Figure S1. (A) The phosphorylated levels of KRAS downstream proteins were significantly increased in mutant KRAS transductants compared with the wild type. Quantification of the western blots in Fig. 2C. p-MEK, p-ERK and p-RSK expression were significantly increased in CACO-2 KRAS mutant cells, and p-ERK was also significantly increased in SW48 cells. n=3. (B) Bcl-xL protein expression was significantly increased in CACO-2 and SW48 KRAS mutants. Quantification of the western blots in Fig. 2E. n=4. $^{*}P<0.05$, $^{**}P<0.01$. Wild, wild-type; p-, phosphorylated.

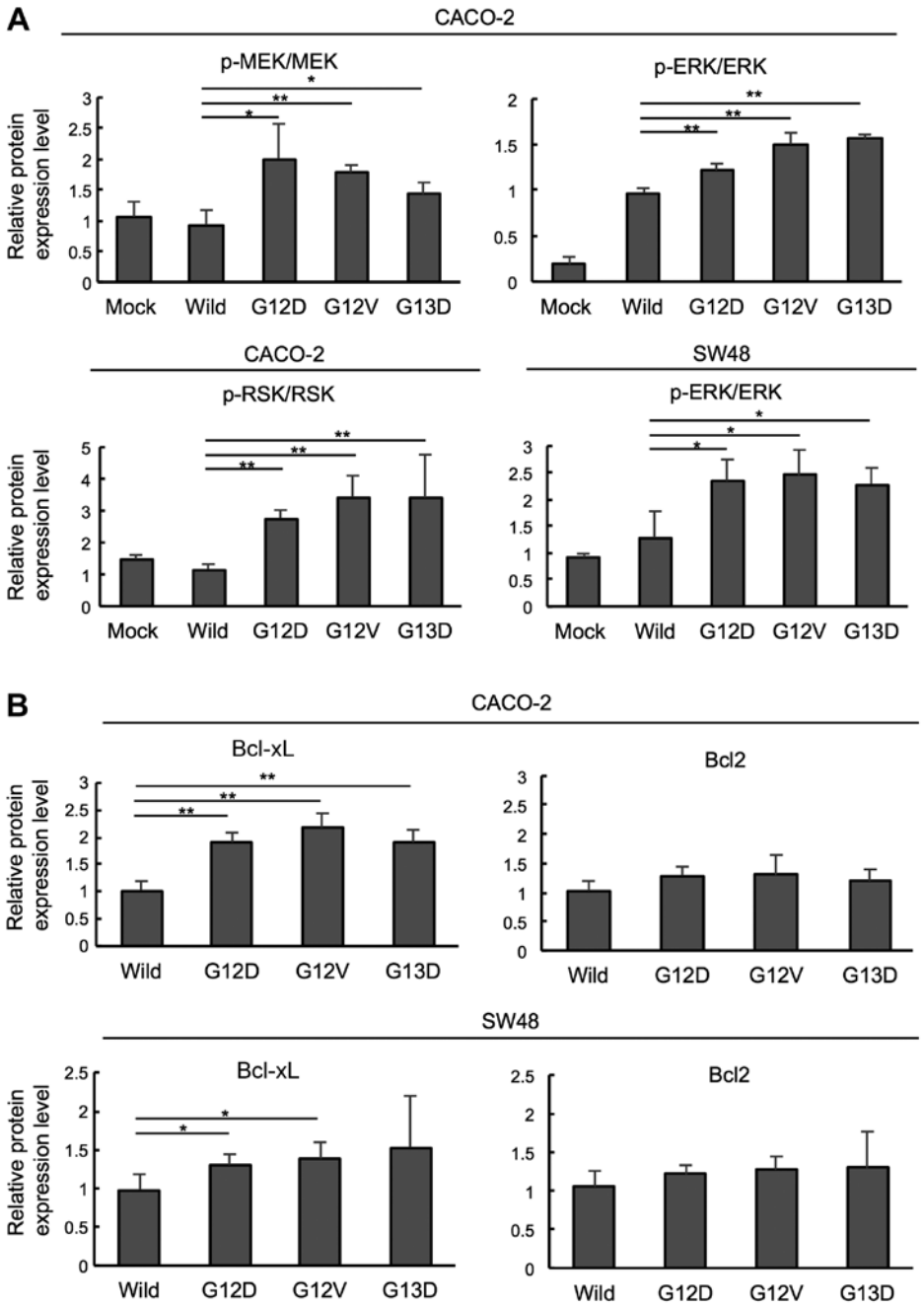

Figure S2. Trametinib decreased p-ERK expression in a dose-dependent manner. Quantification of the western blots in Fig. 3B. n=3. $^{*}$P<0.05, $^{**}$P<0.01. Wild, wild-type; Ctrl, control; p-, phosphorylated.

