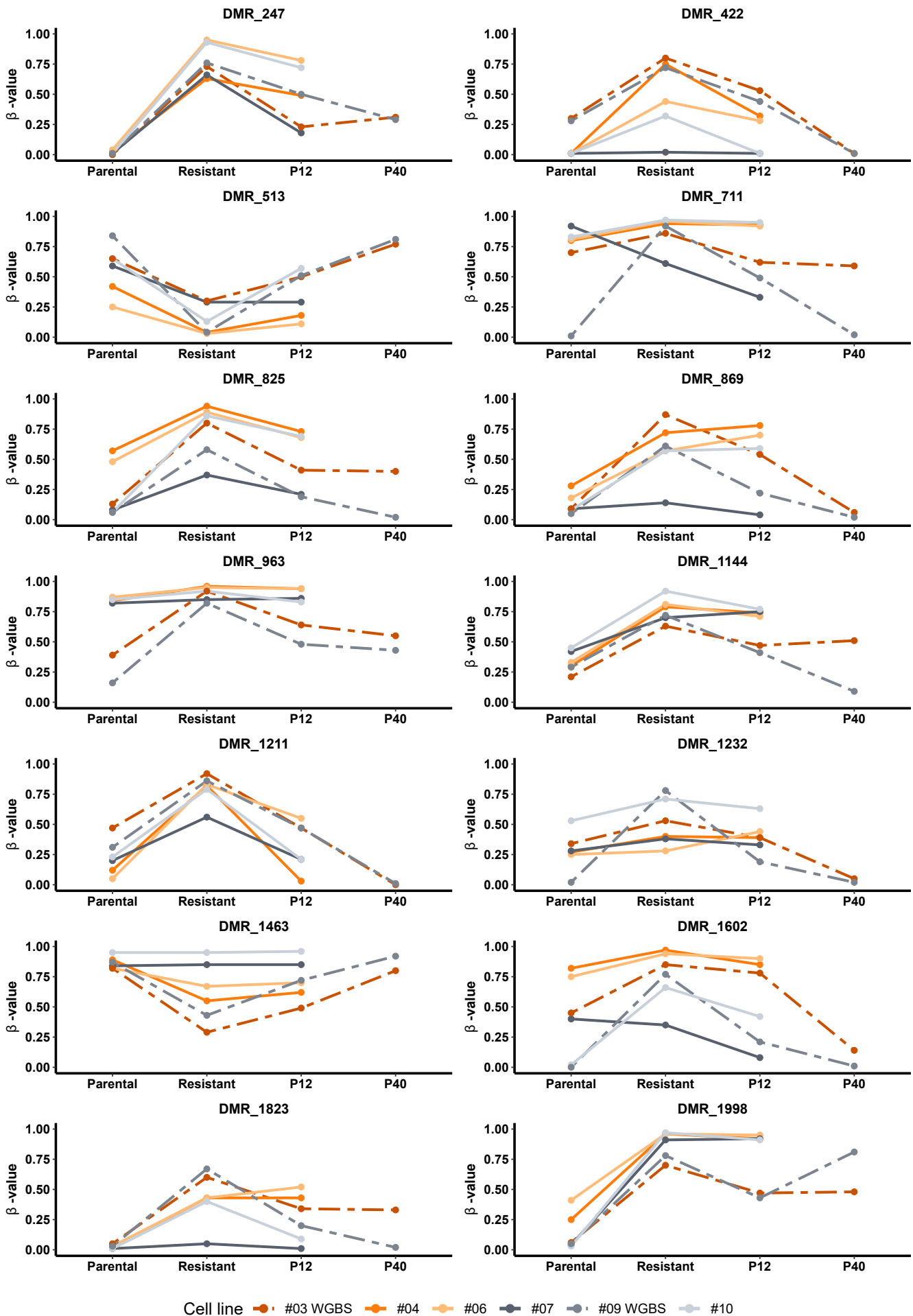
Supplemental Fig. S1

VAF of VpRs called by WGS separated by chromosomes for cell lines #3 (A) and #9 (B). (C,E) VAF of VpRs in resistant compared to P12 cells displayed for cell lines #3 (C) or #9 (E). (D,F) Scatter plot for the VAF of VpPs in resistant compared to P12 in cell lines #3 (D) or #9 (F). Only A > T and T > A variants called by WGS and validated by WBS are shown.



