**Supplementary Data**

**Supplementary Figure Legends**

**Supplementary Figure S1.** BCSC2-derived xenografts recapitulate the original patient tumor. **A,** Representative pictures of BCSC2 cells cultured in 3D and 2D conditions. Scale bar, 100 µm. **B,** Sphere-forming capacity of BCSC2 cells in an anchorage-independent assay (n=3). Data represent means + s.e.m. **C, D,** Representative expression pattern of CD24, CD44 (**C**), EpCAM and CD49f (**D**) in BCSC2 as analyzed by flow cytometry. **E,** Representative growth curves for limiting dilution assay of BCSC2 xenografts in immunocompromised mice. **F, G,** Hematoxylin and eosin (H&E) staining (**F**) and immunohistochemical detection of CK8/18, Ki67, E-cadherin, and vimentin (**F**) and ER, PR and HER2 (**G**) on representative sections of the original BCSC2 patient tumor and the BCSC2-derived xenograft tumor. Scale bar, 100 µm.

**Supplementary Figure S2.** KDM4B, C, or D do not control proliferation and xenograft tumor growth of BCSC1. **A-D,** Western blot analyses performed with anti-KDM4A (**A**), anti-KDM4B (**B**), anti-KDM4C (**C**), anti-KDM4D (**D**), and anti-Tubulin antibodies (**A**-**D**). Samples are lysates from BCSC1 infected with control shRNA (Ctrl; **A**-**D**) and shRNA against KDM4A (**A**), KDM4B (**B**), KDM4C (**C**), and KDM4D (**D**). **E,** Cell proliferation assay. BCSC1 cells were infected with adenoviruses coding for shRNA Ctrl, shRNA KDM4B, KDM4C, or KDM4D (n=3). **F-H,** BCSC1 derived xenograft tumors grown for 43 days in mice. BCSC1 were infected with adenoviruses encoding either shRNA Ctrl or shRNA KDM4D. **F,** Representative BCSC1 xenograft tumors isolated from individual animals. **G,** Increase in tumor volume over time. Data represent means ± s.e.m. **H**, Final tumor weights of the BCSC1 xenografts. Data represent means + s.e.m. For **F-H:** n=9. Data represent means ± s.e.m. (**G**) or mean + s.e.m. (**H**). (**I**) Kaplan-Meier plot showing relapse-free survival of patients with TNBC (ER-/PR-/HER2-) expressing high levels of KDM4A in comparison to patients expressing low levels of KDM4A (high expression: n=191; low expression: n=198). KDM4A gene set used was 203205\_at. Hazard ratio=1.21 (0.79 - 1.86) and logrank P=0.37. The plot was obtained using <http://kmplot.com/analysis/>.

**Supplementary Figure S3.** QC6352 is a potent inhibitor of proliferation and sphere-forming capacity of BCSCs. **A,** Cell proliferation assay. BCSC2 were cultured in the absence (vehicle) or the presence of the indicated concentration of QC6352 (n=3). **B,** Dose-response curve of QC6352 determined in BCSC2 (n=3). **C,** BCSC2 sphere-formation in an anchorage-independent growth assay in absence (vehicle) and presence of the indicated concentrations of QC6352 (n=3). **D,** Primary and secondary sphere-formation of BCSC2 in Matrigel in presence of vehicle or the indicated concentration of QC6352 (n=3). **E-G,** Primary and secondary sphere-formation of BCSC1 (**E**, **G**) or BCSC2 (**F**) in Matrigel in presence of vehicle or the indicated concentrations of the LSD1 inhibitor QC6688 (**E**, **F**) or Paclitaxel (**G**) (n=3). Data represent means ± s.d. (**A**, **B**) or mean + s.e.m. (**C**-**G**), \* p<0.05, \*\*\* p<0.001 by one-way ANOVA (**C**, **D**, **E**, **G**).

**Supplementary Figure S4.** QC6352 controls *EGFR* expression. **A,** Transcription factor binding motifs enriched at KDM4A locations in BCSC1. **B,** Venn diagram displaying the number of locations in BCSC1 (control) and BCSC1 infected with adenovirus coding for shRNA against KDM4A (shRNA KDM4A). **C, D,** Cell proliferation assays. BCSC1 (**C**) and BCSC2 (**D**) were cultured in absence (vehicle) and presence of erlotinib (n=3). **E, F** Dose-response curve of erlotinib in BCSC1 (**E**) and BCSC2 (**F**) (n=3). **G, H,** BCSC1 (**G**) and BCSC2 (**H**) sphere-formation in an anchorage-independent growth assay in the absence (vehicle) or presence of the indicated concentrations of erlotinib. Data represent means ± s.d. (**C**-**F**) or means + s.e.m. (**G**, **H**); \*\*\* p<0.001 by one-way ANOVA (**G**, **H**). (**I-M**) Western blot analyses performed with the indicated antibodies. Samples are lysates from BCSC2 (**I**, **J**) and BCSC1 (**K**-**M**) cultured in the presence of vehicle (-) or QC6352 (**I**) or infected with adenovirus coding for shRNA control (Ctrl) or shRNA against KDM4A-D (**J**-**M**).

**Supplementary Figure S5.** Levels of H3K9me3 increase upon treatment with QC6352. **A,** Pie charts displaying genomic distribution of H3K9me3 in BCSC1 cultured in the presence of vehicle (-) or QC6352 as determined by ChIP-seq analysis.

**Supplementary Figure S6.** QC6352 inhibits BCSC2-derived xenograft tumor growth. (**A**-**E)** Mice bearing BCSC2-derived xenograft tumors were treated for 21 consecutive days with either vehicle or QC6352. **A,** Representative BCSC2 xenograft tumors isolated from individual animals after 21 days of treatment with either vehicle or QC6352. **B,** Increase in tumor volume over time. **C,** Tumor weights after 21 days of treatment with vehicle or QC6352. **D, E,** Representative images of tumors (**D**) and volume quantification of all tumors (**E**) obtained by ultrasound imagery at the start (Day 0) and after 21 days of treatment (Day 21) with either vehicle or QC6352. For **A**-**E**: n=6. Body weight of mice bearing BCSC1 (**F**) or BCSC2 (**G**) xenograft tumors over the treatment time span of 21 consecutive days with either vehicle or QC6352. Data represent means ± s.e.m. (**B**, **F**, **G**) or means +s.e.m. (**C**, **E**); \*\* p<0.01, \*\*\* p<0.001 by one-way ANOVA (**C**, **E**).