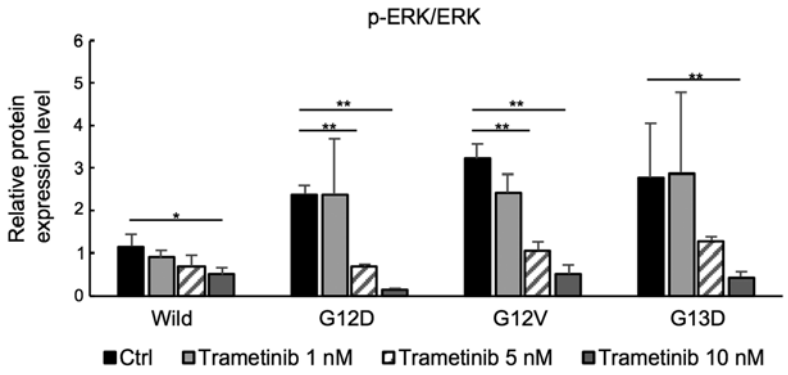

Figure S3. Trametinib (100 nM) induced apoptosis significantly in G12V mutants. (A) Trametinib (25-100 nM) decreased p-ERK/ERK and increased BIM expression in wild and G12V transductants. Trametinib (100 nM) significantly increased cleaved caspase 3 expression in G12V mutants compared with the wild type. (B) No significant change was detected in Bcl-xL and Bcl2 protein expression by high dose trametinib (25-100 nM) therapy. (C) Trametinib (100 nM) and ABT263 (1 $\mu$M) significantly induced cleaved caspase 3 expression in G12V mutants. Quantification of the western blots in Fig. 4A-a,b and c. n=3. $^{*}$P<0.05, $^{**}$P<0.01. Wild, wild-type; Ctrl, control; p-, phosphorylated.

