Figure S1. Enriched gene ontology clusters of genes with altered expression levels associated with E7386 concentrations (correlation coefficient >0.7). (A) Upregulated and (B) downregulated genes in organoids. (C) Upregulated and (D) downregulated genes in CAFs. CAFs, cancer-associate fibroblasts.

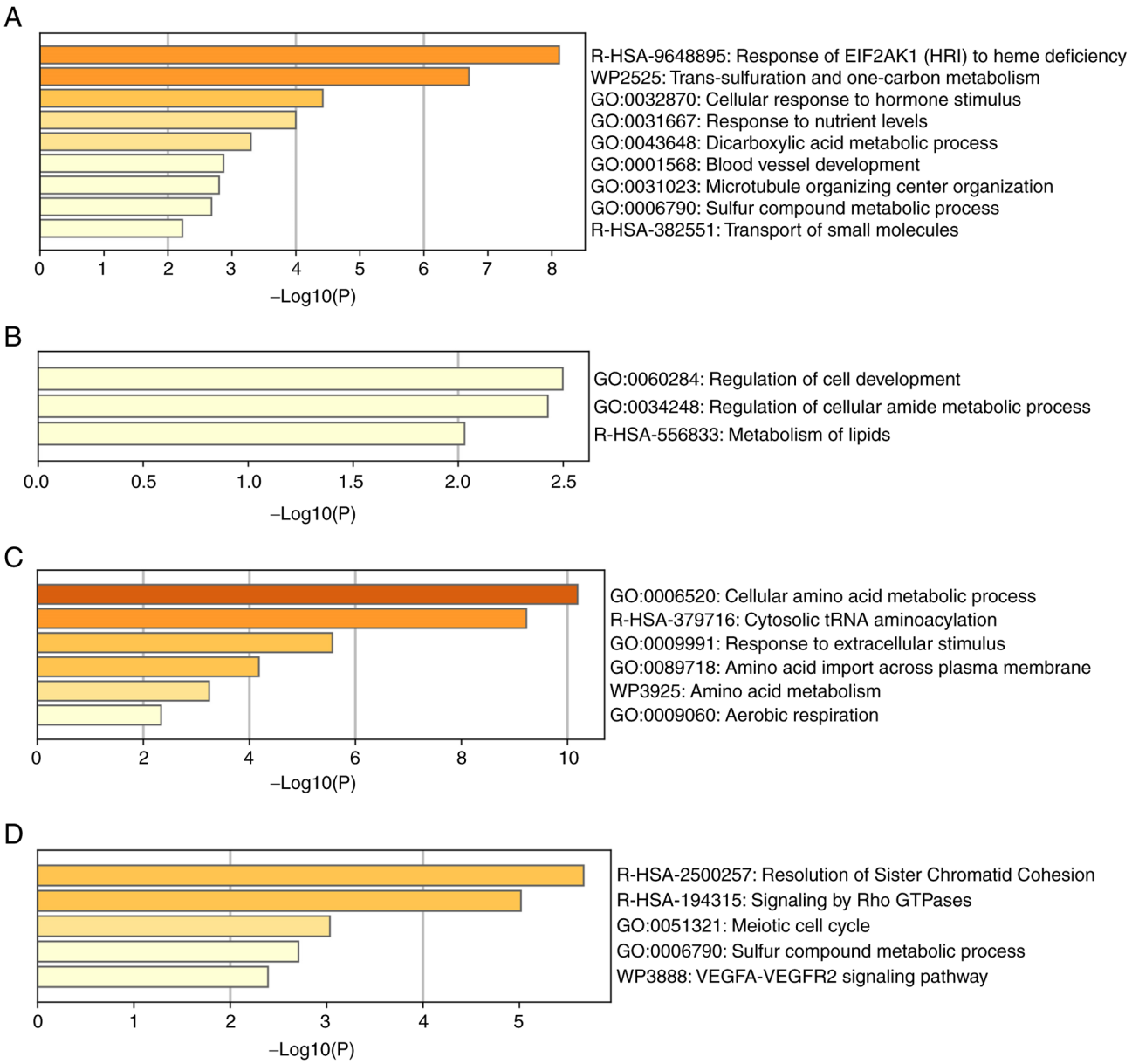

Figure S2. Gene expression changes in organoids and CAFs by E7386 treatment. Volcano plot of the gene expression levels in (A) organoids and (B) CAFs co-cultured with CAFs and organoids, respectively, 24 h after E7386 (100 nM) addition compared with those of control. The y-axis shows the P-value for the differences in gene expression levels by a negative logarithm. The x-axis is the difference in the estimated relative gene expression values. Vertical red lines represent the threshold of the two-fold change, and horizontal red lines represent those of with a significant (P<0.05) change. CAFs, cancer-associate fibroblasts;CHAC1, glutathione-specific γ-glutamylcyclotransferase 1; ULBP1, UL16 binding protein 1; PCK2, phosphoenolpyruvate carboxykinase 2; PSAT1, phosphoserine aminotransferase 1; ASNS, asparagine synthetase (glutamine-hydrolyzing); PHGDH, phosphoglycerate dehydrogenase; GARS, glycyl-tRNA synthetase 1; SMC1A, structural maintenance of chromosomes 1A; SESN2, Sestrin-2; SPC25, SPC25 component of NDC80 kinetochore complex.

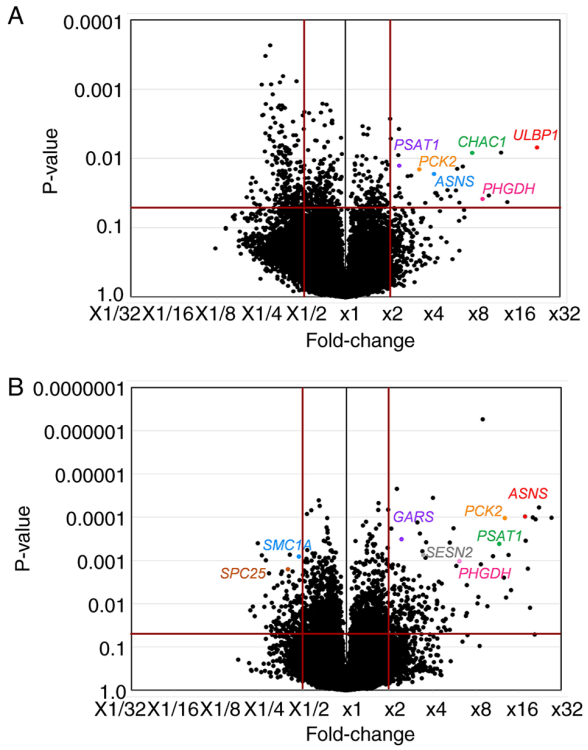

Figure S3. Gene expression changes in organoids and CAFs by E7386 treatment. Heat map showing the gene expression levels in (A) organoids and (B) CAFs 6 and 24 h after E7386 (0, 30 and 100 nM) addition compared with those of control. Data represent normalized, centered and scaled probe intensities on a log2 scale. CAFs, cancer-associate fibroblasts; CHAC1, glutathione-specific γ-glutamylcyclotransferase 1; ULBP1, UL16 binding protein 1; PCK2, phosphoenolpyruvate carboxykinase 2; PSAT1, phosphoserine aminotransferase 1; ASNS, asparagine synthetase (glutamine-hydrolyzing); PHGDH, phosphoglycerate dehydrogenase; ATAD5, ATPase family AAA domain-containing protein 5; MYBL2, MYB proto-oncogene like 2; ZGRF1, zinc finger GRF-type-containing 1; CCNE2, cyclin E2.

