## Supplementary Figure Legends

### Figure S1. Cysteine-dependence associates with low claudin gene expression in TNBC

**(A)** Cell cytotoxicity of various TNBC cells treated with either control or 5 μM erastin was measured by relative protease releasing (n=3; *, $p<0.001$).

**(B)** Heatmap cluster viewing of gene expression in claudin-high and claudin-low TNBCs.

**(C, D**) Gene sets enrich analysis (GSEA) showed upregulation of luminal associated genes and downregulation of metastasis-related genes in claudin-high TNBCs.

**(E)** GSEA indicated that genes with high-CpG-density promoters (HCP) bearing histone H3 trimethylation mark at K27 (H3K27me3) are enriched in claudin-high TNBCs.

**(F**) RT-qPCR analysis of indicated genes in luminal tumor cells, claudin-high, and claudin-low TNBCs.

**(G**) Linear regression analysis of indicated gene expressions in TCGA breast invasive tumors.

### Figure S2. Epigenetic compound library screening identified HDAC6 inhibitors as sensitizers of cysteine depletion in claudin-high TNBC

**(A)** Relative cell survival was measured by ATP level of claudin-high TNBC MDA-MB-436 cells in response to the control (Con), 5 μM erastin (E), 5 μM tubacin (T), or combination of erastin and tubacin (E+T) for 72h post-treatment (n=3, *, $p<0.001$). The cell viability was also assessed by crystal violet staining.

**(B)** Cell viability of HCC70 was assessed by crystal violet staining after exposure to the control, 5 μM erastin, 5 μM tubacin, or combination of erastin and tubacin (E+T) for 72 hours.

**(C)** Cell viability was measured by relative ATP level in luminal MDA-MB-361 and SUM-52, and Her2 positive SKBR3 after the similar treatments to (**A**) for 72 hours (n=3, $^{\#}$**,** $p<0.05$).

**(D)** Relative cell survival of MDA-MB-436 was measured by CellTiter-Glo assay or assessed by crystal violet staining after 72 hours treatment with either the control, 5 μM erastin, different concentrations 1, and 2 μM of Cay10603 (n=3, **, $p<0.001$).

### Figure S3. HDAC6 knockdown does not mimic tubacin-mediated synthetic-lethality

**(A, B, C)** Immunoblotting analysis (Upper panel) of HDAC6 and acetylated tubulin in **(A)** HCC38, **(B)** MDA-MB-436, and **(C)** luminal T47D with infected either with the empty pLKO vector (Vec) and different shHDAC6 constructs; Relative cell survival (Lower panel) was measured by relative ATP level in indicated cells under either control (Con) or erastin treatment for 72 hrs (n=3).

**(D, E)** Cell viability was measured by relative ATP level in HCC38 (**D**; 48 hrs) and MDA-MB-436 (**E**; 72 hrs) cells respectively under either treatment with either control or erastin in combination with indicated concentration of myriocin (Myr) either 10 or 20 μM.

**Figure S4**. **The combined erastin and tubacin treatment increases labile zinc in cells**

**(A)** Living cell imaging of MDA-MB-436 cells was stained by Fluozin-3 and DAPI (Hoechst 33342) under the similar treatments to (**A)** for 18 hrs. The size of scale bar is 50 μm (n=3).

**(B)** Cell survival was measured by relative ATP level in MDA-MB-436 under either control or 3 μM of zinc chelator (TEPN) with combined erastin and tubacin after 72 hrs (n=3).

**Figure S5. PKC activation is required for the tubacin-promoting cell death and cellular labile zinc increasing**

**(A)** Relative cell survival was measured by the ATP level in MDA-MB-436 under either control or 5 μM erastin and 5 μM tubacin (E+T) treatment with or without addition of different doses of PKC inhibitor Gö 6976 or Gö 6983 for 72 hrs (n=3, *, $p<0.005$).

**(B)** Immunoblot analysis of phosphorylated PKC (Pho-PKC) substrates in HCC38 cells under similar treatments to (**A**) for 22 hrs.

**(C)** Representative living cell imaging of HCC38 cells was stained by Fluozin-3 and DAPI (Hoechst 33342) upon the treatments with E+T, or E+T with 5 μM Gö 6983 treatment for 18 hrs. The scale bar represents 30 μm.