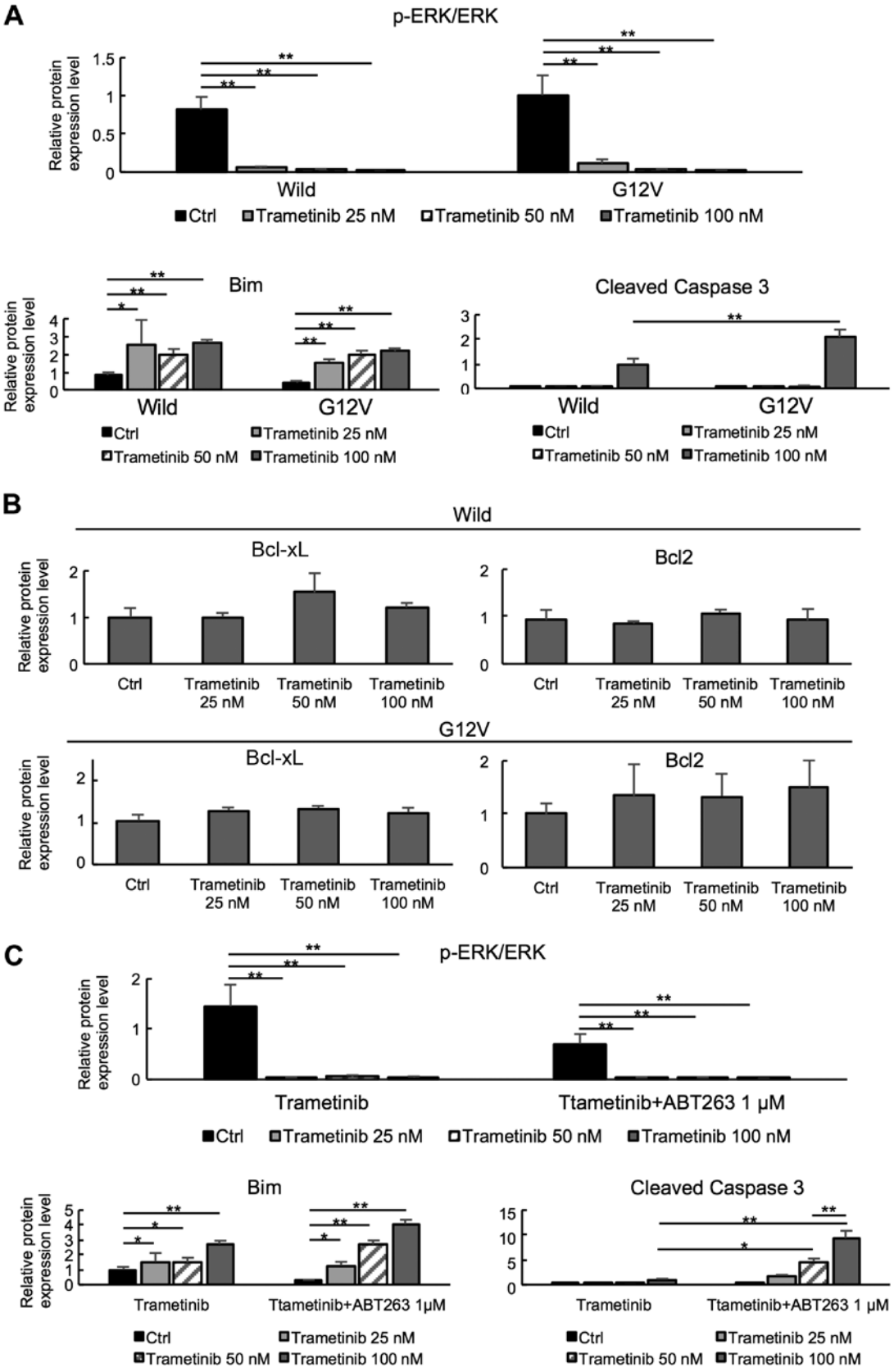

Figure S4. Low dose trametinib induced Bcl-xL protein expression in a dose-dependent manner in G12D and G12V mutants. Bcl-xL expression was significantly increased with 10 nM trametinib in G12D and G12V mutants. No significant changes were detected in Bcl2 expression. Quantification of the western blots in Fig. 4B. n=3. *P<0.05. Wild, wild-type; Ctrl, control.

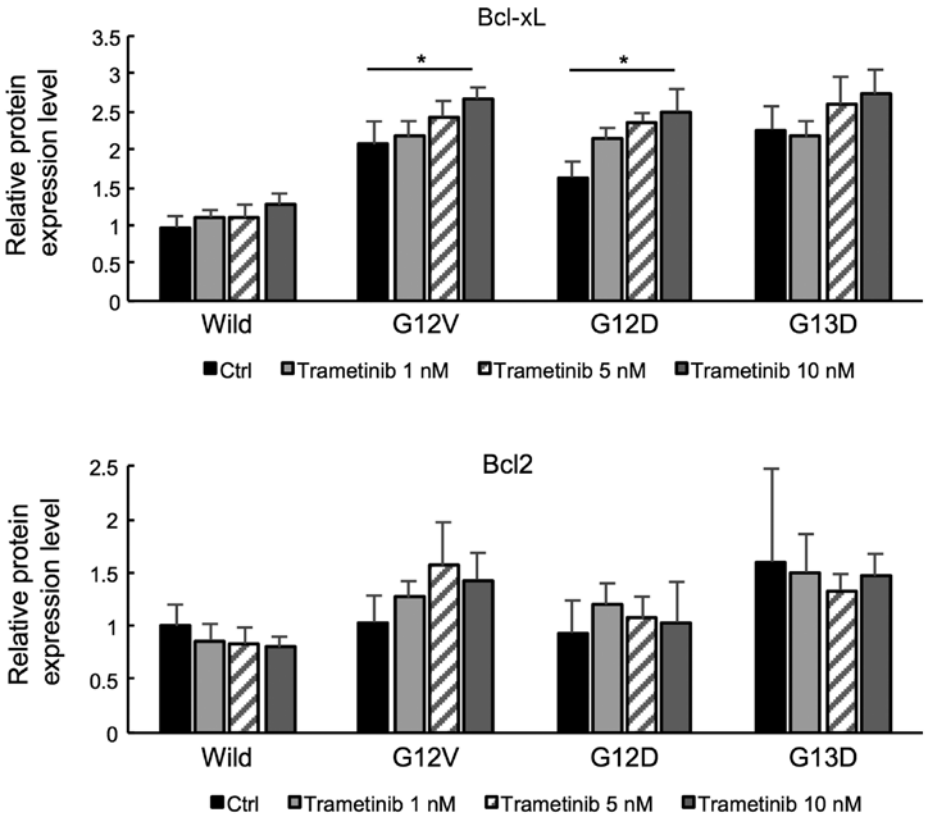

Figure S5. Trametinib and ABT263 combination therapy induced apoptosis in KRAS mutants, particularly in G12V. (A) Low dose trametinib (10 nM) and ABT263 (10 $\mu$M) significantly induced cleaved caspase 3 expression in all KRAS mutants. Quantification of the western blots in Fig. 4C. n=3. Trametinib (50 nM) and ABT263 (1 $\mu$M) increased the percentage of Annexin V-positive cells in all KRAS mutants, although a significant difference was only observed in G12V mutants. (B) Scatterplots of Annexin V/7-AAD assay. (C) Quantification of the Annexin V/7-AAD assay. n=4. $^{*}$P<0.05, $^{**}$P<0.01. Wild, wild-type; Ctrl, control; 7-AAD, 7-aminoactinomycin D.