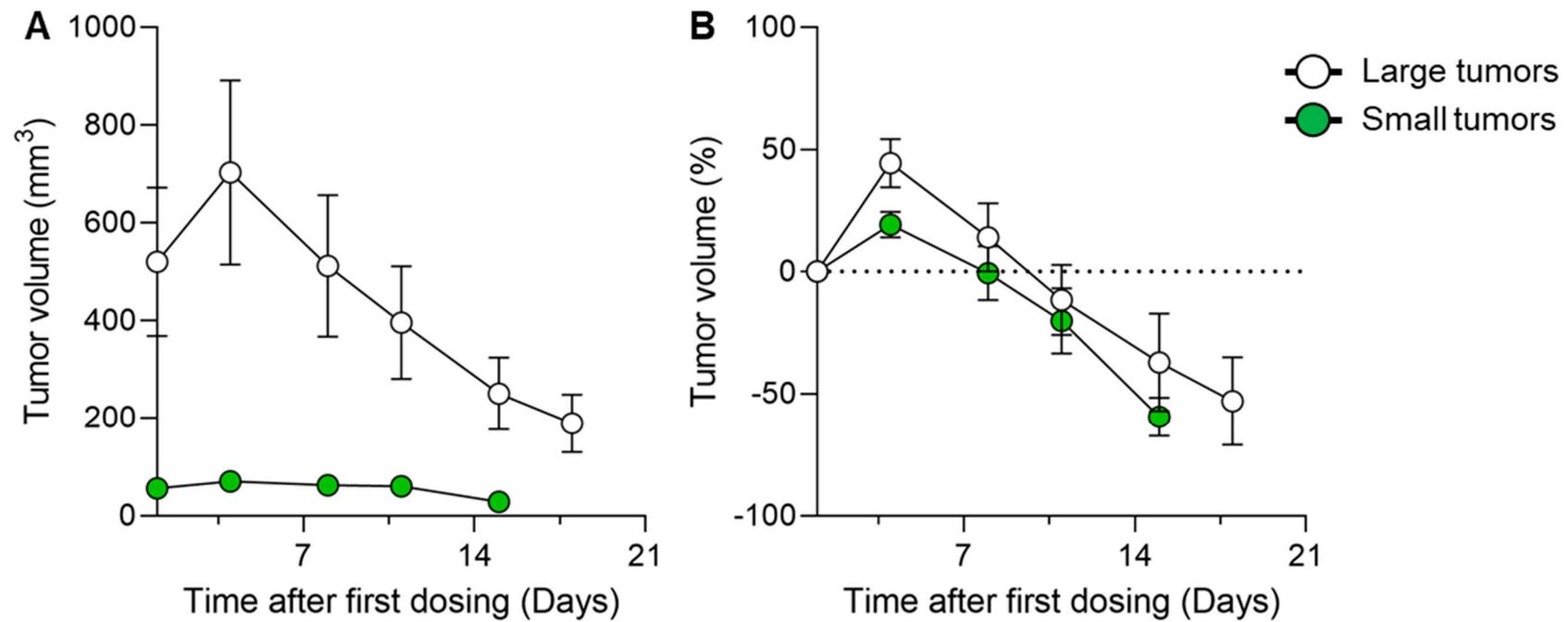
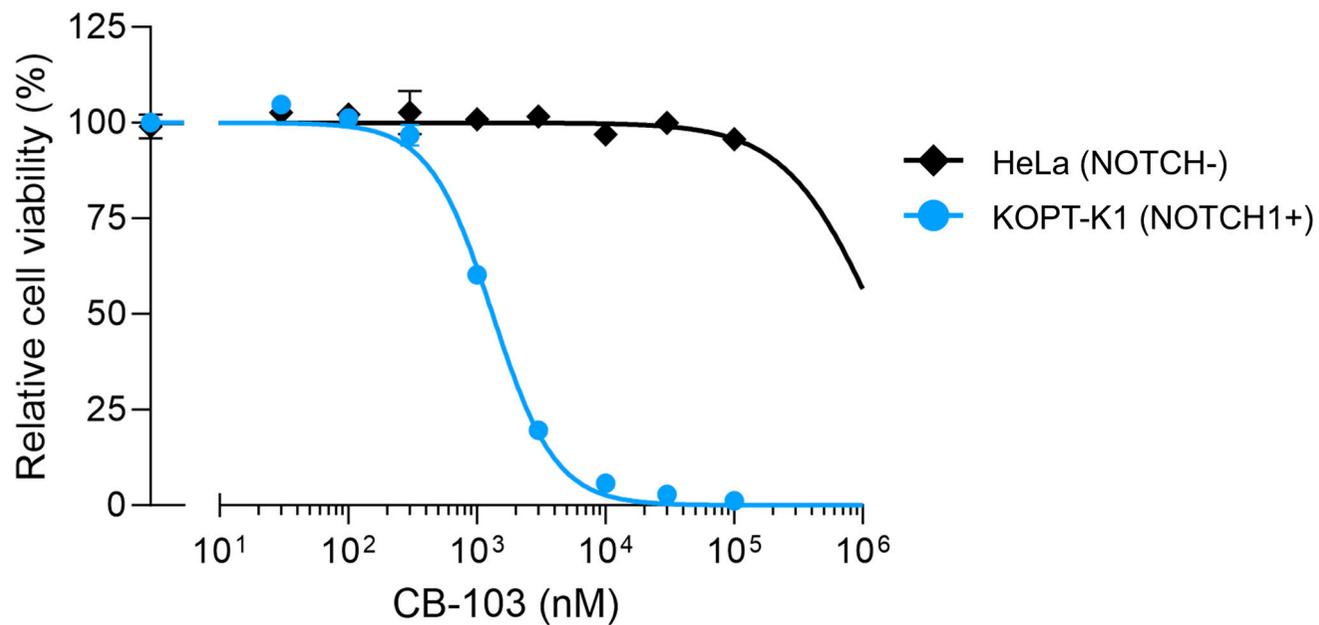


