Figure S1. Quantification of ferroptosis-related proteins and PRMT1 expression in parental and KRAS G12C inhibitor-resistant cells. (A) Densitometric quantification of GPX4 and GCLM protein expression in Mia Paca-2, Mia Paca-2-510 and Mia Paca-2-1553 cells (n=4). (B) Densitometric quantification of PRMT1 protein expression in Mia Paca-2, Mia Paca-2-510 and Mia Paca-2-1553 cells (n=3). Data are presented as the mean ± SEM. One-way ANOVA for multi-group comparisons. *P<0.05, **P<0.01 and ***P<0.001. PRMT1, protein arginine methyltransferase 1; GPX4, glutathione peroxidase 4.

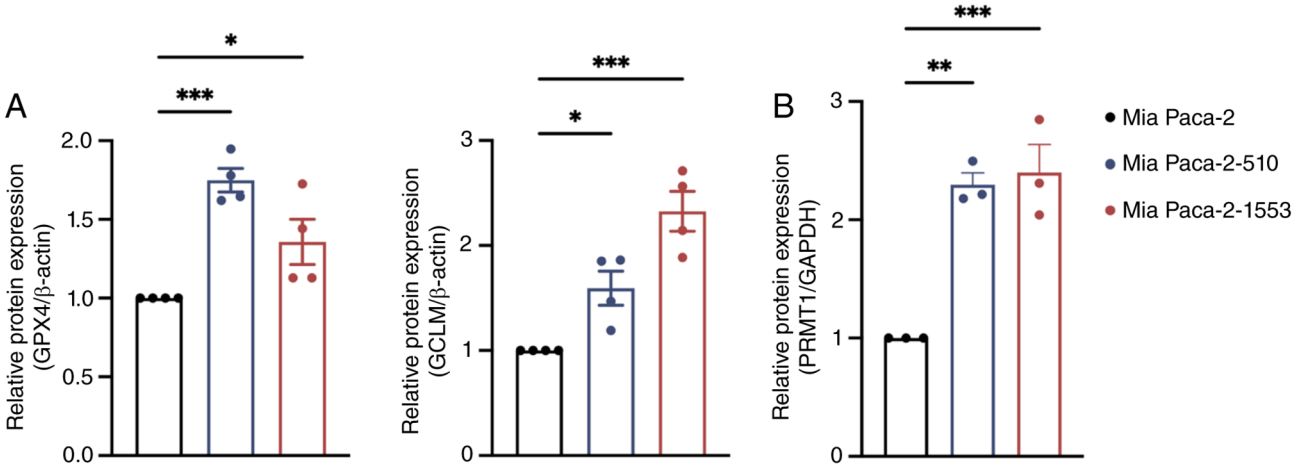


Figure S2. Chou-Talalay analysis of the interaction between KRAS G12C and protein arginine methyltransferase 1 inhibition. (A and B) CI-fraction affected (Fa) plots for AMG510 plus CTS2190 and D-1553 plus CTS2190, respectively, in Mia Paca-2 cells at a fixed 1:3 concentration ratio. (C) CI-Fa analysis of AMG510 plus CTS2190 in Mia Paca-2-510 cells at a fixed 1:3 ratio. (D) CI-Fa analysis of D-1553 plus CTS2190 in Mia Paca-2-1553 cells at a fixed 1:3 ratio. Observed combination data and fitted Chou-Talalay CI-Fa curves are shown. CI <1, CI=1, and CI >1 indicate synergistic, additive, and antagonistic interactions, respectively. CI, combination index.

