**Supplementary Figure Legends**

**Supplementary Figure 1.** **Primary screen of CADD-derived compounds**. A. Histogram displaying values of selected compounds expressed as % Positive Control. The red line indicates the 50% activity mark. The shaded area highlights compounds exhibiting more than 97% inhibition and the orange highlighted bar indicates 1-134. B. NTC assay on compounds derived from the 1-134 similarity searching. Data are expressed in raw values as counts/sec. The orange highlighted bar indicates IMR-1 (1-134-83). C. NTC counter-screen to demonstrate specificity. Black shaded bars indicate probe for Maml1, grey shaded bars indicate probe for Notch1, and white bars indicate probe for CSL using specific antibodies for Maml1, Notch1 and CSL, respectively. Orange shaded bar indicates IMR-1 probed for Maml1.

**Supplemetary Figure 2. IMR-1 inhibits tumor growth.** Graph of OE19 xenograft tumor volumes (in mm3) over time (days) in mice treated with vehicle (DMSO) or IMR-1 (15 mg/kg) administered daily via i.p. injection. Treatment was initiated on day 2 following transplantation of cells and continued until day 28. Data is displayed as average tumor volume (*n* = 5) per group and standard error of the mean.

**Supplementary Figure 3. IMR-1 treatment does not induce weight loss in treated mice.** Graph of mice weight determined during treatment with vehicle (DMSO), IMR**-**1 (15 mg/kg) or DAPT (15 mg/kg), administered daily via i.p. injection over the course of 24 days, in two patient-derived xenograft tumors: EAC29 (left panel) and EAC47 (right panel). Data is displayed as averages (EAC29, *n* = 5, EAC47 *n* = 6) and standard error of the mean.