Fibroblast growth factor (FGF) / FGF receptor (FGFR) gene aberrations such as amplification, mutation and fusion are associated with many types of human cancers. Recently, FGF19 overexpression was observed in approximately 50% of hepatocellular carcinoma (HCC) patients. The FGF19-FGFR4 signaling has been implicated in the development of HCCs in mice. FGFR4 kinase inhibitors are expected to be a targeted therapy for FGF19-expressing HCC. A phase I clinical trial of ASP5878, a novel inhibitor of FGFR1, 2, 3 and 4, is ongoing (NCT02038673). Among 128 kinases, only 9 kinases including FGFR1-4 and FGFR3/4 mutations were inhibited more than 50% by ASP5878 (200 nmol/L). The IC_{50} values of ASP5878 against FGFR1, 2, 3 and 4 kinases were 0.47, 0.60, 0.74 and 3.5 nmol/L, respectively. ASP5878 inhibited cell proliferation of HCC cell lines with FGF19 overexpression. IC_{50} values were 8.5, 27, and 21 nmol/L in Hep3B2.1-7, HuH-7 and JHH-7, respectively. ASP5878 inhibited activation of downstream signaling molecules, FRS2 and ERK, and induced apoptosis in Hep3B2.1-7 cells. Oral dosing of ASP5878 at 3 mg/kg induced sustained tumor regression in the Hep3B2.1-7 subcutaneous xenograft model, which was poorly responsive to sorafenib. In an HuH-7 orthotopic inoculation mouse model, ASP5878 induced complete tumor regression and dramatically extended the survival. In addition, oral dosing of ASP5878 reduced plasma levels of FGF19 in the HuH-7 subcutaneous xenograft model. These results suggest that ASP5878 is a potentially effective therapeutic agent for FGF19-expressing HCC.