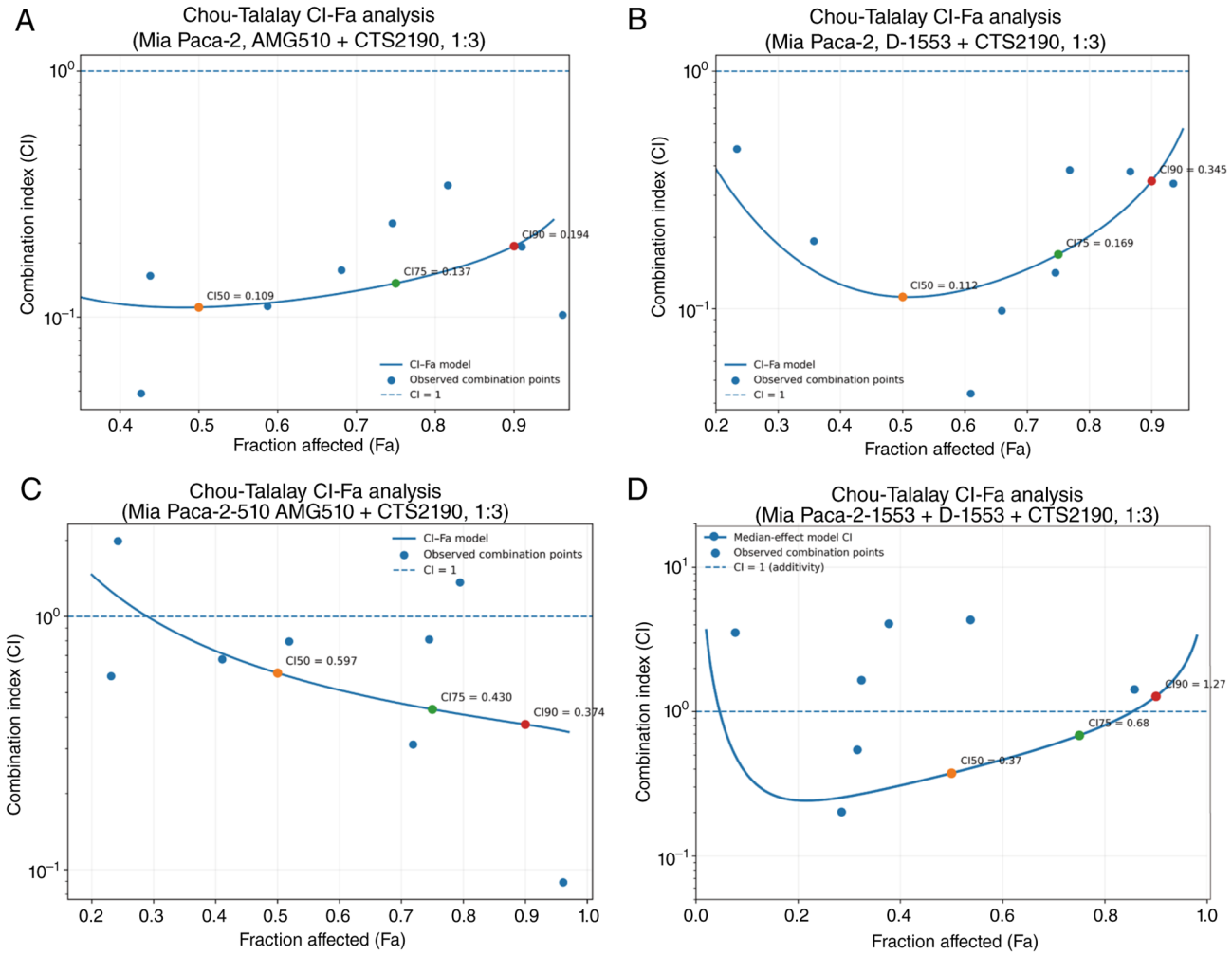


Figure S3. Combined inhibition of KRAS G12C and protein arginine methyltransferase 1 enhances growth inhibition in H358 cells and their resistant derivatives. (A and B) Cell viability of H358 cells following treatment with AMG510, CTS2190, or AMG510 combined with 100 or 300 nM CTS2190, respectively (n=4). (C and D) Cell viability of H358 cells following treatment with D-1553, CTS2190, or D-1553 combined with 100 or 300 nM CTS2190, respectively (n=4). (E and F) Cell viability of H358-510 cells following treatment with AMG510, CTS2190, or AMG510 combined with 300 or 1,000 nM CTS2190, respectively (n=4). (G and H) Cell viability of H358-1553 cells following treatment with D-1553, CTS2190, or D-1553 combined with 300 or 1,000 nM CTS2190, respectively (n=4). Cell viability was assessed using the Cell Counting Kit-8 assay. Data are presented as the mean ± SEM.