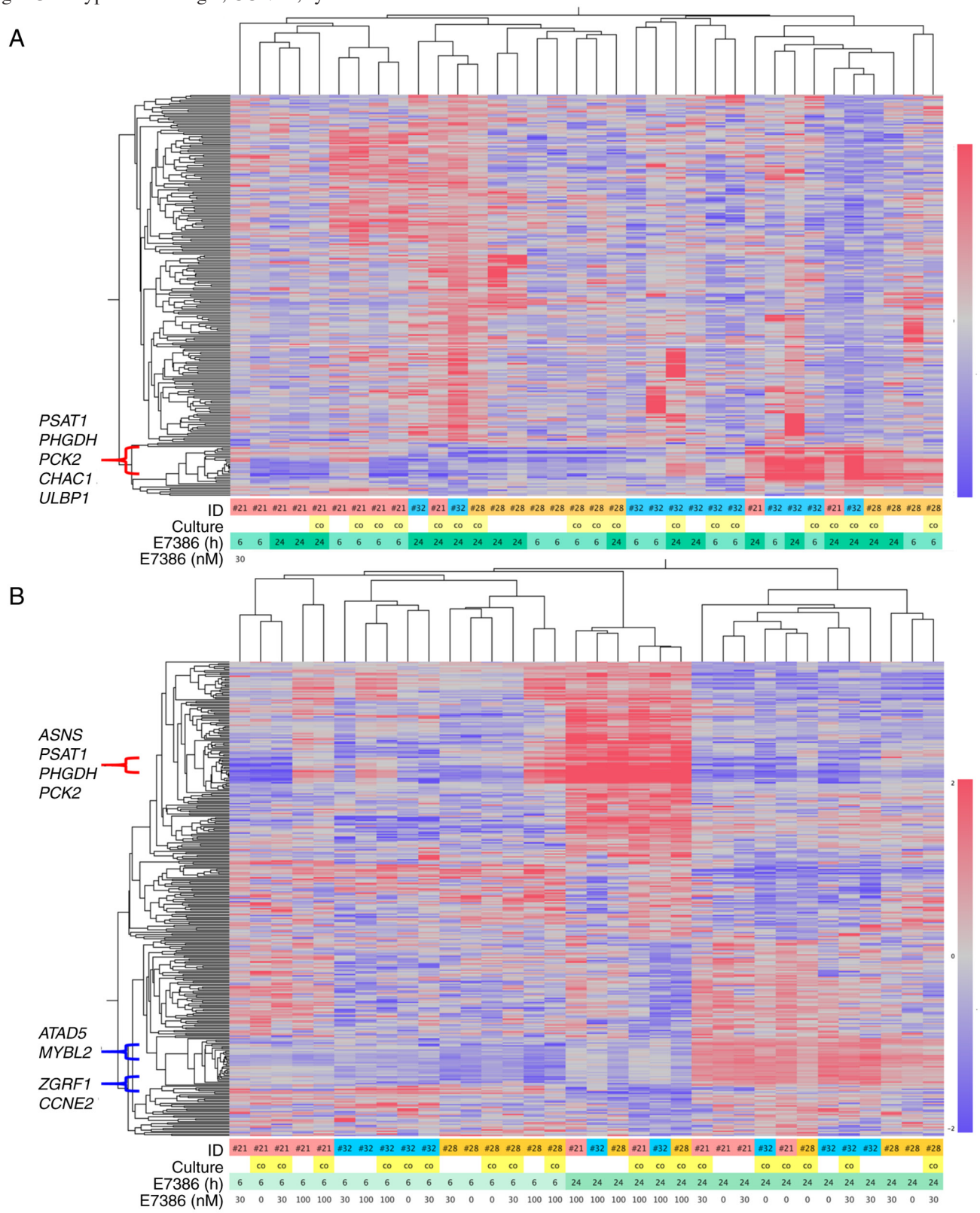

Figure S4. Metabolome data map of metabolites including amino acids and their derivatives in organoids from cases 21, 28 and 32 after treatment with E7380 for 24 h. Columns, average concentrations of metabolites (nmol/g DNA). Bars, SD. N.D., the metabolite concentration was below the detection limit of the analysis.

