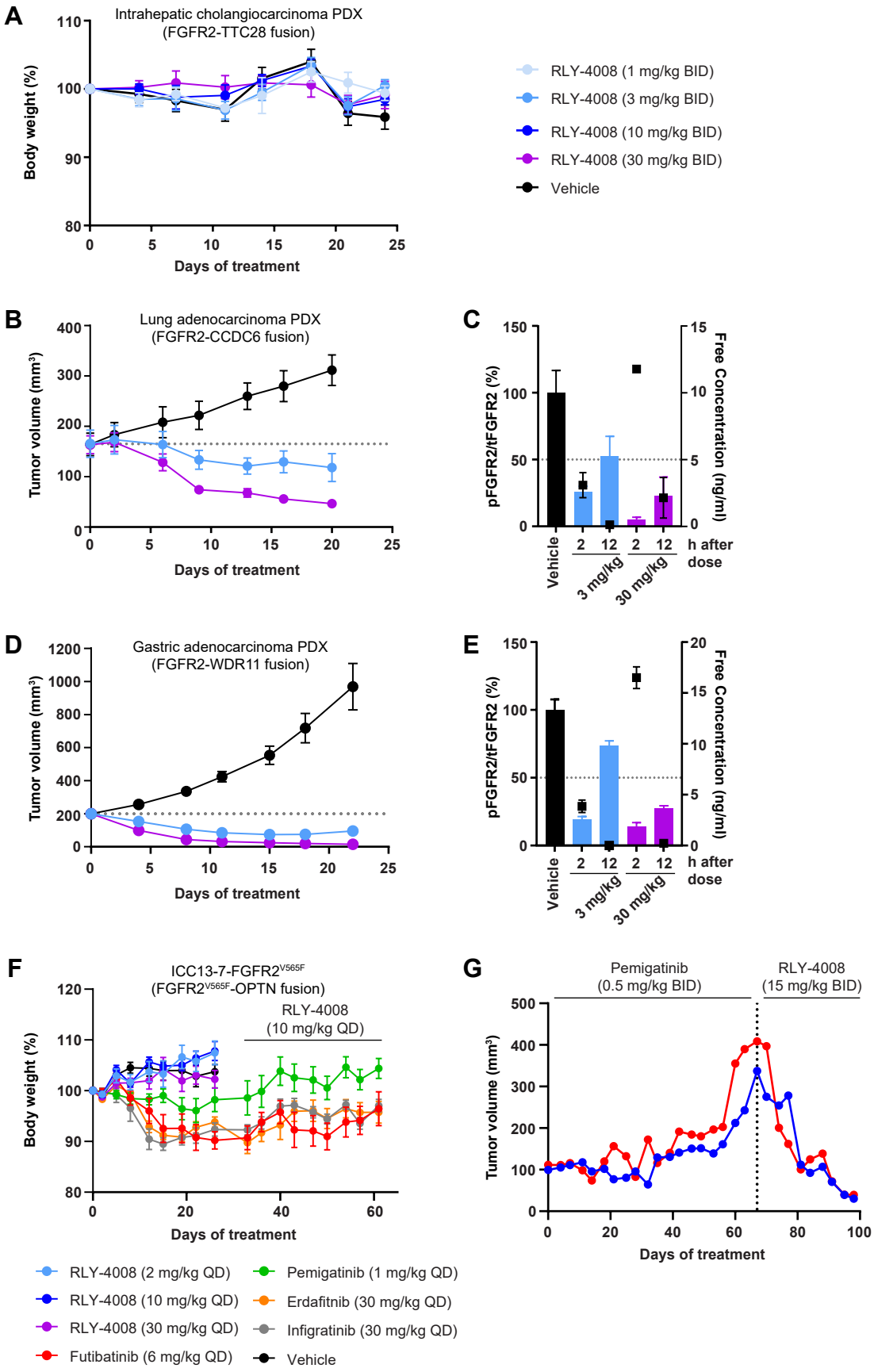
Supplementary Figure S2



Supplementary Figure S2. Treatment with RLY-4008 is well-tolerated and leads to dose-dependent inhibition of FGFR2 and tumor regression in multiple FGFR2-altered tumor models. **A-E,** Refer to legend at top right. **A,** RLY-4008 is well-tolerated when administered orally at doses up to 30 mg/kg twice daily. Data are from the FGFR2-TTC28 intrahepatic cholangiocarcinoma patient-derived xenograft model shown in Fig. 3A, B (n=6/group) and are presented as mean ± SEM. **B, D,** Dotted line indicates tumor volume prior to initiation of treatment. **B,** Antitumor activity of RLY-4008 in an FGFR2-CCDC6 lung adenocarcinoma patient-derived xenograft model (n=8/group). Data are mean ± SEM. **C,E,** Dotted line indicates 50% pFGFR2/tFGFR2 (50% inhibition of pFGFR2). **C,** Dose-dependent inhibition of FGFR2 in FGFR2-CCDC6 tumors. Animals were sacrificed and tumors harvested at the indicated time points after the final dose on the third day of dosing. Tumor lysates were analyzed via pFGFR2 (Y653/654) ELISA and total FGFR2 HTRF; pFGFR2 normalized to total FGFR2 is reported (n=3/group). Free plasma concentration of RLY-4008 is reported. Data are mean ± SEM. **D,** Antitumor activity of RLY-4008 in an FGFR2-WDR11 gastric adenocarcinoma patient-derived xenograft model (n=8/group). Data are mean ± SEM. **E,** Dose-dependent inhibition of FGFR2 in FGFR2-WDR11 tumors. Animals were sacrificed and tumors harvested at the indicated time points after the final dose on the third day of dosing. Tumor lysates and plasma were analyzed and reported as in **(C)** (n=3/group). **F,** Body weight of animals in the ICC13-7-FGFR2^{V564F} xenograft model dosed with RLY-4008 and pan-FGFRi futibatinib, pemigatinib, erdafitinib and infigratinib. RLY-4008 is well-tolerated while pan-FGFRi demonstrate varying levels of body weight loss over 28 days of treatment. Following 28 days of treatment on the indicated inhibitors, animals on pan-FGFRi were changed to treatment with 10 mg/kg RLY-4008 once daily. Treatment with RLY-4008 restores body weight. Data are mean ± SEM (n=8/group). **G,** RLY-4008 overcomes acquired resistance to pemigatinib. Anitumor activity of pemigatinib followed by RLY-4008 in an FGFR2-TTC28 intrahepatic cholangiocarcinoma patient-derived xenograft model. Animals were dosed with pemigatinib (0.5 mg/kg twice daily) for 68 days followed by treatment with RLY-4008 (15 mg/kg twice daily) from days 69-98. Dotted line indicates day 68 of treatment. Each line represents one animal.