**Supplementary Figure Legend**

**Figure S1.** The success rate and average days of constructing PLC organoids and PDX model. **(A)** The success rate of establishing tumor organoids of each PLC subtype. **(B)** The success rate of establishing tumor PDX models of each PLC subtype. **(C)** The duration of tumor organoids’ culture from tissue separation to the first passage was 13.0 ± 4.7, 13.8 ± 3.4, and 21.5 ± 7.8 days for HCC, ICC, and CHC, respectively. **(D)** The duration of PDX construction from the first tumor implantation to the second implantation was 25.1 ± 5.4, 33. 0 ± 5.7, and 27.5 ± 2.1 days for HCC, ICC, and CHC, respectively.

**Figure S2.** Immunohistochemistry of tumor tissues, organoids, and ODX and PDX from PLC patients of major histotypes. **(A)** Expression of AFP in tumor tissues, tumor organoids, ODX, and PDX derived from HCC-25, HCC-118, ICC-6, and CHC-3 patients. **(B)** Expression of CK-19 in tissues, organoids, ODX, and PDX. **(C)** Expression of EpCAM in tissues, organoids, ODX and PDX. Scale bars, 50 μm. CK19, cytokeratin 19; PLC, primary liver cancer; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; CHC, hepatocellular cholangiocarcinoma; PDX, patient-derived xenograft; and ODX, organoids-derived xenograft.

**Figure S3.** The stemness- and epithelial–mesenchymal transition-related gene sets enriched in each of the four acquired sorafenib-resistant HCC organoids: **(A)** gene sets enriched in the organoid of HCC-52; **(B)** gene sets enriched in the organoid of HCC-118; **(C)** gene sets enriched in the organoid of HCC-10; and **(D)** gene sets enriched in the organoid of HCC-25. NES, normalized enrichment score; FDR, false discovery rate.

**Figure S4.** The heterogeneity of stemness- and epithelial–mesenchymal transition-related gene expression patterns in four HCC organoids with and without acquired sorafenib resistance. **(A)** Western blotting showed the expression patterns of N-cadherin, Vimentin, Claudin-1, CD44, ABCG2, and EpCAM in HCC-118, HCC-25, HCC-10, and HCC-52 parental and sorafenib-resistant organoids, respectively. **(B)** Immunohistochemistry showed the expression of CD44, EpCAM, N-cadherin, and Vimentin in the parental and acquired sorafenib-resistant organoids of HCC-118 and HCC-25. Scale bars, 50 μm.

**Figure S5.** Association of the differentially expressed genes in acquired sorafenib-resistant HCC organoids with the prognosis: **(A)** overall survival; and **(B)** recurrence-free survival.