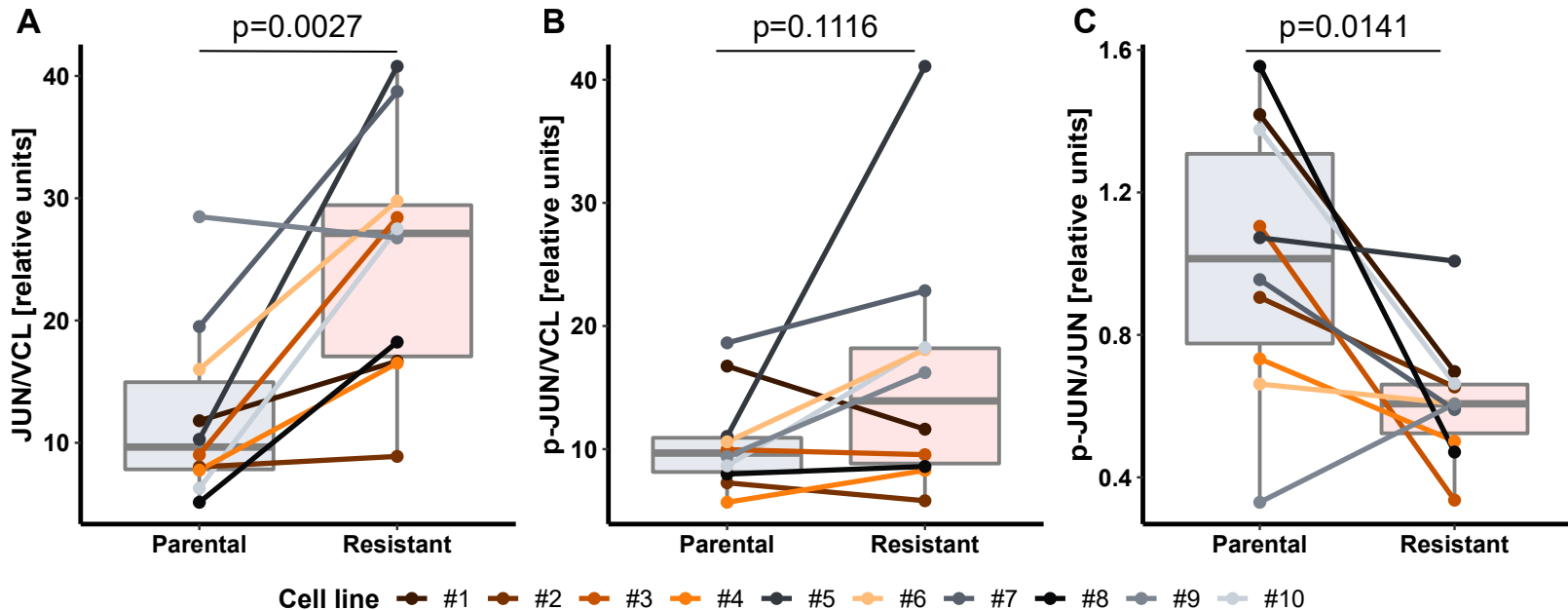
Supplemental Fig. S2

(A,B) Correlation of methylation and expression changes of DMRs between parental and resistant cells and their nearest downstream gene separated by their location according to CpG islands (A) or genes (B). The respective Pearson correlation coefficient was calculated. Numbers indicate the number of events in the quadrant. In brackets the number of significantly differently expressed genes (adjusted p-value < 0.05 and \log_2 fold change < -1 or > 1) are displayed. Dotted grey lines mark \log_2 fold changes of 1 or -1. (C) Methylation pattern of 217 reverting DMRs divided into hypo- (blue) and hypermethylated (red) regions. (D) Mean DNA methylation of 217 reverting DMRs \pm SEM separated into hypo- and hypermethylated regions. (E) Validation results of 15 DMRs analyzed by targeted deep bisulfite sequencing in four independent cell lines. In addition, features and annotations are displayed for each DMR.