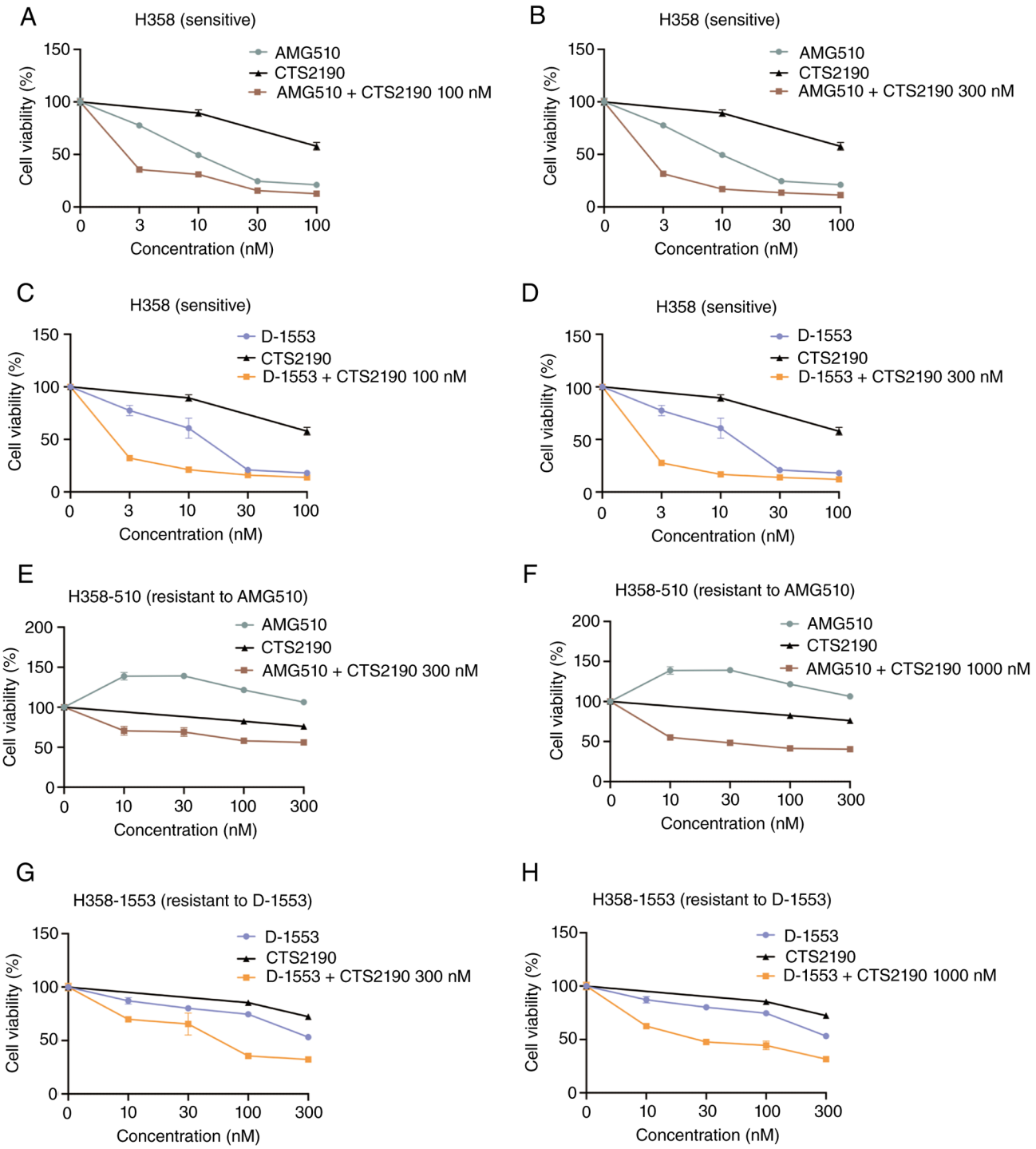


Figure S4. Individual tumor growth profiles and histopathological changes following combined KRAS G12C and PRMT1 inhibition. (A) Individual tumor growth curves of Mia Paca-2 xenografts following treatment with vehicle, AMG510, D-1553, CTS2190, AMG510 plus CTS2190, or D-1553 plus CTS2190. (B) Representative H&E staining of Mia Paca-2 xenograft tumors following the indicated treatments. Scale bars, 100 μm. (C) Individual tumor growth curves of Mia Paca-2-510 xenografts treated with vehicle, AMG510, CTS2190, or AMG510 plus CTS2190. (D) Individual tumor growth curves of Mia Paca-2-1553 xenografts treated with vehicle, D-1553, CTS2190, or D-1553 plus CTS2190. (E) Representative H&E staining of Mia Paca-2-510 and Mia Paca-2-1553 xenograft tumors following the indicated treatments. Scale bars, 100 μm.