**Supplementary Figure S1.** Pharmacokinetics, pharmacodynamics and weight of mice during in vivo studies. **(A)** Plasma concentration of CB-103 at 0.25, 0.5, 1, 2, 4, 8, 12 hours after single dose at 60 mg/kg. Each dot represents mean  $\pm$  SEM of  $n=3$  mice. **(B)** Dose dependent downregulation of Marginal Zone B (MZB) cells in mice upon 7 days of CB-103 daily dosing; flow cytometry data showing percentage of MZB cells of representative mouse from vehicle control, 40 mg/kg and 60mg/kg of CB-103 treatment; **(C)** Histogram plot of the mean  $\pm$  SEM frequency of MZB cells for each dosing group ( $n=4$ ). **(D)** Weight plot of mice in the target engagement cohort in the MZB cell experiment. **(E)** Weight chart of mice in the Fulvestrant efficacy cohort indicating tolerability of doses. **(F)** Weight chart of mice in the paclitaxel efficacy cohort indicating tolerability of doses.



**Supplementary Figure S2.** Efficacy of CB103 + paclitaxel therapy on small and large TNBC tumors. NSG immune compromised female mice engrafted subcutaneously with TNBC cell line HCC1187 were treated with combination therapy (CB-103 60 mg/kg QDx5 + Paclitaxel 10 mg/kg Q7D) once average tumor volume reached 50 mm<sup>3</sup> (green dots) or 500 mm<sup>3</sup> (white dots). Tumor growth was evaluated by measuring tumor volume (A) or the percentage difference of volume from beginning of dosing (B).



**Supplementary Figure S3.** CB-103 specifically affects the viability of NOTCH+ cell lines. CB-103 was titrated (30 nm - 100  $\mu$ M) on NOTCH1-positive KOPT-K1 cells or on NOTCH-negative HeLa cells (negative control) for four days and the viability of each condition was measured by PrestoBlue™ assay. Each dot represents mean  $\pm$  SD of 3 technical replicates. The line represents the dose-response fit generated by GraphPad Prism 10.0 using log(inhibitor) vs response and variable slope (four parameters) setting.