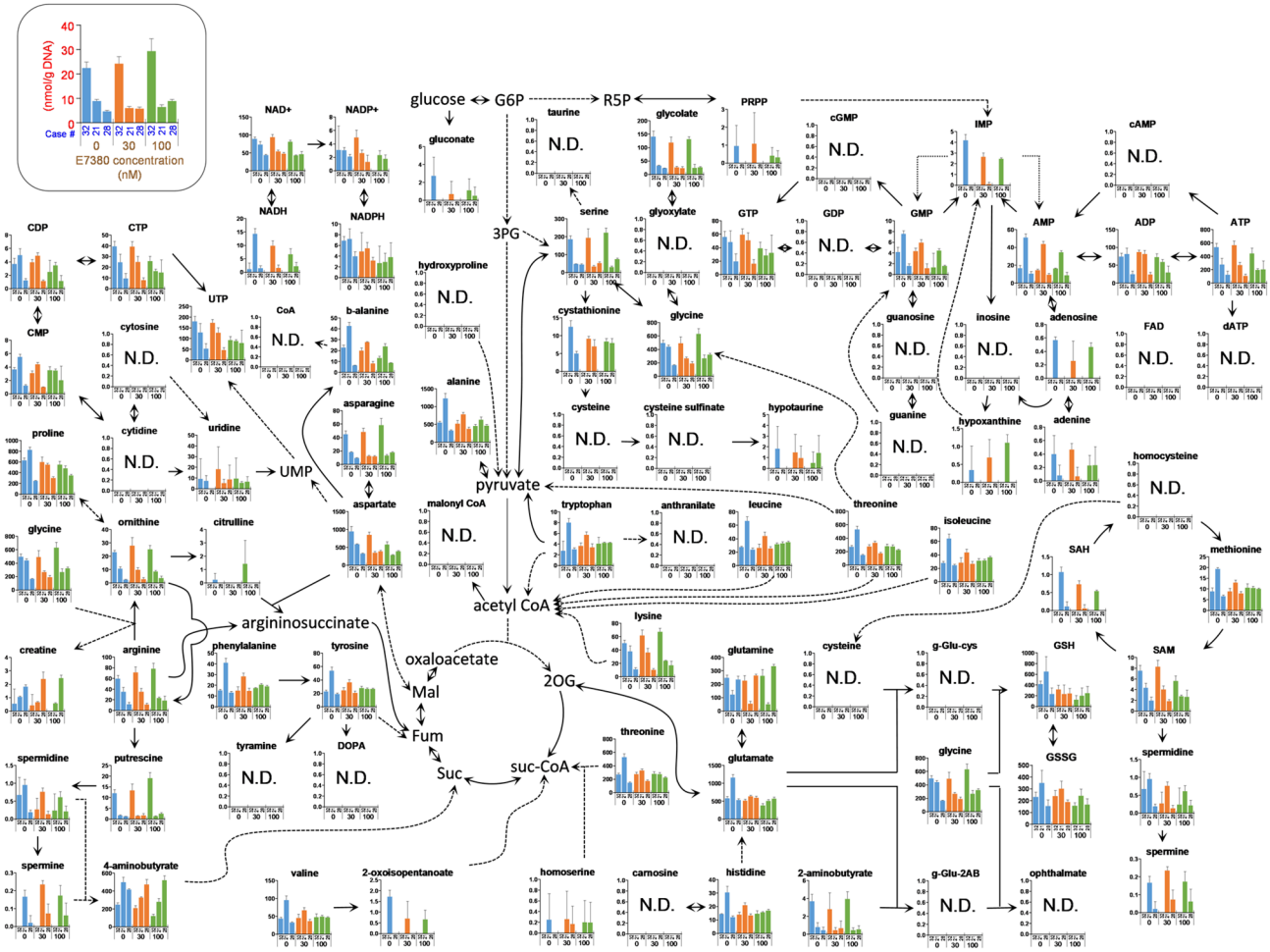

Figure S5. Average changes in the volumes of PDX from cases 21 and 28 after treatment with E7380 twice a day for 14 days. Data are presented as the mean ± SD. PDX, patient-derived xenografts.