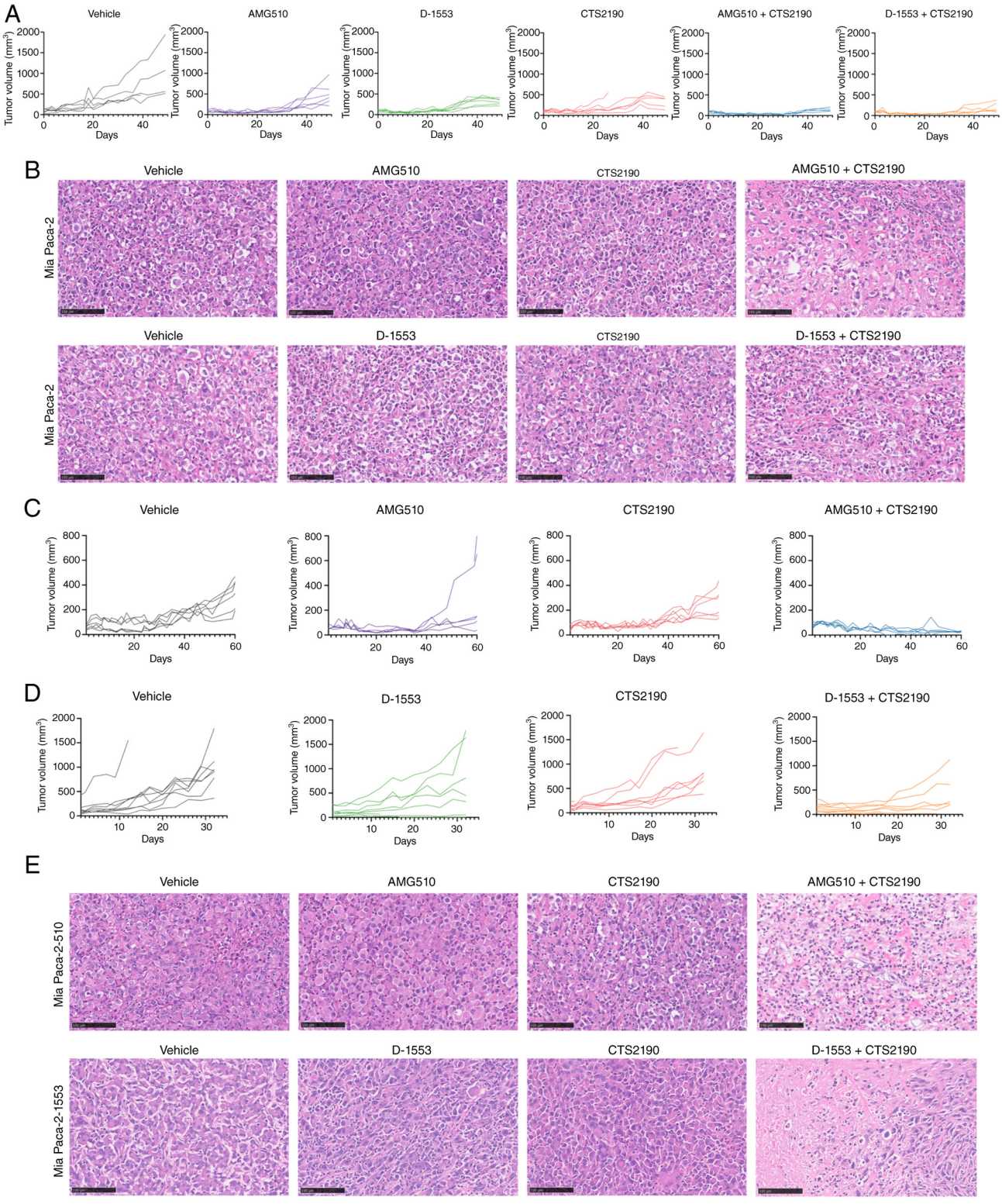


Figure S5. Effect of combined treatment on the liver of mice. (A) Serum ALT and AST levels in WT mice and mice bearing Mia Paca-2, Mia Paca-2-510, or Mia Paca-2-1553 xenografts following the indicated treatments. Data are presented as the mean ± SEM. (B) Representative H&E staining of liver tissues from mice bearing Mia Paca-2, Mia Paca-2-510, or Mia Paca-2-1553 xenografts after the indicated treatments. Scale bars, 250 μm. One-way ANOVA was used for multi-group comparisons. ns, not significant. ALT, alanine aminotransferase; AST, aspartate aminotransferase; WT, wild-type.

