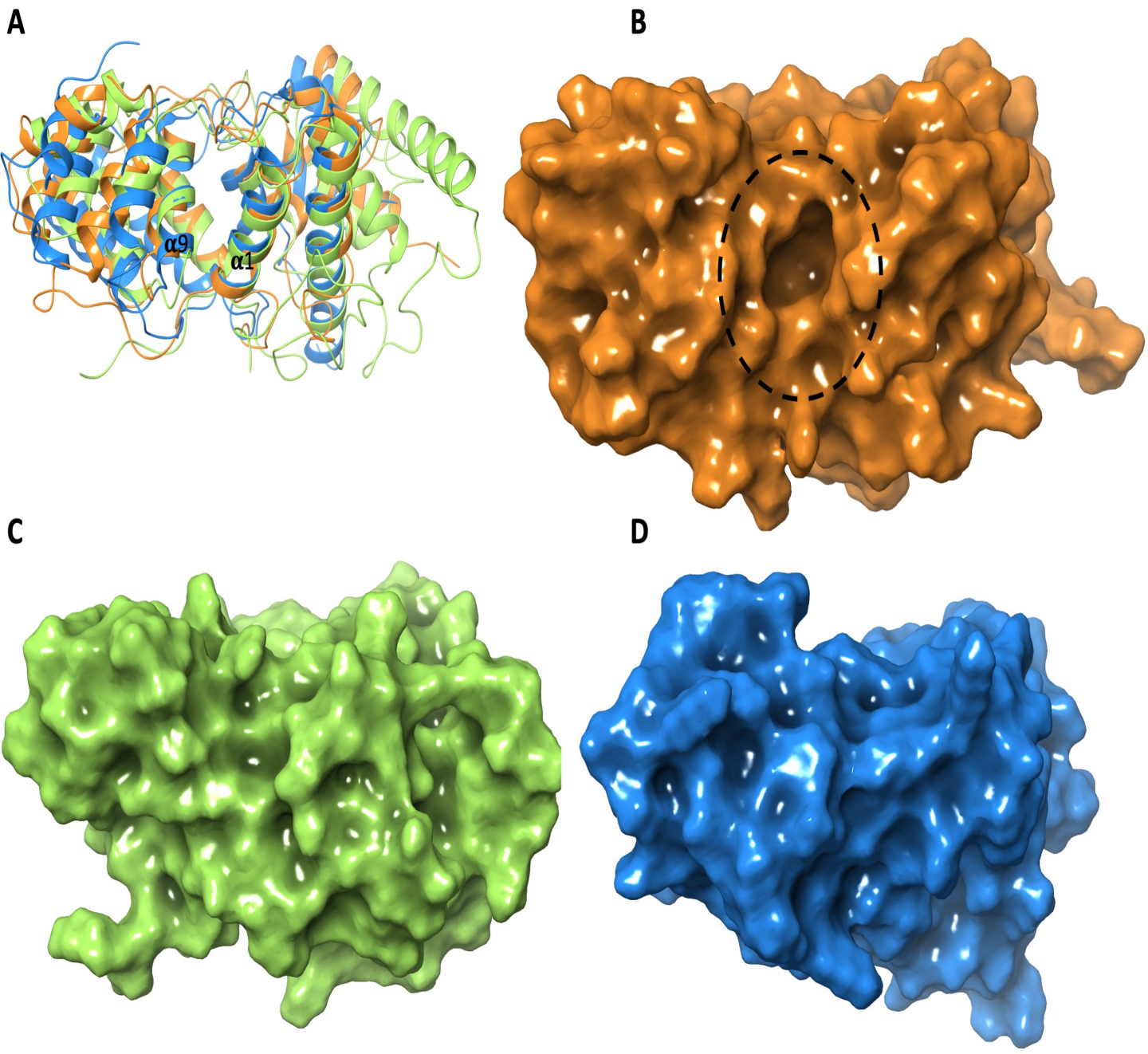
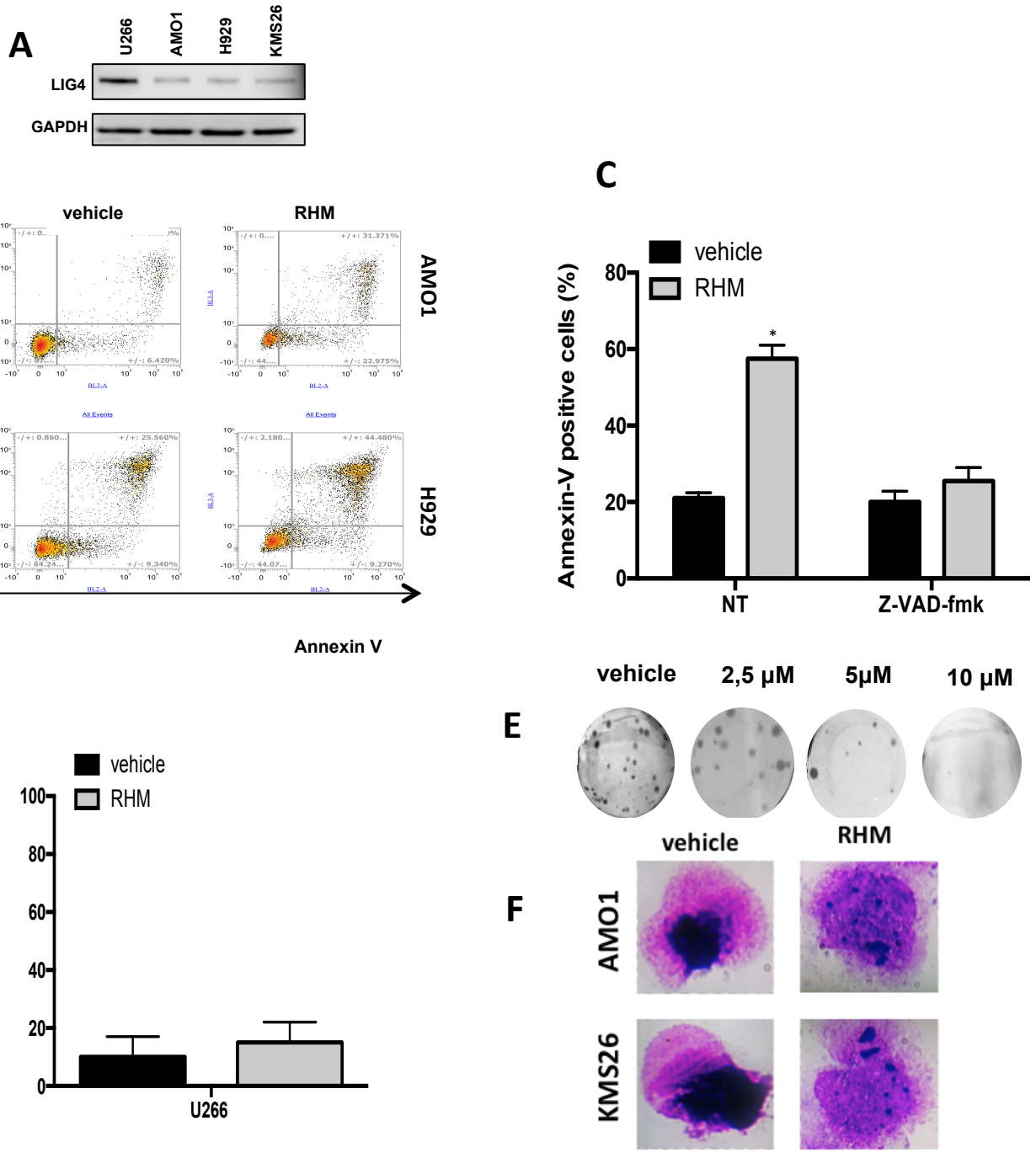



**Supplementary Figure 1.** A. Cartoon backbone representation of the superimposed DNA Binding Domains (DBD) of DNA Ligase I (green), III (orange) and IV (blue). B. Surface view of the DBD of ligase III (PDB ID 3L2P) . The positively charged groove targeted in the virtual screening is encircled by the dashed line. C. Surface view of the DBD of ligase I (PDB ID 1X9N). D. Surface view of the DBD of ligase IV (PDB ID 3W5O).




**Supplementary Figure 2. A.** Immunoblot analysis of LIG4 expression in MM cell lines. GAPDH was used as loading control. **B.** Representative FACS traces of Annexin V assay in AMO1 and H929 cells 4 days after RHM treatment (5 µM). **C.** H929 cells were treated with vehicle or RHM (5 µM). 6 hours after either DMSO (NT) or Z-VAD-FMK were added to culture medium, at final concentration of 25 µM. Annexin V staining 4 days after treatment is shown. **D.** Annexin V assay on U266 cells after 4 days of treatment with vehicle or RHM (5 µM). **E.** Colony formation of AMO1 cells treated with vehicle or increasing dose of RHM. Light microscopy after 2 weeks is shown. **F**.H&E stain of AMO1 and KMS26 cells after 5 days of treatment with vehicle or RHM (5 µM).