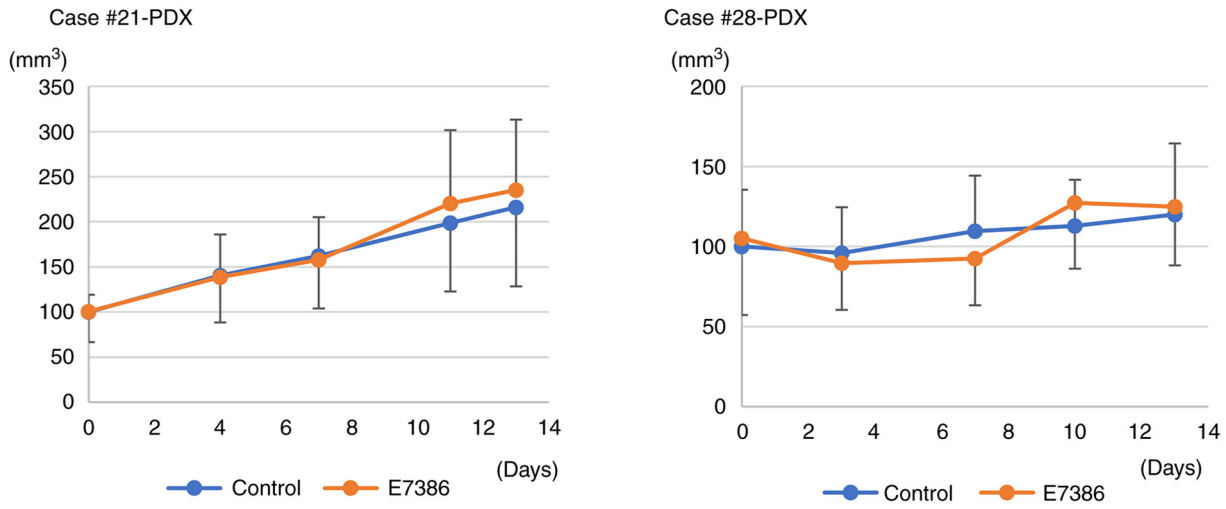

Figure S6. Macroscopic appearance of patient-derived xenografts from cases 21 and 28 after treatment with E7380 twice a day for 14 days. Scale bar, 1 cm. PDX, patient-derived xenografts.