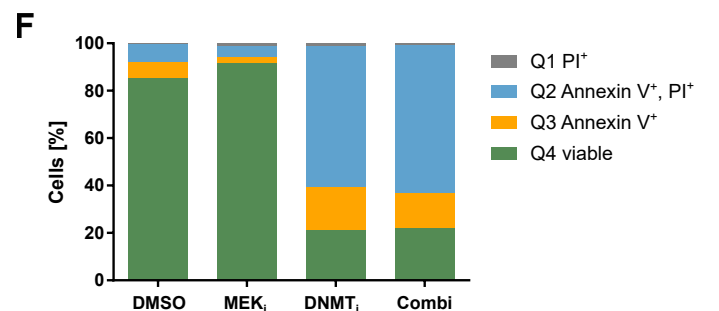
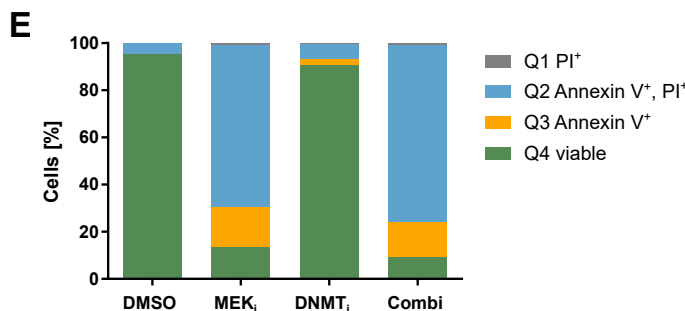
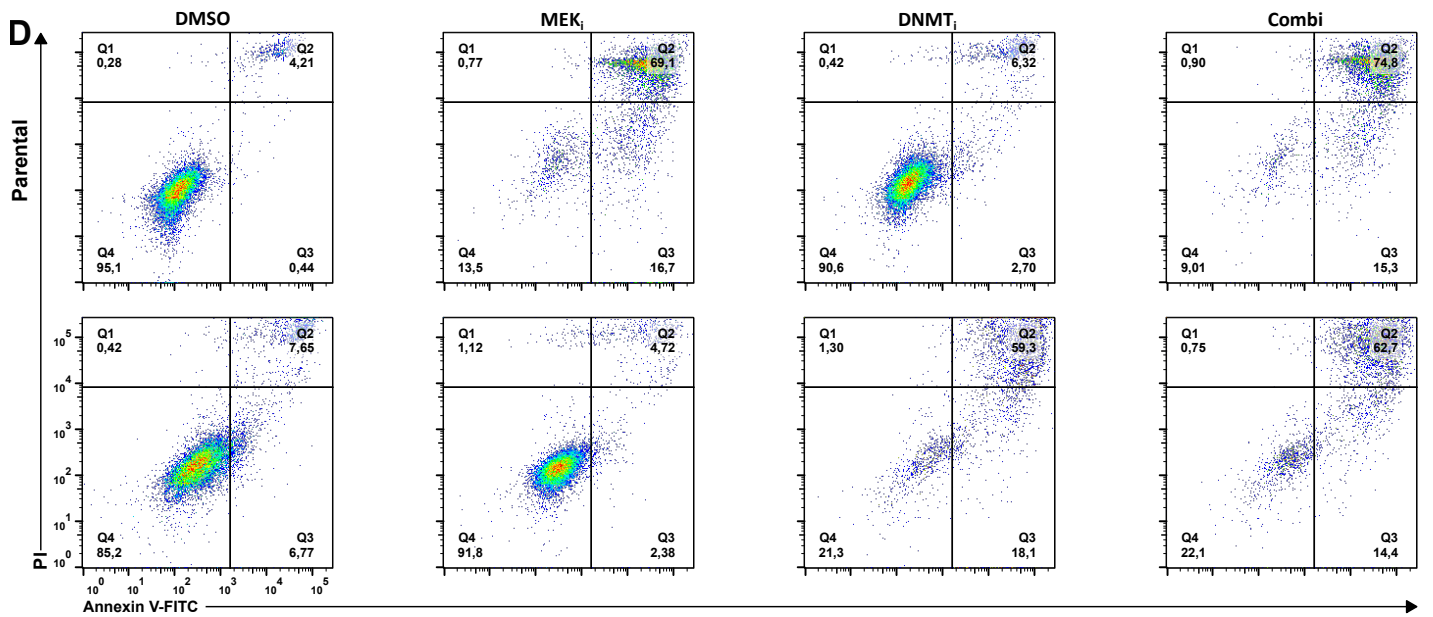