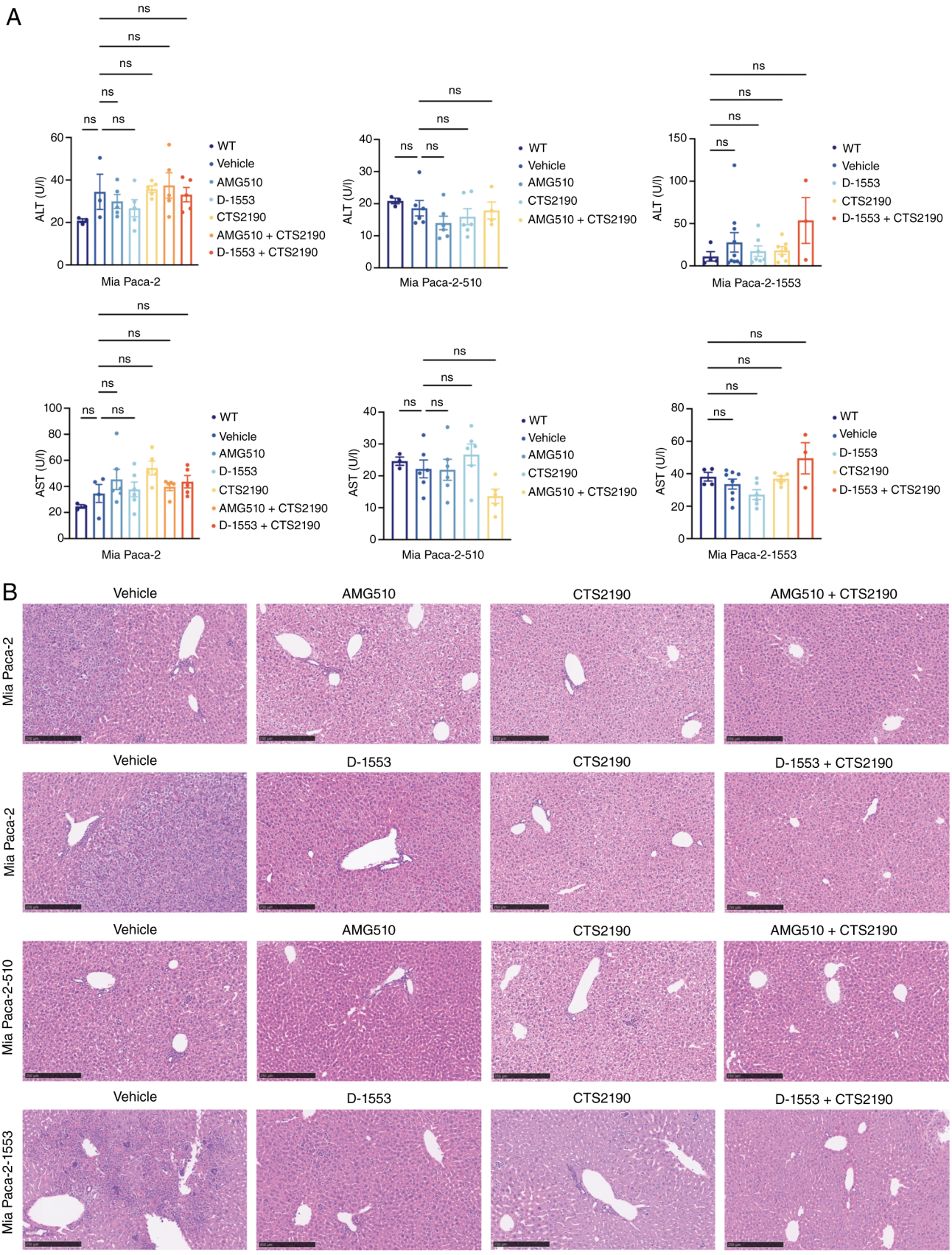


Figure S6. Quantification of ferroptosis-related protein expression following combined KRAS G12C and protein arginine methyltransferase 1 inhibition. (A) Densitometric quantification of GPX4, SLC7A11 and GCLM protein expression in Mia Paca-2 cells following treatment with the corresponding KRAS G12C inhibitor, CTS2190, or their combination (n=3). (B) Densitometric quantification of GPX4, SLC7A11 and GCLM protein expression in Mia Paca-2-510 and Mia Paca-2-1553 cells following treatment with AMG510 or D-1553, CTS2190, or the corresponding combination (n=3). Data are presented as the mean ± SEM. One-way ANOVA for multi-group comparisons. *P<0.05, **P<0.01, ***P<0.001 and ****P<0.0001. GPX4, glutathione peroxidase 4; SLC7A11, solute carrier family 7 member 11; ns, not statistically significant.