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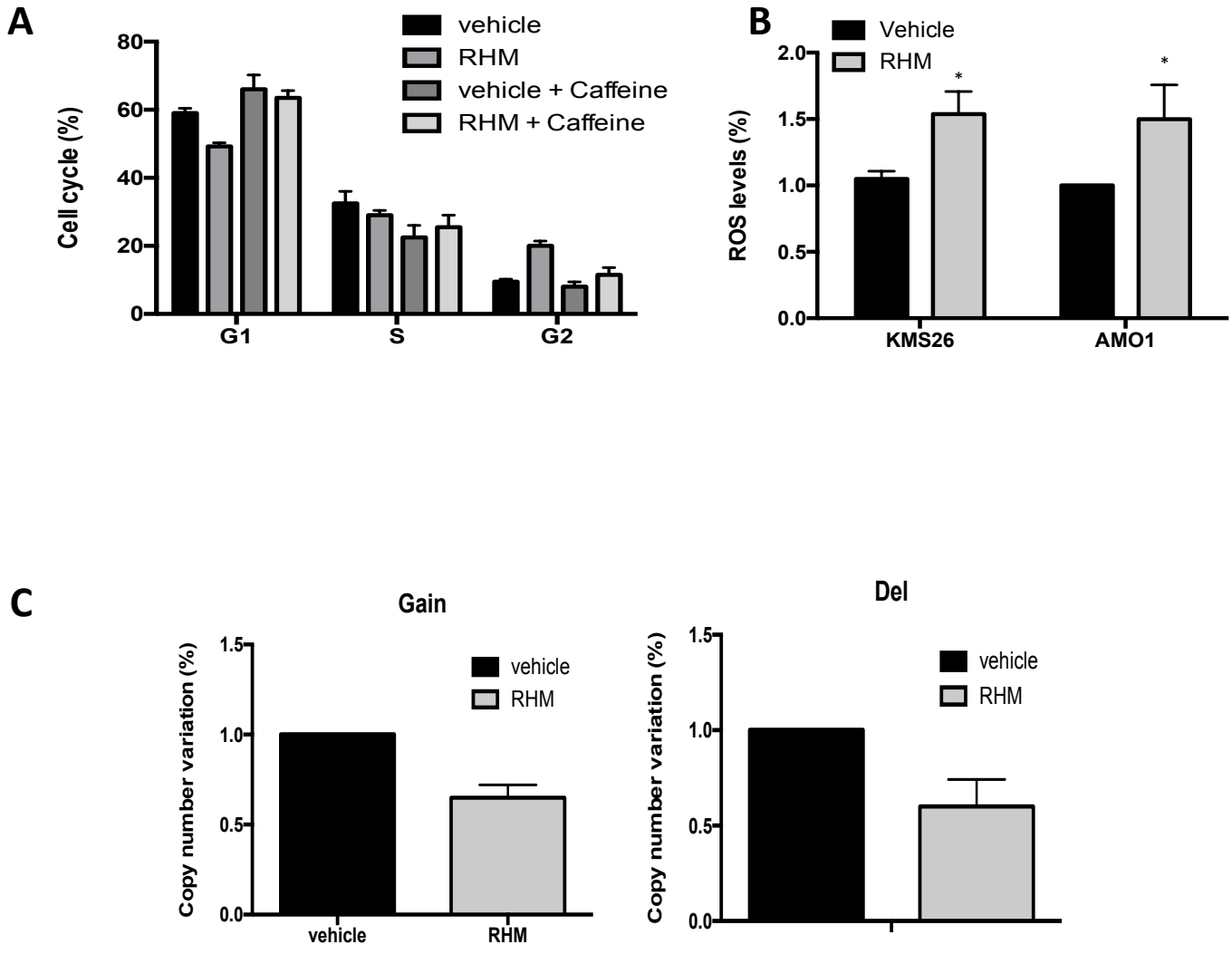
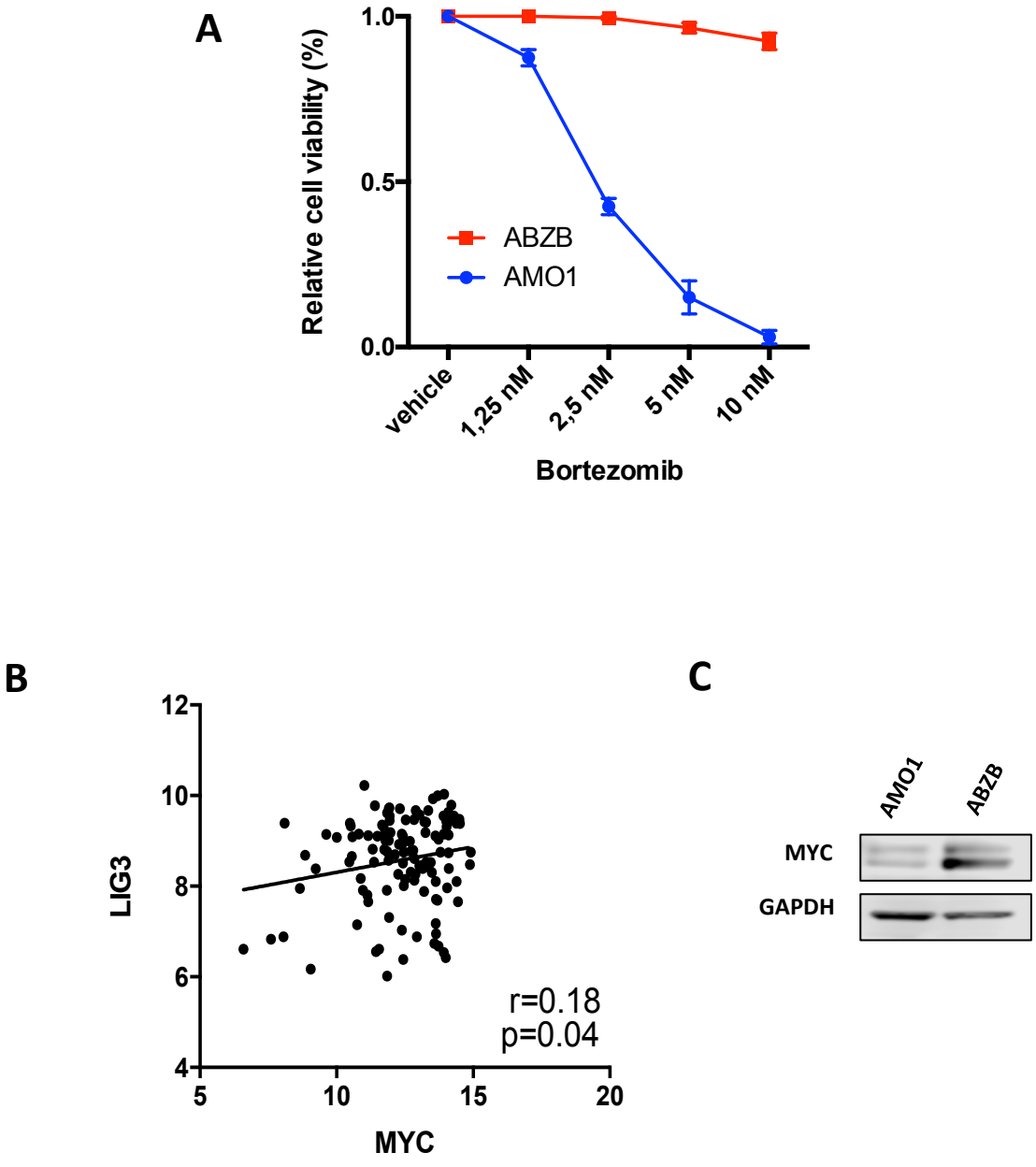



**Supplementary Figure 3. A.** Cell cycle analysis in H929 cells treated with RHM (5 µM) with or without Caffeine (5 mM) for 48h. **B.** ROS-Glo H2O2 assay performed in AMO1 and KMS26 cells 48h after treatment with vehicle or RHM (5 µM). **C.** Relative percentage of CNV acquisition in AMO1 treated with RHM (2,5 µM) or vehicle, as evaluated by Affymetrix CytoScan HD Array analysis.




**Supplementary Figure 4. A.** Cell viability of AMO1 and ABZB, treated with vehicle or increasing dose of Bortezomib for 48h. **B.** Graphs of correlations between endogenous mRNA expression levels of LIG3 and MYC in MM patents with EFS<24 months, from GSE24080 public dataset. **C.** Immunoblot analysis of MYC expression in AMO1 and ABZB cells. GAPDH was used as loading control.