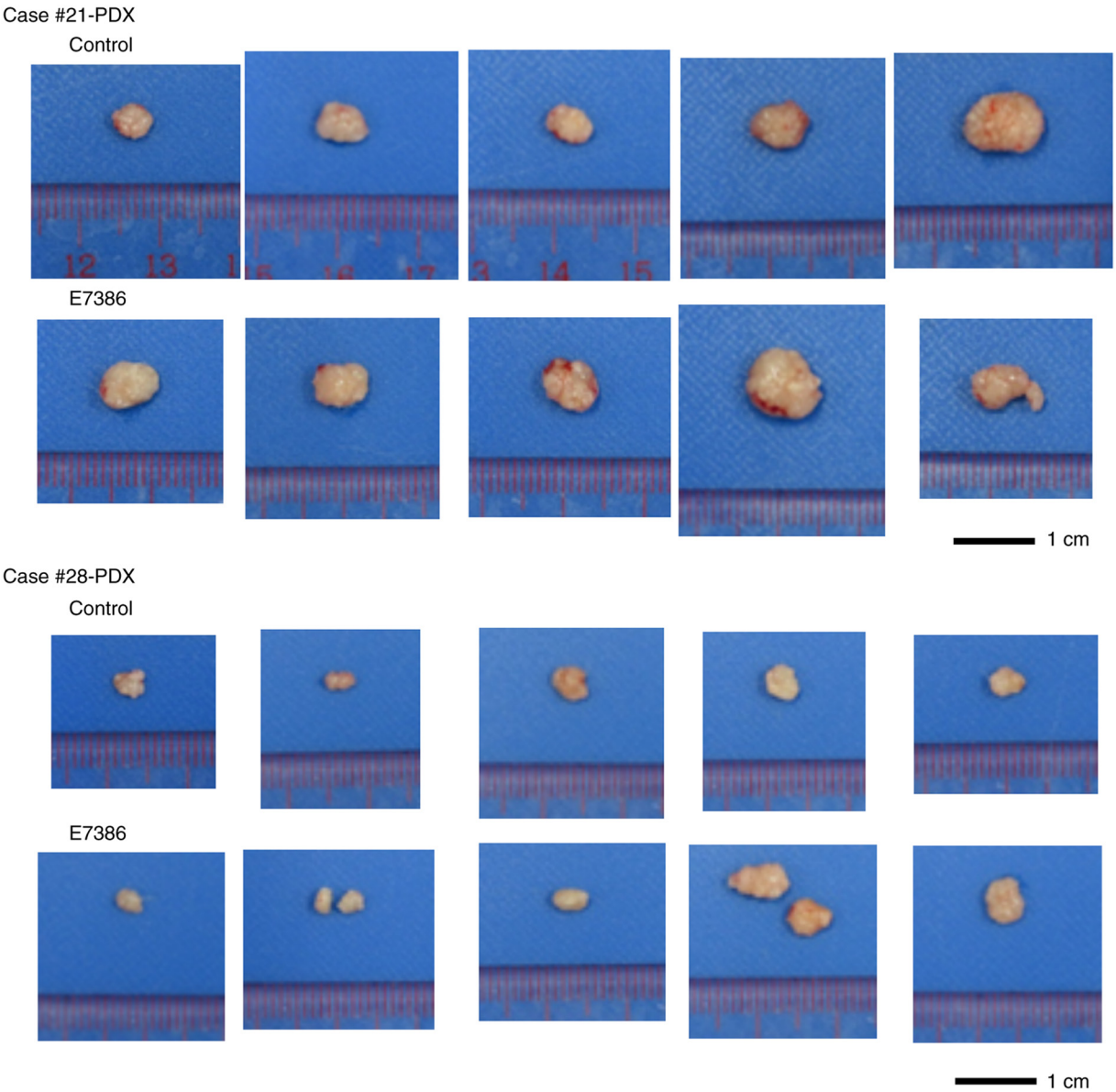

Figure S7. Immunoblotting for the expression levels of (A) PCK2 and (B) β-catenin relative to (C) β-actin in PDXs of case 21 treated with E7380 at 0 and 50 mg/kg bodyweight BID for 14 days. Immunoblotting for (D) PCK2 and (E) β-catenin relative to (F) β-actin in PDXs of case 28 treated with E7380 as same as case 21. PCK2, phosphoenolpyruvate carboxykinase 2; PDX, patient-derived xenografts; BID, twice a day.