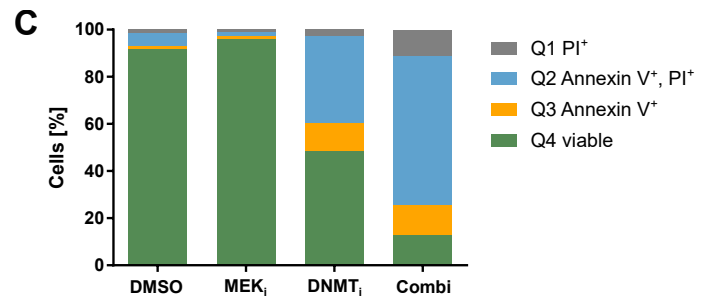
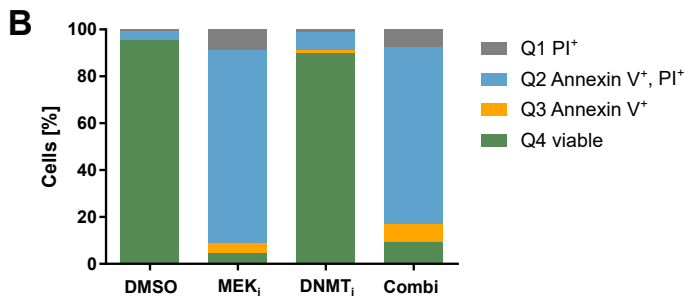
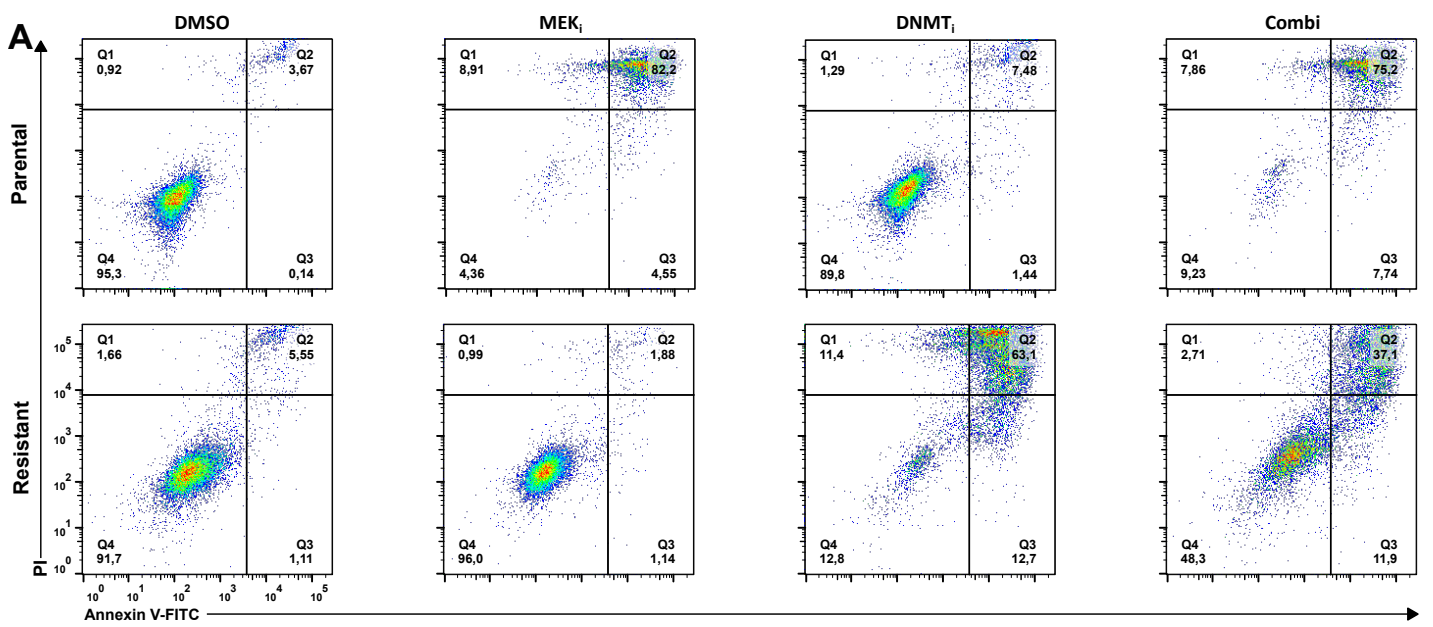
Supplemental Fig. S3