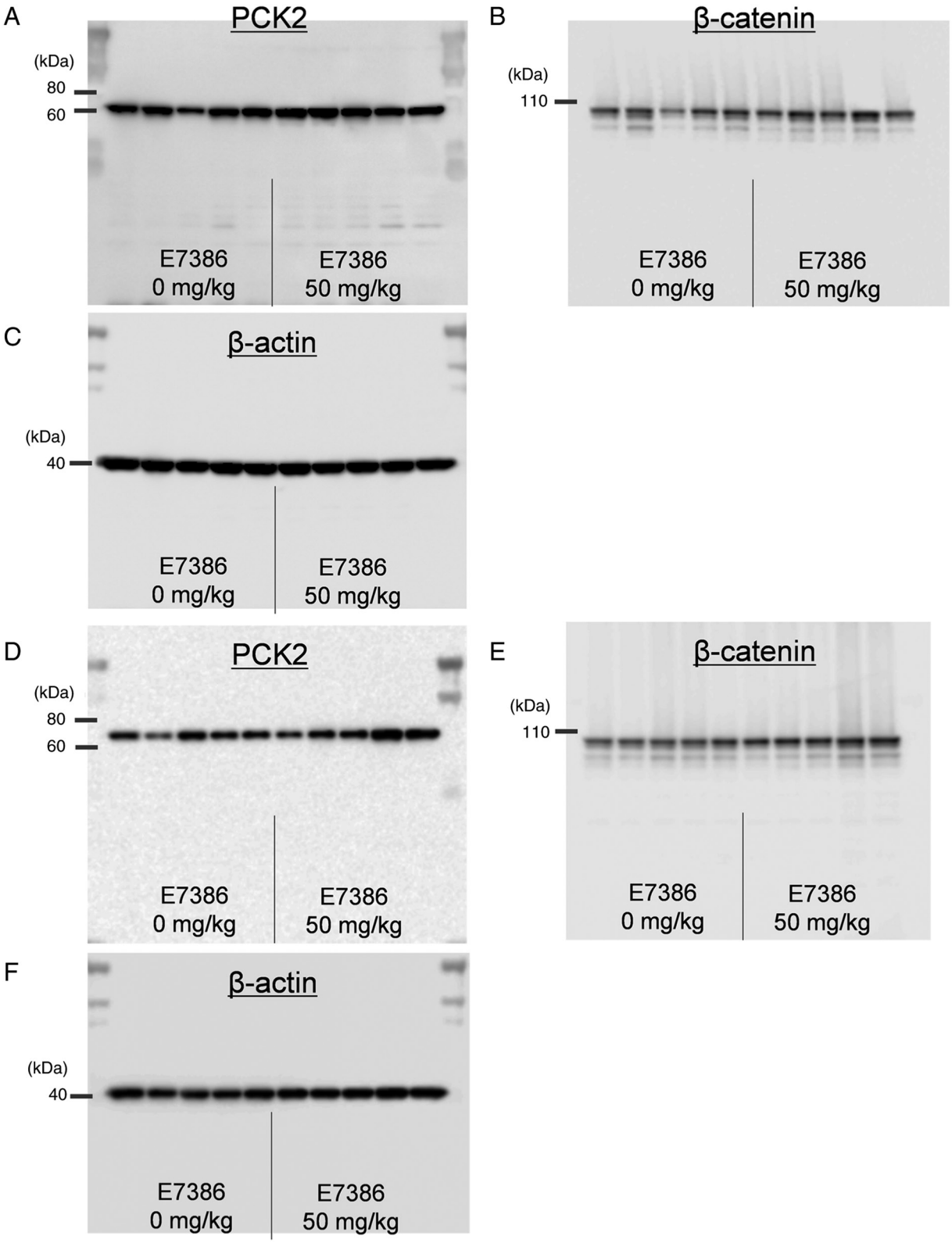

Figure S8. Average (A) PCK2/β-actin ratios and (B) β-catenin/β-actin ratios measured in immunoblotting analysis in PDXs of case 28 treated with E7380 at 0 and 50 mg/kg bodyweight BID for 14 days. Data are presented as the mean ± SD. PCK2, phosphoenolpyruvate carboxykinase 2; PDX, patient-derived xenografts; BID, twice a day.

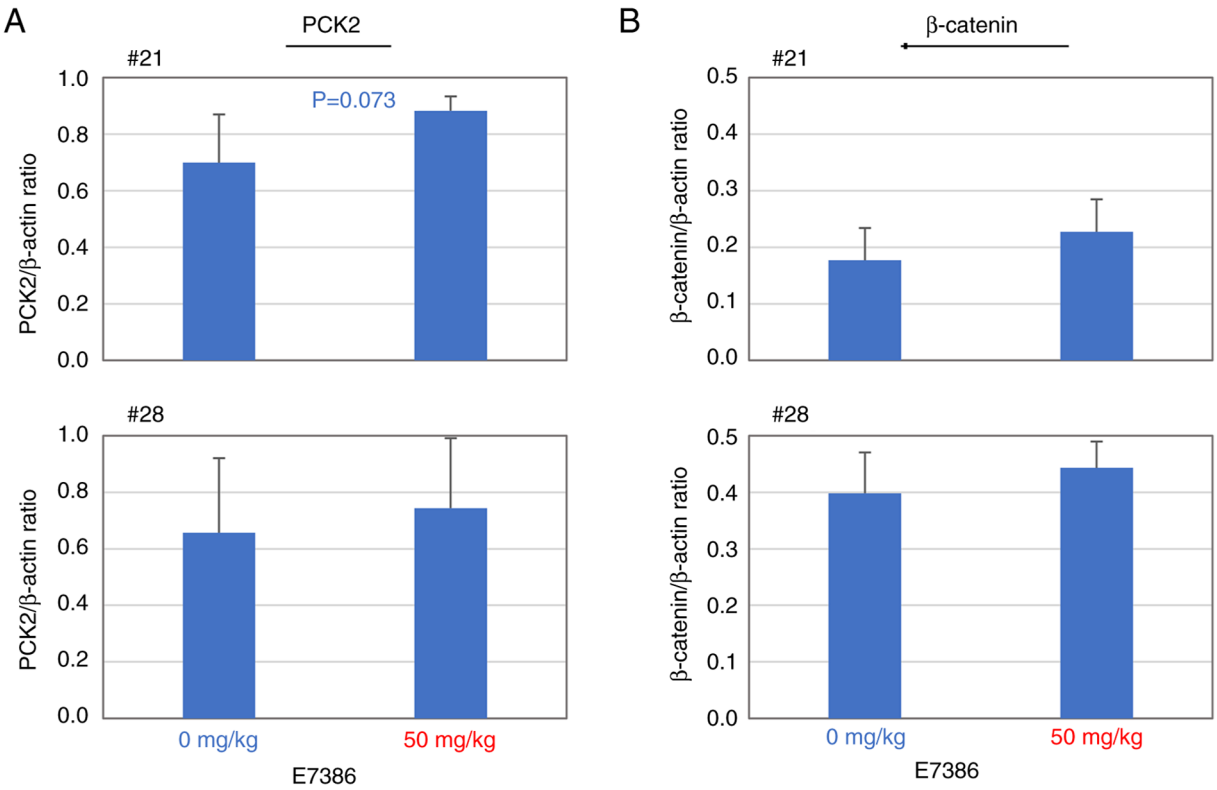

Figure S9. (A) Quantitative imaging analysis of αSMA expression from immunohistochemistry staining in the PDX treated with E7380 twice a day for 14 days. (B) Immunohistochemistry staining for αSMA in the PDX of cases 21 and 28 treated with E7380. Scale bars, 50 μm. Immunohistochemical staining for case 28 are also presented in Fig. 5D. αSMA, α-smooth muscle actin; PDX, patient-derived xenografts; ns, not significant.