Individual methylation patterns of 14 DMRs validated by targeted deep bisulfite sequencing in four independent cell lines compared to cell lines #3 and #9 analyzed by WGBS. In addition, P40 of #3 and #9 was measured by targeted deep bisulfite sequencing. DMR_929 is displayed in Fig. 4D,E.



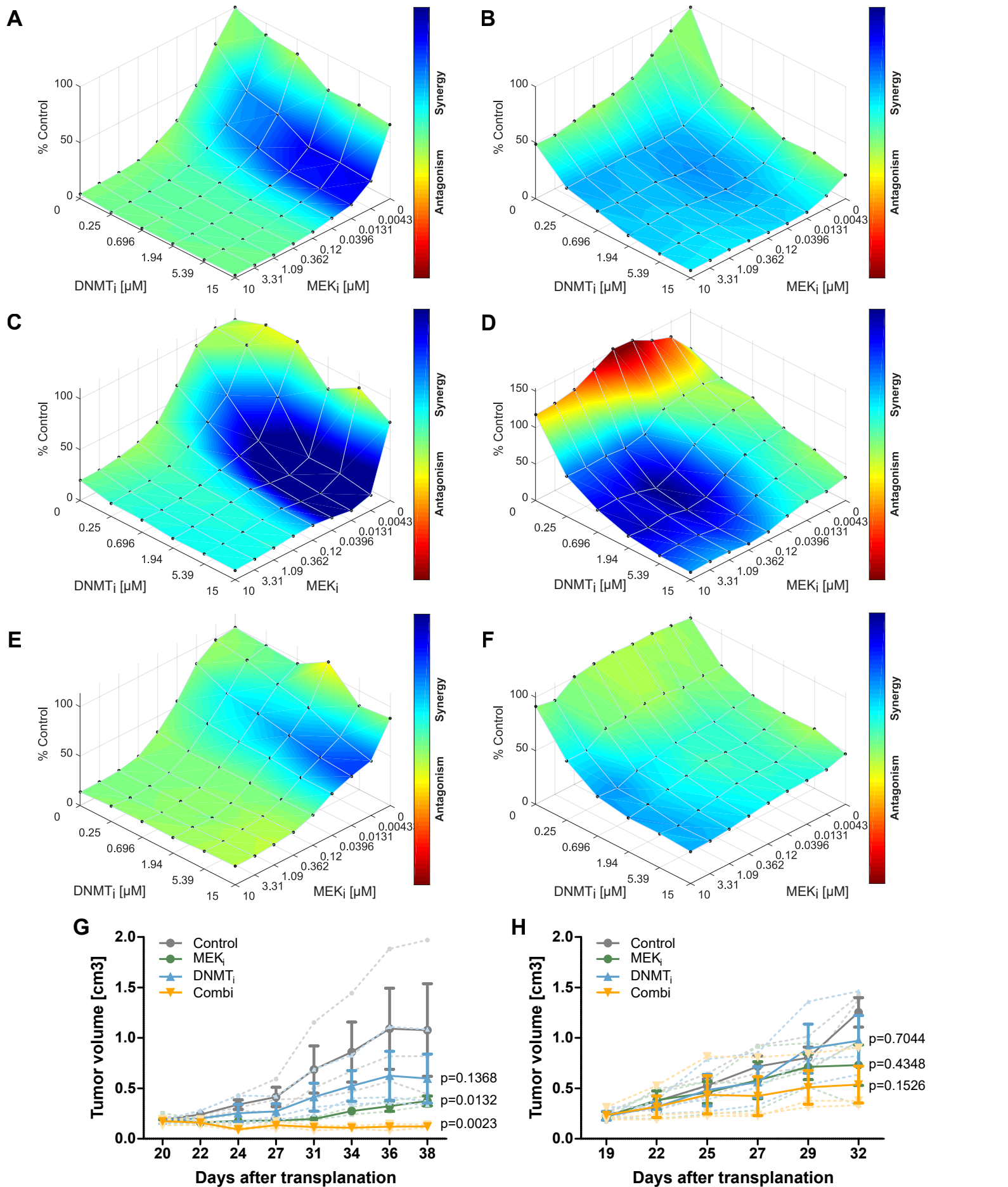
Supplemental Fig. S4

Relative protein expression of total JUN (**A**) or p-JUN (**B**) compared to VCL in parental and resistant cells. (**C**) Proportion of p-JUN to JUN. Statistics were calculated using the two-tailed paired Student's t-test.



Supplemental Fig. S5

Annexin V-FITC/PI co-staining measured by FACS after 84 h of indicated treatment. **(A-C)** Dot plots **(A)** and quantification for cell line #3 parental **(B)** and resistant **(C)**. **(D-F)** Dot plots **(D)** and quantification for cell line #4 parental **(E)** and resistant **(F)**.



Supplemental Fig. S6

(A-F) Synergy analysis of MEK_i plus DNMT_i using the Loewe method of the Combenefit software shown for cell lines #4 **(A,B)**, #9 **(C,D)** and #10 **(E,F)**. Results for parental cells are shown left, while resistant cells are displayed in the right panels, respectively. **(G,H)** Two different PDX of PDAC treated either with MEK_i, DNMT_i or the combination. Solid lines represent the mean tumor volume of the three mice per treatment group ± SEM.